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NON-CONVENTIONAL PATHOPHYSIOLOGY TARGETS FOR NEW TREATMENT REGIMES OF DEPRESSION: A COMPREHENSIVE REVIEW

Riya Yadav[1], Abhishek Sharma[1,2*], Rubina Bhutani[1], Garima Kapoor[3], Priti Tiwari[2], Mamta Dagar[1], Hemant Kumar[2], Vikas Jogpal[1], Sameer Rastogi[2]

[1]Department of Pharmacy, School of Medical & Allied Sciences, G.D. Goenka University, Gurugram-Sohna Road, Gurugram, Haryana, India-122103.
[2]School of Pharmacy, Noida International University, Yamuna Expressway, Gautam Budh Nagar, Uttar Pradesh, India-203201
[3] School of Pharmacy, KIET, KIET Group of Institutions, Ghaziabad, Uttar Pradesh, India-201206

Corresponding Author: abhi.bharadwaj15@gmail.com; +91-9050726787
Abhishek Sharma
ORCID: 0000-0001-7859-867X
[1]Department of Pharmacy, School of Medical & Allied Sciences, G.D. Goenka University, Gurugram-Sohna Road, Gurugram, Haryana, India-122103.

[2] School of Pharmacy, Noida International University, Yamuna Expressway, Gautam Budh Nagar, Uttar Pradesh, India-203201

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ABSTRACT

Background: Major Depression, a debilitating mental health disorder affecting millions worldwide, presents a significant public health challenge. While conventional treatments such as psychotherapy and pharmacotherapy have demonstrated efficacy, a substantial portion of patients experience limited response or intolerable side effects. This highlights the pressing need for novel, more effective treatment modalities based on non-conventional unexplored targets.

Main body of the abstract: This review explores the current landscape of Major Depression treatment, emphasizing the critical juncture at which we stand, necessitating a paradigm shift towards many unexplored sights and innovative approaches. Drawing on extensive literature reviews and clinical insights, this review scrutinizes emerging treatment modalities, including but not limited to, dysregulation and overactivity of Hypothalamus-Pituitary-Adrenal (HPA) axis, monoamine hypothesis, implication of inflammation, circadian rhythm disturbances, histone modifications- epigenetics of depression, GABA & Glutamate disturbances, implication of endogenous κ opioid systems, transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), Tissue-type plasminogen activator implication and novel pharmacotherapies targeting specific neurochemical pathways.

Short conclusion: These interventions exhibit promising results in preliminary trials as they were found playing crucial roles in pathogenesis, and have potential to revolutionize treatment outcomes for individuals grappling with low response to conventional treatment regimens and treatment-resistant depression. Therefore, focussing on the unexplored craters of pathophysiology targets of depression can lead to development of new era anti-depressants.

Key words: Antidepressant; Depression; Chronic unpredictable stress; Biomarkers; Pathophysiology Targets.

BACKGROUND

Mood and depressive disorders are considered the most common and severe psychiatric illnesses [1]. 3.8% of current population suffers depression, in which 5% are adults (4% men and 6% women) and 5.7% older than 60 years. Estimated 280 million people approximately in the world suffers from depression [2]. A study reported prevalence of more than seven hundred thousand deaths with suicide every year and about 45.7 million people are affected in India [3]. Approximately 20% of the American population is affected by mood disorders with incidence of about 10% yearly, in which 6.7% is for Major Depressive Disorder (MDD) [4].

Major Depressive disorder (MDD) is a very prevalent mental condition characterized by changes in mood and emotions affecting an individual's overall ability to perform daily life activities and tasks. Patients with major depression exhibit a variety of changes in critical functional domains such as sleep, appetite, psychomotor activity, cognition, and mood [1]. As stated by the WHO factsheet, Depression is a very prevalent illness associated with continual state of sadness and anhedonia, along with an incapability to carry out daily activities, for a period of at least two weeks [2]. Also, it has been observed irrational and self-medication of many drugs also pose high risk of developing mood disorders [5].

Current review puts strong emphasis on several neurobiological, physiological, environmental, and genetic pathways involved in the progression of depression including mostly studied monoamine hypothesis along with several novel targets and pathways involved in disease's pathogenesis. Disease burden on public health is substantially increasing with low rates of effectiveness and remission with delayed response taking several weeks-months in exhibiting efficacy, also greater rates of relapse once response is obtained with current anti-depressant treatments. These limitations impose greater threat to the patients and newer antidepressants overcoming these problems requires more targeted approach which could improve the treatment regimen. Here, we will discuss evidences and associated factors contributing to the behavioral deficits which could possibly precipitate depression, opening a plethora of targets for advanced pharmacotherapy and treatment. Depression is a debilitating psychiatric disorder which substantially adds to the global disease burden. Nearly 322 million people have been estimated to be affected by the disorder which is 21% of the world's population [6]. As stated by WHO Factsheet (by the data of 13 September 2021, 5% of adults and 5.7% of older adults (>60 years) are affected by the disease, stirring 3.8% of the population around the world [7.] With a major impact and several clinical complications arising related to cardiovascular system and stress, WHO predicted earlier in past that by the year 2020, Depression would be 2nd leading cause of fatalities worldwide [8]. Being cause of huge worldwide disabilities, this illness would generate colossal economic downfalls in the modern society, with a marked prevalence in the developing than the developed countries. Morbidities and mortalities related to the disease are becoming increasingly high which makes it a serious disorder and making it the commonest causes of diminution of lives. It has been shown that women have approximately 10%-25% and men have 5%-12% of the risk of developing depression, which makes women higher at-risk group [9]. An estimated presence of depressive disorders was as high as 3.9% in South Asia with 3.9% in India [10]. A cross-sectional study involving multisite populations, conducted as National Mental Health Survey (NMHS) of India across 12 states of India in a phase-wise manner with varying geographic and cultural diversity assessed the prevalence of mental/depresive disorders evidently reported depressive disorders (12 months) burden to be

1.44% with major depressive disorder was 6.62% in rural south India. Ample data provided by this survey recognised depressive disorders as a serious health problem and how India would contribute substantially to the global burden of depressive disorders [3]. Studies consquently reported rise in post-pubertal depression in adolescents with 14.19 % prevalence, Center for Epidemiological Studies-Depression Revised (CESD-R) Scale utilised to assess the presence of disorder was reportedly (16 or above). High scores had high suicide ideations [11].

METHODOLOGY INVOLVED

This exploratory literature search for this review assessment was steered in Google Scholar, PubMed, Embase and other scientific databases. The search was limited to publications reported pathophysiology targets not very much explored for their anti-depressive potential either by behavioural or biochemical or both types of analysis in pre-clinical animal models of depression, along with epidemiology and various contributing factors for low efficiency of current treatments of depression as illustrated in Figure 1.

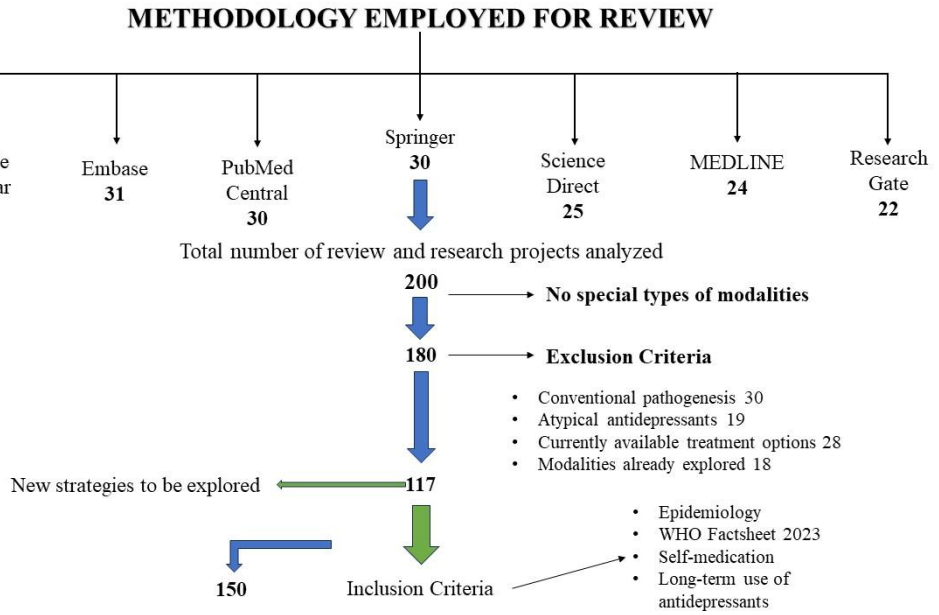

Figure 1: Flow Chart Illustration of Review of Literature

This figure explains the process of rigorous literature identification and synthesis of information from various databases of quality literature for available unexplored potential pathophysiological targets of depression along with inclusion and exclusion criterions.

SIGNATURE SIGNS & SYMPTOMS

Major Depressive Disorder is characterized by a paradigm of symptoms affecting emotional, motivational, cognitive, and physiological parts of the brain [12]. A condition of co-morbid anxiety [13] or numerous chronic diseased conditions can be a contributing factor to depression [4] Initial symptoms of depression are most seen between 20-40 years of age. Also, above 60 years more than half of the elderly population witnesses the initial symptoms of the illness [9]. Primary symptoms of depression include loss of interest in pleasurable activities once enjoyed by the individual anhedonia, persistent feeling of worthlessness and guilt, low mood, diminished energy levels (fatigue) and lack of motivation due to chronic stress. Significant changes are observed in concentration, appetite (weight loss or weight gain), sleeping patterns

are affected causing either insomnia or hypersomnia, recurrent suicidal and death thoughts [7]. Presence of at-least two primary and two additional symptoms mentioned above and in Figure 2 together lasting for over two weeks serves as a diagnostic measure for the disease [14].

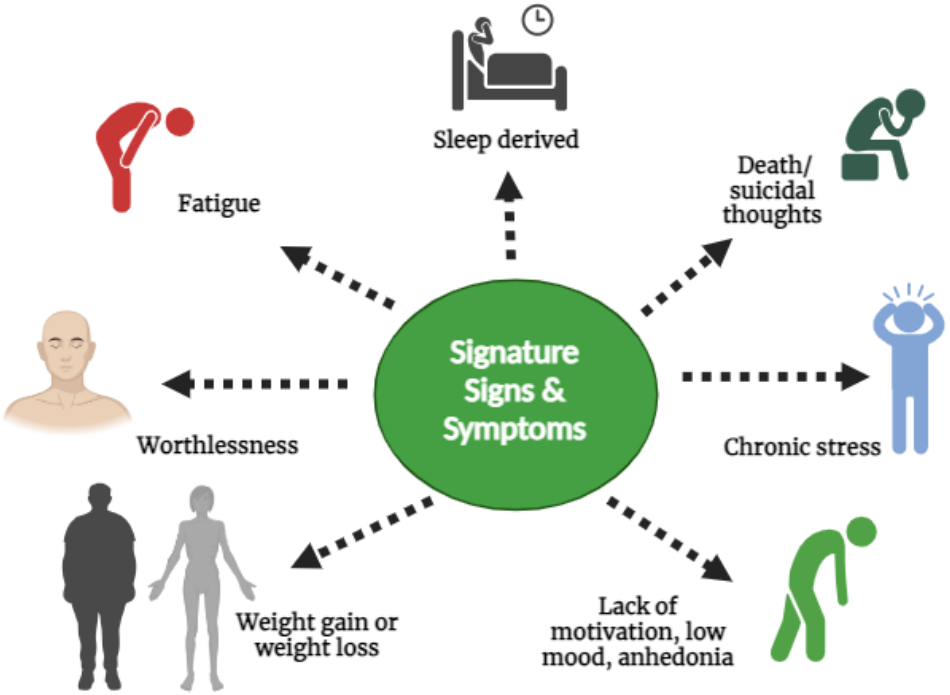

Figure 2: Flow Chart Illustration of Signs & Symptoms

This figure depicts various signature signs and symptoms involved major depression. Diagrammatic representation highlights the major one which should be prevailing for at least two or more than two weeks of period with the subject for a confirmatory diagnosis of depression.

MECHANISMS AND HYPOTHESES INVOLVED IN PATHOGENESIS

Underlying features of MDD are very much diverse and patients can now be classified according to different categories based upon the predisposing factors or etiologies [4, 15, 16]. Depression alters mental health, mood and behavioral domains and upon research, connection of disease's pathogenesis was found to be related with various mechanisms and theories including alterations of neurotransmitters in the central nervous system (CNS), predominantly noradrenaline (NA) or norepinephrine (NE), serotonin or 5-hydroxytryptamine (5-HT) and dopamine (DA), inflammatory processes, stress related mediators, inadequacy of nutrition [9]. Factors influencing genetics also play a prominent part in the pathophysiology. Estimated 50% of causative factors are genetic, due to polymorphism in genes related to important neurotransmitters involved, genes regulating anti-inflammatory cytokines and circadian rhythm disturbances also illustrated in Figure 3. Combined research and studies in the field of depression made major speculations about involvement of cellular plasticity suggesting how processes contributing to neurodegeneration can afflict mood disorders [7, 17]. Half of the predisposition to the disease occurs due to involvement of non-genetic factors such as emotional trauma, viral infections (e.g., Borna virus), and even some random processes during brain development [14] and disturbances in the gut brain axis [18].

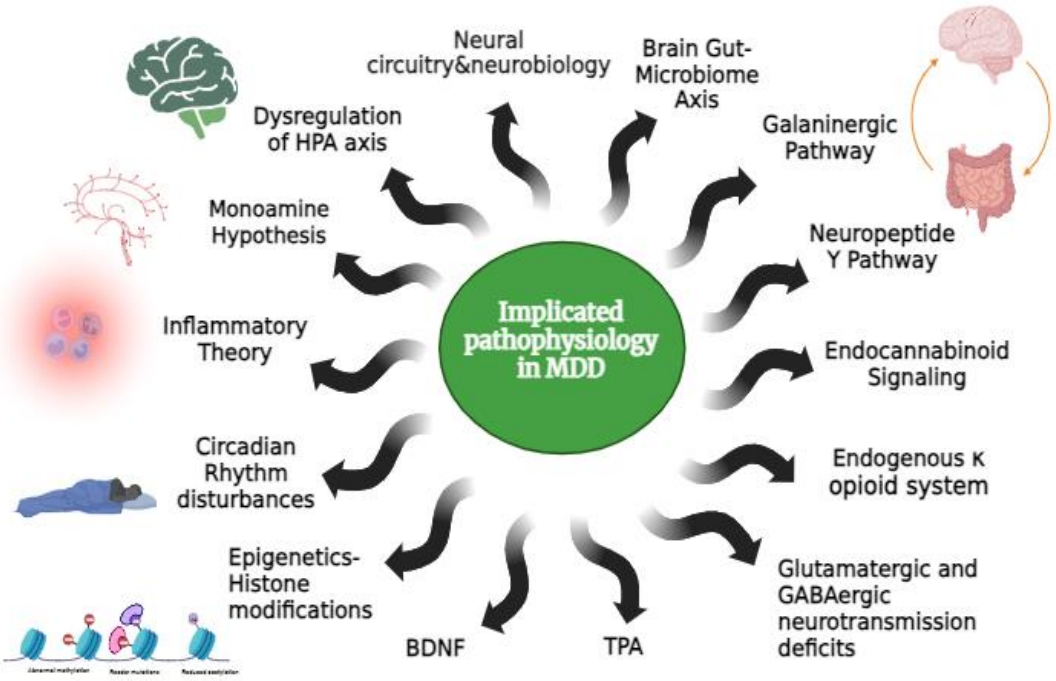

Figure 3: Target pathogenesis which can be explored for new novel treatment regimens of depression.

This figure illustrates the identified pathophysiological pathways involved from the literature extracted from various quality databases. Included pathophysiological targets can be explored further for development of novel and highly effective treatment modules of depression.

Neurobiology & Neural Circuitry

Several regions of brain have been indicated in progression of disorder which regulate memory, learning, mood, reward, and emotional processes [19]. But still, we have rudimentary knowledge about involvement of these areas in the progression and affliction of the disease. Broad range of symptoms indicate involvement of many areas of brain. Autopsies and human brain imaging studies obtained from the patients with depression reported abnormalities and blood flow changes in several areas, including regions of prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus [20, 21, 22]. Additionally, some human imaging studies shows correlation of cellular loss in prefrontal cortex and amygdala of those suffering with mood disorders with a selective attenuation of brain volume causing depression [23]. Regional reduction in the brain could be due to neurodegeneration or reduction in neurogenesis. There is an indication of selective neuronal loss in patients with MDD in the paraventricular nucleus of hypothalamus [17]. Apprehension of selective functions of these regional brain parts under normal conditions contributes to a better understanding of disease's pathogenesis. All these brain areas conjointly form a highly interactive neural circuitry which helps in further formulation of neural circuitry involved in depression. Frontal areas of cortex (FC) or neocortex and hippocampal region might mediate cognitive aspects of depression such as, hopelessness, feelings of worthlessness, impairments in memory, guilt, doom, suicidality and might also function more vastly in regulation of emotional and behavioral abnormalities [24]. Striatum (particularly the ventral striatum or nucleus accumbens, NAc), and amygdala along

with some related brain areas are crucial in mediating apathetic and reward responses to emotional stimuli and, could modulate anhedonic, anxiety and diminished motivational behaviors in patients with depression. Role of hypothalamus (Hyp) has been implicated in neurovegetative symptoms of depression, such as too much or too little appetite, sleep and energy, as well as loss of interest in pleasurable activities [14, 25]. Networks involving forebrain is modulated by the monoaminergic innervations from midbrain and brainstem nuclei [dopaminergic input by ventral tegmental area (VTA), serotonin (5-HT) from the dorsal raphe (DR) and norepinephrine from the locus coeruleus (LC)]. These neurotransmitters control alertness, awareness and modulates the prominence of emotional stimuli [19, 26]. Figure 4 illustrates the implication of Glutamatergic; Dopaminergic and GABAergic Pathways in Depression.

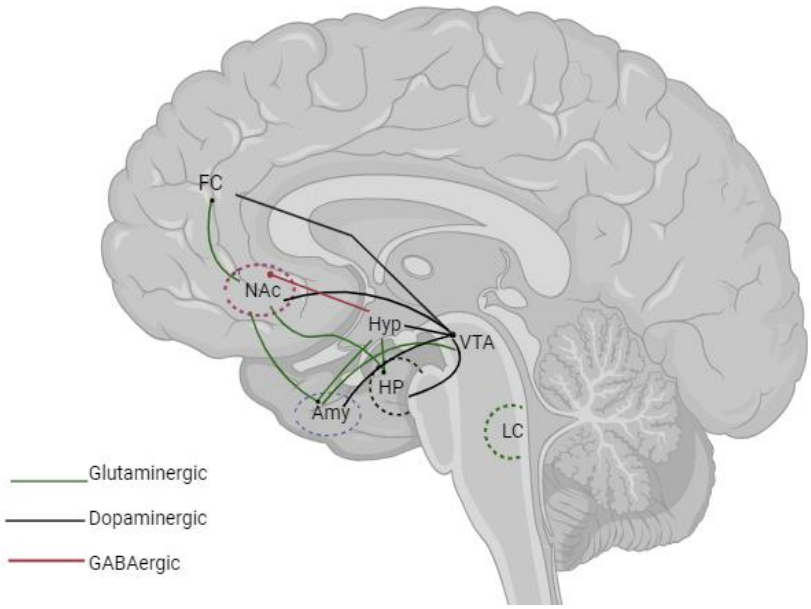

Figure 4: Implication of Glutamatergic; Dopaminergic and GABAergic Pathways in Depression.

This figure characterises the implication of Glutamatergic; Dopaminergic and GABAergic Pathways via several different areas of brain in Depression. As Glutamate; GABA and Dopamine have different pathways in different regions of brain, their synchronous deviation is being responsible for pathogenesis of depression.

Dysregulation and overactivity of Hypothalamus-Pituitary-Adrenal (HPA) axis

Hypothalamus-pituitary-adrenal (HPA) axis is one of the essential components by which one's brain cope up with acute and chronic stress responses in stress-related disorders such as MDD [27]. Activation of HPA axis is prominent in perceiving stress. It's hyperactivity and over-stimulation has been implicated in severe depression [28,29]. Neurons of paraventricular nucleus in hypothalamus causes secretion of corticotropin-releasing factor (CRF), which in turn modulates synthesis and secretion of adrenocorticotropin (ACTH) from the anterior pituitary. This leads to stimulation of glucocorticoid release from the adrenal cortex [30]. Manifestation of depression in patients with over-expression of CRF in the hypothalamus, greater levels of CRF in cerebrospinal fluid (CSF) and diminished feedback inhibition of the axis by glucocorticoids and CRF makes HPA regulation a profound area of interest in the disease progression [20]. Studies

suggest normalization of the axis might contribute to stable remission of depressive symptoms. Mechanisms of HPA axis are operated by numerous brain pathways, including the hippocampal region and the amygdala. CRF serves as a neurotransmitter in amygdala and bed nucleus of the stria terminalis (BNST), and these areas of brain are involved in generation of anxiety-like behavior. Substantial increase of CRF in locus coeruleus have been found in patients with depression and excessive levels of glucocorticoids might be causative mechanism which manifests small reductions in hippocampal volume in patients with depression or post-traumatic stress disorder, but this still remains controversial [14,20].

Monoamine Hypothesis of Depression

The neuronal relationships mainly rely on neurotransmitters which carry out transmission of signals in the nervous system. Release of the neurotransmitters occurs from neuronal ends in response to a wave of depolarization and some are released into the synaptic cleft and decomposed. Reuptake mechanism causes partial recovery of such neurotransmitters. Release and reuptake are affected in disorders like depression [9]. Monoamine hypothesis suggested that a marked depletion in the overall levels of serotonin, norepinephrine, and dopamine in the central nervous system [31]. Breakdown and diminished levels of neurotransmitters occurs in the hippocampus, limbic system and frontal cortex contributing to depressive symptoms. Monoamine oxidase plays a major role in the metabolism of monoaminergic neurotransmitters [32].

Serotonin

Serotonin, a neurotransmitter exhibits biogenic amine group and is a derivative of amino-acid tryptophan [33]. Among different serotonergic receptors, e.g., 5-HT1A, 5-HT1B, 5-HT2Ab, 5-HT3, and 5-HT4, 5-HT1A receptor is responsible for memory, recognition and learning processes [9]. Studies and major evidences show a dysfunctional serotonergic system leading to depression which supports the biogenic monoamine hypothesis of depression. Several reports show decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), a major serotonin metabolite in the cerebrospinal fluid (CSF) of depressed patients, but these findings have not been consistent. A model for neuronal serotonin receptors was proposed which reported reduced amount of serotonin transporter domain and diminished uptake of serotonin in the platelets of antidepressant-naïve depressed patients [31]. Upon analyzation and research, pathogenesis of depression was linked with reduction in 5-HT1A receptor binding and neurotransmission deficits in the central nervous system [9]. Significant lack of serotonergic transmission in serotonin system has been indicated in etiology of MDD [34]. MDD involves substantial changes in the mechanism of serotonin reuptake and diminished level of L-tryptophan, a serotonin precursor which alters behavior such as mood, sleep, wakefulness, memory and learning [35].

Norepinephrine

Monoamine hypothesis of depression suggested that the reduction in the activity of norepinephrine neurons contributes to the development and progression of depression [9, 36]. Upon studies related to the levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major noradrenergic metabolite, indicated a slight correlation between the MHPG levels and the depressive symptomatology. Release and stimulation of NE is regulated by the presynaptic α2-adrenergic receptors. Increased auto receptor activity and subsequent decrease in the NE may be involved in the etiology. Brain imaging studies have shown a substantial increase in the density and affinity of α2-adrenergic receptors in the frontal cortex area and might, to a lesser

extent, in the hypothalamus, amygdala, hippocampus, and cerebellum of depressed suicide victims. Monitoring the activity of β-adrenergic receptors in depression patients has been regarded as a marker of antidepressant efficacy in the treatment of patients [31]. Depressive patients have shown alterations in the sensitivity of the receptors [37].

Dopamine

The dopamine (DA) system is involved in modulation of motor behavior, cognition and emotion and some emerging studies suggests links between the disruptions in the dopamine system and the pathogenesis of several psychiatric disorders including depression [38,39]. A deficient dopamine condition in CNS might be the causative factor for depressive and "foggy brain" [9]. Symptoms such as anhedonia and lack of motivation have been linked to a dysfunctional DA system. Diminished levels of DA are observed within medial frontal cortical regions involving amygdala [40]. A depression of DA neuronal firing was observed in the acute activation of the DA system by amphetamine or stress- induced DA neuron activation where the duration of stress was short term but in conditions of consequent or chronic depression, the DA neuronal density is affected. When rats were exposed to chronic cold or unpredictable chronic mild stressors (UCMS), about 50% decrease in the VTA DA neuronal population was observed with an increased immobility in forced swim test. Numerous findings identified hyperactivity in prefrontal cortical area and hyper-responsiveness in amygdala in depression. Targeting these domains or reversing hyperactivity in these areas could be effective in treatment [38]. A brief view is being shared in Table 1 for currently available treatment options for depression.

TABLE 1: CURRENTLY AVAILABLE TREATMENT REGIMEN FOR DEPRESSION

Treatments		**Mode of action**
MEDICATION BASED	**Tricyclic antidepressants** Clomipramine, Imipramine, Desipramine, Amitriptyline	Inhibition of membrane transporters for monoamines (mixed NA and 5-HT reuptake)
	Selective Serotonin Reuptake Inhibitors (SSRIs) Fluoxetine, Citalopram, Sertraline, Paroxetine, Fluvoxamine, Escitalopram	Cause inhibitory action towards selective-serotonin reuptake
	Noradrenaline Reuptake Inhibitors (NARIs) Atomoxetine, Reboxetine	Suppression of selective-noradrenaline reuptake
	Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) Duloxetine, Venlafaxine	Combinational noradrenaline and serotonin reuptake inhibition

	Monoamine Oxidase Inhibitors (MAOIs) Tranylcypromine, Phenelzine	Hindering monoamine oxidase A (MAO_A) [MAO_B inhibition does not have anti-depressants effects]
	Lithium	It has numerous molecular mechanisms (inhibition of G-proteins, adenylyl cyclase, phosphatidylinositol phosphatases) but its use in
		mania, bipolar and as antidepressant is unknown
	Atypical Antidepressants Bupropion, Mirtazapine, Tianeptine	Unknown, mode of action is based on monoamine-based mechanisms
NON-MEDICATION BASED/SOMATIC	Electroconvulsive Therapy	General electrical brain stimulation
	Magnetic Stimulation	Magnetic brain stimulation
	Deep Brain Stimulation	Stimulation of abnormally working cingulate cortex in severely ill patients for attenuating depression
	Vagus Nerve Stimulation	Afferent vagal brainstem pathway stimulation (left cervical vagus nerve) in regions implicated in mood / depressive disorders (antidepressant effects)
	Psychotherapeutic Modality Cognitive-behavioral therapy	Unknown, involving new learning about coping with problems.

Inflammatory Theory of Depression

Several theories were hypothesized by authors linking depression and the immune system function. Interactions between nervous, immune and endocrine systems were observed. Cytokines, large protein molecules regulate the immune system response and also affect the metabolism of DA, NE and 5-HT in the nuclei of the brain. Enhanced secretions both through the direct stimulation of the HPA axis and modifications in gluco-corticosteroid receptor sensitization [41,42]. Downregulation in the levels of cytokines can lead to insufficient mediation or can inhibit the normal immune response leading to disease manifestation and has been linked to major depression [17,43,44]. In 1991, Smith discovered the association between increased

cytokine secretion by macrophages and its role in depression. He pointed out the fact that administration of cytokines to subjects induced depressive symptoms and interleukin-1 might aggravate hormonal disorders associated with major depressive disorder. This theory gave explanation about important links between depression and the macrophage activation in inflammatory processes. The ability of estrogens in macrophage activation can make females more vulnerable to depression. Several studies suggested that patients with severe depressive episodes showed higher IL-6 levels than that of patients with moderate symptoms and healthy individuals [4,41].

Circadian Rhythm Disturbances and Melatonergic Pathways

Circadian rhythms oscillate with an approximate 24 hours periodicity and regulates numerous physiological and behavioral parameters [45] such as sleep, temperature, mood and hormonal secretion. Abnormal 24 h rhythms have been reported in patients with MDD which could be the possible reason for symptoms of fatigue and insomnia [46, 47,48]. Around 60-90 % of the patients, depending upon the severity of depression, experience insomnia and hypersomnia [49]. Depressive disorders may result into disrupted circadian rhythms as a repercussion of disoriented Suprachiasmatic nucleus (SCN) of hypothalamus along with an abnormal circulating rhythmicity of melatonin from pineal gland responsible for synchronization of the 24 h light/dark cycle [50,51]. Numerous studies indicated circadian gene involvement in the brain reward regulation, with a prominent influence of Clk, a Pas-domain-containing transcriptional factor which generates circadian rhythms at molecular level at VTA-NA pathway contributing to symptoms of depression [20].

Synchronization of circadian rhythms is fulfilled by melatonergic receptors and disturbances in the rhythms has been implicated in MDD [52], which makes it an attractive targeted approach [50, 53, 54]. Exogeneous melatonin and melatonin receptor agonists could serve an effective treatment in correction of disrupted circadian and sleep-wake rhythms in psychiatric patients provided evidence from large, well designed controlled trials [55].

The half-life of all known drugs with melatonin is somewhat 30-50 min. Melatonin, as a chrono biotic, even at very low doses (0.5-1 mg) maintains fairly good amounts in the body, also enhances sleep propensity improving sleep initiation and maintenance disorders when administered acutely. Chronic treatment with melatonin demonstrated stimulation of dendritic maturation and hippocampal neurogenesis in mice [56].

The Brain-Gut-Microbiome Axis

Brain-gut-microbiome axis is a pathway that facilitates bidirectional (two-way) interchange of information between the microbiota of the GIT and nervous system. Vagal nerve serves as a supporting media for establishing connection and communication in the axis [18]. It is a representation of multiple interactions among the central nervous system (CNS), endocrine chemical signal system, immune system, microbiome, functions and effects involving barriers and metabolism in the gut and the brain [57]. Any imbalance in the axis triggers various kinds of mental and mood disorders like MDD [58]. Numerous findings and evidence from the preclinical stages suggests prominent role of brain-gut-microbiome axis in the pathophysiology of depression [59, 60]. Depression is associated with alterations in the gut motility and regional transit, immune function, mood and visceral sensitivity [61]. Anomalous levels of gut microbiome associated short chain fatty acids (acetic acid, propionic acid, pentanoic acid) and neurotransmitters (norepinephrine, 5-HT, 5-HIAA) were found in depressed mice and levels

were comparatively low as that of control mice [62]. Changes in alanine, L-threonine, serine and tyrosine levels is also reported in the fecal microbiome [63]. Administration of microbiome or their metabolites can alleviate depression-like phenotypes or treatment with combinations of short chain fatty acids such as acetate, butyrate, and propionate in mice [59].

Involvement of Neuropeptide Pathways

Galaninergic Pathways

Ascending and descending projections from a small nucleus in the pons, Locus coeruleus (LC) innervate major portions of the central nervous system with abundance of the major neurotransmitter NE (major source). This brain area is implicated in stress-related disorders and is responsible for wakefulness modulation. NE neurons express neuropeptides such as Galanin as co-transmitters [64]. Several studies came across the initial presence of Galanin in the early 1980s in porcine gut, with its expression throughout both brain and body of humans and rodents. Galanin is responsible for eliciting modulatory actions in various processes including nociception, feeding, seizures along with cognitive and behavioral responses (mood and stress responses) [65]. Galaninergic systems have been solitarily responsible in stress-induced behavior in rodents and stress-related disorders such as depression in humans. Enhanced noradrenergic transmission stimulates galanin transmission, in stressful conditions which indicates co-transmission [66]. Three major types of GAL receptors (GALR) depending on GALR subtype are involved in depressive disorders. Inhibitory G proteins (G_i/G_o) are activated mainly by GALR1 and GALR3 while excitatory signaling is stimulated via GALR2 coupling with G_q/G11. GAL1 and GAL3 receptor activation produces depression like behavior while GALR2 modulation results in improvement of depressive behavior [67]. Various preclinical studies suggest differential roles of GAL receptors, GALR1 stimulation resulted in enhanced immobility in FST but decreased immobility in TST and FST with GALR3 antagonist. GALR2 activation also resulted in a greater state of reduced immobility during FST [68].

Neuropeptide Y Pathways

Neuropeptide Y (NPY) neuronal pathway system is considered to be an attractive target in mood disorders, including depressive behavioral disorders. Distribution is wide, with highest concentration in limbic and cortical regions. Huge population of NPY-immunoreactive cells is present in hippocampus inside polymorphic layer of dentate gyrus [69]. NPY is a 36-aminoacid peptide, known to inhibit glutamatergic neurotransmissions and stimulates various pathological processes such as memory and learning, aging, nociception, food intake [69,70]. It regulates circadian rhythm, blood pressure and heart rate along with mood and locomotory functions [71]. It is a natural ligand of GPCRs involved in activation of Y-receptors (Y_1-Y_6). Glutamate release suppression is most prominent while selective synaptic transmission is inhibited by NPY [70]. NPY receptors are divided into six classes, Y1, Y2, Y3, Y4, Y5, and Y6 and stimulation of these NPY receptors through $G_{i\alpha}$ inhibits adenylate cyclase activity, consequently decreasing cyclic adenosine monophosphate and protein kinase A activity [69].

NPY evidently plays a major role in neuroprotection, and is implicated in the progression of depression and anxiety disorders [72]. Some studies depicted NPY neuroprotective effects through the stimulation of Y1 or Y5 receptors. Neuroprotective effects were offered through intravitreal injection of glutamate in glutamate-induced injury model in retina [73]. Reduction in NPY expression is observed in the hippocampus, amygdala and cerebrospinal fluid but hypothalamus witnessed an increased expression among depressive patients [70].

Endocannabinoid Signaling System Involvement

The endocannabinoid signaling (ECS) system is involved in modulation of short- and long-term synaptic plasticity mechanisms. It is crucial for processing CNS physiological domains such as reward, stress, memory extinction and fear [74, 75]. Numerous viable studies suggested the involvement of ECS in the etiology of MDD [76,77]. Normal fundamental processes mentioned above are reportedly disrupted. ECS system consists of various components, the receptors, degrading enzymes and endocannabinoid ligands which are pivotal modulators for cognitive, emotional and stressful behaviors [76]. Subsequent deficits in the components elicits anxiogenic and depressive effect while improvements are noticed with further elevation of signaling [78]. N-arachidonyl ethanolamine (AEA or anandamide) and 2-arachidonoyl glycerol (2-AG) are two major endogenous endocannabinoid ligands [79], synthesized 'on-demand' by several calcium independent and dependent pathways through phospholipid precursors in the postsynaptic membrane. These ligands mediate homeostasis and brain's short- and long-term synaptic plasticity [80]. Two main cannabinoid receptors are, CB1 and CB2 act through coupling with inhibitory G proteins (Gi/o) along with cAMP stimulation through Gq/11 under specific circumstances and recruitment of beta-arrestins for arrestin-dependent pathway signaling [81]. CB1 receptor dense distribution is found in limbic areas mainly indicated for stress and cognition, hippocampus, amygdala, nucleus accumbens and paraventricular nucleus in hypothalamus, abundance is found in prefrontal cortex, also includes cerebellum, basal ganglia, peripheral and in glial cells [82]. Intact function of CB1 ensures healthy mood, while CB1-knockout studies suggested its influential role in depression. Study on CB1-knockout mice displayed depression-like symptoms with increased corticosterone, and how knockout sufficiently made animal susceptible to stress. Decreased CBI receptor in NAc might be a good biomarker in diagnosis [83,84]. CB2 receptor is found to be associated in peripheral, immune tissues and in some subsets of brain neurons [85,86]. These receptors are responsible for modulation of emotional and non-emotional processes and their functionalities are reduced in major psychiatric disorders, such as major depression, opioid/substance abuse and schizophrenia [87]. Genetic polymorphisms and deletions in CB2 receptor gene, CNR2 reportedly resulted in precipitation of depression and other psychiatric disorders in many animal studies [88,89]. ECS is involved in regulation of HPA axis and studies suggest its role in enhanced activation of HPA axis during stress and anxiety-related behaviors [80,87,90]. Endocannabinoids might be involved in stress-induced reward modulation processes but contradictory results were obtained upon further review [80].

Several pharmacological and genetic mechanisms contributed to the evidences of endocannabinoids and signaling pathways in the pathogenesis of MDD but still there is a lack of literature to make a strong opinion about the individual involvement of ECS components and its role in depression.

Glutamatergic and GABAergic Neurotransmission Deficits

Alterations in the brain's connectivity involving MDD could be a consequence of dysregulated levels of two neurotransmitters which are the primary excitatory neurotransmitter, glutamate and inhibitory, GABA. They provide external inputs to the cerebral cortex and regulate the flow of information into the brain both intrinsically and extrinsically [91]. Abnormal levels of these neurotransmitters in the brains of subjects with depressive and mood disorders has paved a pathway contributing to MDD and its treatment [92].

Glutamatergic pathways play a significant function in all physiologically important factors in depressed patients [93]. Most of the earlier studies reported alterations in glutamate levels in brain's cerebrospinal fluid (CSF), blood and brain tissue but overall outcomes still lack and requires further investigation. Rodent studies have associated depression-resembling behaviors with alternations in cortical glutamate levels, dendritic formation and synaptic markers adhering to both acute and chronic stress paradigms [91,94,95]. Parts of medial frontal cortex reported lower levels of glutamate metabolites using proton magnetic resonance spectroscopy (MRS) in vivo [96]. This reduction in the levels of neurotransmitter could be a result of dysregulated synthesis mechanisms, metabolism and/or reuptake into glial and neuronal regions [97]. Metabotropic glutamate receptors (mGluR) include – the first group (mGluR1 and 5), II (mGluR2/3) and III (mGluR4,6,7 and 8) receptors [98]. First ones show positive coupling towards phospholipase C (G_q) while group II and III towards Gi, subsequently suppressing adenylyl cyclase and glutamate modulating depressive states [93]. Expression of mGluR2/3 receptors was found to be reduced in cingulate cortex of patients with MDD in postmortem studies [99], but another study showed no such alterations in anterior cingulate cortex among patients with MDD and healthy subjects [100]. A meta-analytic investigational study reported that genes responsible for glutamate synaptic neurotransmission were associated with MDD (4,346 subjects with MDD vs. 4,430 controls) [101].

Prefrontal cortex comprises of heterogeneous population of glutamatergic excitatory neurons and GABAergic inhibitory interneurons, with neocortex containing somewhat 25% of neurons as GABAergic interneurons [102]. Reduction in intra-cortical GABAergic transmission and certain imbalances in excitatory and inhibitory neuronal transmission in prefrontal cortex substantially contributes to the etiology of psychiatric disorders such as depression [103]. Clinical studies reportedly presented evidences regarding the decreased GABA levels in cortical regions [102,103]. Three major markers of electrophysiological, morphological, and molecular-level characteristics nonoverlapping the GABA interneurons, somatostatin (SST), parvalbumin (PV) are most prominent in the study of GABA inter-neuronal expression. Depressed patients witnessed significant reductions in SST interneurons in the prefrontal cortex with lower expression in other important regions implicated in depressive disorders [104]. Preclinical studies reported attenuated GABA synthetic enzymes and neuropeptide levels in chronic stress induced models in prefrontal and other cortical regions of brain [102,103]. A 7-week chronic stress exposure study in rats specifically reduced the number of GABAergic neurons orbitofrontal cortex [105]. Altered GABA levels possessing mutant animal models have been used to obtain significance about the pathology involving GABAergic neurotransmission, some reported precipitation of psychiatric-like phenotypes (depressive symptomology) with a cluster of behavioral deficits [103,106]. Evidences about individual targeting of metabotropic glutamate receptors are still lacking and requires more study, also mechanisms involving stress and GABA subtypes SST and PV interneurons are unclear.

Implication of Endogenous κ Opioid Systems

Several investigations show dysregulation of endogenous opioid system in the patients with MDD through neuroimaging, genetics, analysis of postmortem brain tissue and PET (Positron Emission Tomography) for investigating any changes in KOR binding in patients with MDD or mood disorders [107]. KOR (Kappa Opioid receptor) contains dynorphin (DYN) and its κ

opioid receptor which is involved in peripheral and centrally mediated analgesia, regulation of neuronal excitability in brain which influences basic learning, cognitive and motor functions. DYN/KOP system facilitates endocrine release and reward function. This activation reportedly decreases dopamine (DA) in the mesolimbic structural pathway. It overlaps neuronal circuits joining midbrain monoamine innervations with forebrain limbic structures promoting regulation of reward, stress and mood [108]. Evidences suggests that endogenous opioid system might alleviate depressive disorders [109,110,111]. Stimulation of KOR exhibited depressive behavioral deficits. Postmortem studies in patients with MDD also depicted major alterations in genes regulating KOR neurotransmission [112]. Preclinical studies also supported the altered KOR/DYN signaling in pathophysiology of MDD [113,114]. Maternally separated mice in early life led to alterations in genes expressing KOR neurotransmission in amygdala leaving other areas unaffected [115].

Implication of Genetic and Environmental Vulnerability in Depression

Epidemiological studies have shown that roughly 40%-50% risk of developing depression is genetic which makes it a highly heritable disorder [14]. This inheritance of mood disorder especially MDD, could get further ameliorated by severe stressful life events. This theory is often invoked as the "stress diathesis" theory of MDD. Genetics plays an important role in predisposition of MDD which can be estimated from the twin studies showing proportionated result of total variance in a trait due to genetic disrupted alterations at 37% [19]. However, there is a lack of information about the genes that underlie human vulnerability to depression, also genetic vulnerability in humas cannot be reproduced or replicated in laboratory animals. Investigations mostly rely on the combinations of environmental triggers and neurobehavioral endpoints for screening procedures on laboratory animals [20]. Depression is a highly complex disorder with the involvement of many genes. Any individual gene can relatively pronounce a small effect which could be very tough to detect and analyze through experiments. Complications may arise with the presence of variants in different genes contributing to the disease in each family [14]. Major supporting element for gene-by-environment correlation model in triggering of a major depressive episode comes from larger cohort studies involving approach of "epigenetics" [116,117]. One such classic hallmark gene in MDD (the gene encoding serotonin transporter – 5-HTT) was involved in occurrence of a new episode of depression but was only dependent on the number of stressful life events the patients had in the previous three months [19]. Incidence of functional polymorphism in the promoter region of serotonin transporter gene (5-HTT) altering transcription was reported, introducing variations such as shorter allele (SS) variation reducing the transcriptional virtue of serotonin afflicting MDD, psychiatric disorders and major depression in response to stressful life events and episodes. Polymorphism occurs as a result of a 44 deletion (SS)/insertion (LL) of base pairs in the 5' modulatory region LPR (linked polymorphic region) resulting in the divergent expression of 5-HTT binding sites in cell lines. Several findings and studies linked the expression of 5-HTT and elements of environment suggesting the emergence of depression due to combined effects of stressful events and genetic polymorphism in the gene [35].

Histone modifications- epigenetics of depression

Epigenetics bridges connectivity between the genetic and environmental factors, like in stressful conditions epigenetic alterations and certain modifications might cause alterations in genetic expressions such as editing in mRNA and non-coding RNA, gene silencing, X-

chromosome inactivation, genomic imprinting etc. [118, 119]. Histone and DNA together make up the chromatin, however histone modifications can be used as biomarker or genetic tool for assessment and prediction of genetic expressions. Various histone modifications such as histone acetylation, methylation [120], crotonylation, β-hydroxybutyrylation and phosphorylation demonstrated their significance in regulation of MDD [121,122]. Reduction in H3 acetylation with substantial increase in histone modifications to H3 lysine 9 methylation- at CaMKIIα promoter region in NAc upon chronic fluoxetine treatment in MDD patients [123]. Some studies depicted inhibition of BDNF in the hippocampal region of mice with MDD, and its overexpression along with enhanced H3 acetylation at BDNF promoter regions [122]. Furthermore, different forms of histone acetylation were observed, as reported by a study associated with chronic social defeat stress paradigm in rats. Increased acetylation of H3K9/14, H4K5,8,12,16ac in the dorsal raphe of rats were observed. These changes suggest correlation of these behavioral responses to stress and depressive disorders [124, 125].

Involvement of Neurotrophic Factors- Brain Derived Neurotrophic Factor (BDNF)

Unlike many hypotheses and theories, the neurotrophic or neuroplasticity theory of depression displays abnormal functionalities in neuronal plasticity caused by insufficiency in neurotrophic signaling, which is regarded as an influential factor promoting depression [126, 127,128]. First of the neurotrophic factors discovered was NGF (nerve growth factor) in the 1950s, [129] while BDNF (brain-derived neurotrophic factor) in the 1980s [130]. This contributed to subsequent development of other factors of neurotrophins family, NT-3 (neurotrophin-3) and NT-4 (neurotrophin-4). These factors are responsible for neuronal plasticity modulation and fulfills neuronal survival, synaptogenesis and differentiation, exhibition of these responses occurs through binding to Trk (tyrosine kinase receptor) and $p75^{NTR}$ (p75 neurotrophin receptor) [131]. BDNF is a part of structurally related family of neurotrophins (peptides), which interacts with Trk A-C and p75NTR. BDNF's expression through the Trk-B receptor is very crucial for neuroprotection and neurogenesis [132]. It is the most highly expressible factor in the limbic system among the neurotrophins family synthesized by neurons which critically regulates synaptic plasticity, survival and neuronal function in adult brain, also modulates cell migration, proliferation, maturation and their developmental survival [133]. BDNF in mammals regulates synaptic plasticity in neuronal networks and axonal growth implicated in depressive symptomatology. More specifically its promotion in dopamine uptake and neuronal survival along with their differentiation might be responsible for clinically manifesting MDD. Reduced levels of this factor have been observed in patients with depressive or mood disorders [134, 135]. Many studies have shown significant differences in BDNF methylation and peripheral blood mRNA levels in healthy groups and patients with MDD [136,137]. Lower expression of BDNF and TrkB receptor have been reported in postmortem brain samples of depressed patients. In rodent models depicting stress, hippocampal and cortex region reported reduced BDNF levels [131]. Region specific BDNF knockdown was reportedly responsible for induction of depressive behaviors and reduction in hippocampal neurogenesis due to lower BDNF protein levels [138]. Animals exposed to chronic unpredictable/mild stress procedure, displayed behavior resembling the state of depression depicting aftermath of exposure of stressors in vulnerable and resilient animals. It was shown that vulnerable animals reported lower hippocampal BDNF expression [139]. Though several studies reported implication of BDNF or other neurotrophins but inconsistent results (limitations during conduction) and lack of proper investigation at

molecular levels which are sparse, may contradict the connection between BDNF levels and severity of manifestations in depressive states involving some experimental protocols.

Involvement of Tissue-Type Plasminogen Activator (TPA) & Plasminogen Activator Inhibitor-1 (PAI-1)

tPA is a proteolytic enzyme found in blood and brain as a thrombolytic enzyme and neuronal synaptic plasticity modulator, respectively. It activates plasminogen to plasmin and tPA-plasmin pathway has a profound effect in the etiology of MDD and other psychiatric stresses [140, 141]. Brain witnesses high expression of tPA with association to processes like learning, memory, stress responses, neuronal degeneration, and addiction [142]. BDNF, an important neurotropic factor implicated in MDD is firstly synthesized as pre-pro BDNF and pro-BDNF which is transformed to mature BDNF by plasmin through plasminogen activation. Opposite biological effects and functionalities of pro-BDNF and mature-BDNF are observed through p75 and TrkB coupling [131,132,140]. This regulation is critically important in the pathogenesis of MDD. Elevated depression-like behaviors were observed in hippocampal tPA knock-down mice with one or more standard protocols along with lenti-viral tPA over-expression in the hippocampal region demonstrated anti-depressant and anxiolytic-like effect [143]. Significant improvements in depression-like behaviors were observed in post-stroke depression rat model, where PAI-1 abolished depressive behaviors via tPA /BDNF/ TrkB pathway and implication of these also depicted in Figure 5 [144]. Lacking PAI-1 can act as a predisposing factor for MDD and hence it can be a potential approach to deliver efficient novel drugs to patients [145].

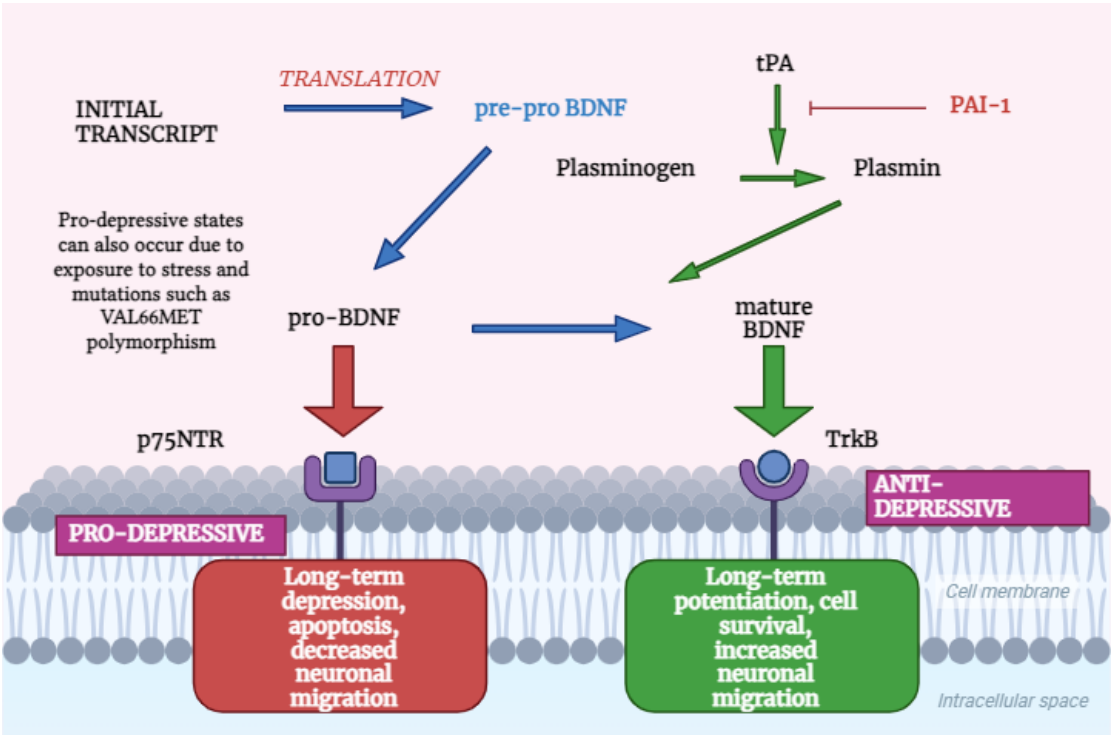

Figure 5: Implication of tPA and PAI-1 in Depression.

This figure stamps roles of tissue-type plasminogen activator (TPA) & plasminogen activator inhibitor-1 (PAI-1) in etiology of depression as possible posited links have been identified from literature.

Resolvins

Resolvins are a class of specialized pro-resolving lipid mediators found in organs and fluids. They are enzymatically produced and originate from acids like DHA (resulting in RvD1 and RvD2) and EPA (yielding RvE1, 2, and 3). Recent pre-clinical studies have revealed that both RvDs and RvEs possess antidepressant properties. Administering RvD1, RvD2, or AT-RvD1 through methods such as intracerebroventricular (ICV) injection, prefrontal cortex (PFC) infusion, or hippocampal infusion led to a reduction in depressive-like behaviors. However, this antidepressant effect was reversed when two antagonists, formyl peptide receptor 2/lipoxin A4 receptor (FPR2/ALX) and GPR18, were administered, or with inhibition of the mammalian target of rapamycin complex 1 by rapamycin. Additionally, cultured hippocampal neurons exhibited decreased dendritic and axonal length when treated with FPR2/ALX. RvD1 activated the AMPAR and PI3K pathways, while RvD2 activated the mitogen-activated protein kinase kinase (MEK)-ERK pathway. Similar results were observed with EPA-derived resolvins. In mice, LPS-induced depressive-like behaviors were mitigated after ICV injections of RvE1 and RvE2 [146]. Notably, a ChemR23 agonist (a G protein-coupled receptor) reversed depressive-like behaviors, underscoring the importance of ChemR23 agonistic activity for the antidepressant potential of RvE1 and RvE2. These studies collectively highlight the antidepressant capabilities of resolvins [147, 148, 149]. Given that administration has predominantly involved ventricular or direct brain injection, a crucial next step will be determining dosage and efficacy for more convenient delivery methods. Furthermore, the fact that resolvins are derived from DHA provides further rationale for exploring the benefits of DHA supplementation[150].

DISCUSSION & CONCLUSION

Cortisol, tPA and PAI-1, BDNF, Endogenous κ Opioid Systems, Monoamines, Resolvins, and various biomarkers in primates are identified to synchronize neurogenesis, neuronal survival, and neuronal excitability; exalted levels of cortisol and these biomarkers may be held responsible for the signs of depression by harming these vital functions of brain. Hypothalamic–pituitary–adrenal (HPA) axis is found to be roused through stress regime, with subsequent upsurge in glucocorticoids in circulation like corticosterone in case of rodents or cortisol in case of primates. It has been reflected that hypersecretion of CRH (corticotropin-releasing hormone) in hypothalamus promotes HPA system hyperactivity in patients of major depression. Chronic antidepressant treatment in rodents displayed lowering of hyperactive HPA axis. Therefore, drawing back hyperactive operating degrees of HPA (Hypothalamic–pituitary–adrenal) axis towards normal levels might be implicated as one major factor in the treatment of depression. Substantiated by prior explorations where chronic unpredictable stress regime damaged oxidant and anti-oxidant balance (intensified and exalted lipid peroxidation and plasma nitrite levels along with abridged catalase activity and reduced glutathione levels) in tissues of brain, apparently via occurrence of disproportionate reactive oxygen species. Triggering of inflammatory response, escalated monoamine breakdown, and anomalies in lipids may lead to exalted production of lipid peroxidation, reactive oxygen species, and abridged antioxidant enzyme actions might be correlated to distorted physiology in depression. Search for novel strategies for MDD has been a constant breakthrough for decades. However, monoamine pathways and its targeting medications will sustain as a cornerstone of depressive pharmacotherapy but to overcome some consistent problems against the disorder such as antidepressant resistance and to make further progresses for a more personalized approach in

patient therapy is significantly required. Perpetual exploration for more biomarkers to target through scavenging new targets is pivotal for future medication development, as MDD displays heterogeneity in several aspects. The forementioned pathways could provide efficaciously rapid and symptomatic relief in the disease, creating a plethora of treatments. More efforts are crucial for development of these treatments along with long-term trials supporting the persistence and origin of the disorder. Thus, further rigorous preclinical and clinical explorations are still required to evolve new insights and treatment regimens to authenticate these non-explored potential pathophysiology targets of Major Depression.

ABBREVIATIONS

MDD - Major Depressive disorder
WHO – World Health Organization
CNS – Central Nervous System
NA/NE – Noradrenaline/Norepinephrine
5-HT – 5-hydroxytryptamine
DA – Dopamine
FC- Frontal cortex
PFC – Pre-frontal cortex
VTA – Ventral tegmental area
NAc – Nucleus accumbens
LC – Locus coeruleus
Hyp – Hypothalamus
DR- Dorsal raphe
HPA – Hypothalamus-pituitary-adrenal axis
CRF – corticotropin-releasing factor
ACTH – adrenocorticotropin
Amy- amygdala
BNST – Bed nucleus of stria terminalis
GABA – Gamma-aminobutyric acid
GIT – Gastro-intestinal tract
GAL – Galanin
FST – Forced swim test
TST – Tail suspension test
NPY – Neuropeptide- Y
ECS – Endocannabinoid signalling
CNR2 – Cannabinoid receptor 2 gene
GABA – Gamma amino-butyric acid
KOR – Kappa opioid receptors
BDNF – Brain-derived neurotropic factor
Trk B – Tyrosine receptor kinase B
SST – somatostatin
PV – parvalbumin
$p75^{NTR}$ - p75 neurotrophin receptor
TPA – tissue plasminogen activator
CSF – Cerebral spinal fluid

REFERENCES

1. Beurel E, Toups M, Nemeroff CB (2020) The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron 107(2):234-256. doi: 10.1016/j.neuron.2020.06.002
2. WHO Factsheet 2023. https://www.who.int/news-room/fact-sheets/detail/depression. Accessed on September 11, 2023.
3. Arvind BA, Gururaj G, Loganathan S, et al (2019) Prevalence and socioeconomic impact of depressive disorders in India: multisite population-based cross-sectional study. BMJ Open 9(6): e027250. doi:10.1136/bmjopen-2018-027250
4. Ménard C, Hodes GE, Russo SJ (2016) Pathogenesis of depression: Insights from human and rodent studies. Neuroscience 321:138-162. doi: 10.1016/j.neuroscience.2015.05.053
5. Sharma A, Kapoor G, Kumar S, Bhutani R, Sharma D, Chettri S. (2022) Evaluation of medication/drug use rationale and impediments due to influencing perception of self-medication. Journal of Pharmaceutical Negative Results 2022:2329-2336. doi:10.47750/pnr.2022.13. S07.318
6. Avula SK, Khan A, Halim SA, et al (2022) Synthesis and antidepressant-like effects of new 5-epi-incensole and 5-epi- incensole acetate in chronic unpredictable mild stress model of depression; behavioural and biochemical correlates. Biomed Pharmacother. 156: 113960. doi: 10.1016/j.biopha.2022.113960
7. Dobrek L, Głowacka K (2023) Depression and Its Phytopharmacotherapy-A Narrative Review. Int J Mol Sci 24(5):4772. doi:10.3390/ijms24054772
8. Kerzare D, Menghani S, Khedekar PB (2018) Synthesis, characterization, antidepressant activity and docking studies of some novel indole bearing azetidinone derivatives. Indian Journal of Pharmaceutical Education and Research 52(1):110-121. doi:10.5530/ijper.52.1.13
9. Matraszek-Gawron R, Chwil M, Terlecka P, Skoczylas MM (2019) Recent Studies on Anti-Depressant Bioactive Substances in Selected Species from the Genera Hemerocallis and Gladiolus: A Systematic Review. Pharmaceuticals (Basel) 12(4):172. doi:10.3390/ph12040172
10. Ogbo FA, Mathsyaraja S, Koti RK, Perz J, Page A (2018) The burden of depressive disorders in South Asia, 1990-2016: findings from the global burden of disease study. BMC Psychiatry 18(1):333. doi:10.1186/s12888-018-1918-1
11. Sagar R, Selvakumar N (2021) Prevalence of Depression in Indian Adolescents. Indian J Pediatr 88(5):427-428. doi:10.1007/s12098-021-03750-4

12. Ausderau KK, Colman RJ, Kabakov S, Schultz-Darken N, Emborg ME (2023) Evaluating depression- and anxiety-like behaviors in non-human primates. Front Behav Neurosci 16: 1006065. doi:10.3389/fnbeh.2022.1006065
13. Parhiala P, Marttunen M, Gergov V, Torppa M, Ranta K (2022) Predictors of outcome after a time-limited psychosocial intervention for adolescent depression. Front Psychol 13: 955261. doi:10.3389/fpsyg.2022.955261
14. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002) Neurobiology of depression. Neuron 34(1):13-25. doi:10.1016/s0896-6273(02)00653-0
15. Petković A, Chaudhury D (2022) Encore: Behavioural animal models of stress, depression and mood disorders. Front Behav Neurosci 16: 931964. doi:10.3389/fnbeh.2022.931964
16. Filatova EV, Shadrina MI, Slominsky PA (2021) Major Depression: One Brain, One Disease, One Set of Intertwined Processes. Cells 10(6):1283. doi:10.3390/cells10061283
17. Hurley LL, Tizabi Y (2013) Neuroinflammation, neurodegeneration, and depression. Neurotox Res 23(2):131-144. doi:10.1007/s12640-012-9348-1
18. Irum N, Afzal T, Faraz MH, Aslam Z, Rasheed F (2023) The role of gut microbiota in depression: an analysis of the gut-brain axis. Front Behav Neurosci 17: 1185522. doi:10.3389/fnbeh.2023.1185522
19. Chiriţă AL, Gheorman V, Bondari D, Rogoveanu I (2015) Current understanding of the neurobiology of major depressive disorder. Rom J Morphol Embryol 56(2):651-658.
20. Berton O, Nestler EJ (2006) New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 7(2):137-151. doi:10.1038/nrn1846
21. Lima-Ojeda JM, Rupprecht R, Baghai TC (2018) Neurobiology of depression: A neurodevelopmental approach. World J Biol Psychiatry 19(5):349-359. doi:10.1080/15622975.2017.1289240
22. Bashford-Largo J, R Blair RJ, Blair KS, et al (2023) Identification of structural brain alterations in adolescents with depressive symptomatology. Brain Res Bull 201:110723. doi: 10.1016/j.brainresbull.2023.110723
23. Won E, Ham BJ (2016) Imaging genetics studies on monoaminergic genes in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 64:311-319. doi: 10.1016/j.pnpbp.2015.03.014
24. Fakhoury M (2015) New insights into the neurobiological mechanisms of major depressive disorders. Gen Hosp Psychiatry 37(2):172-177. doi: 10.1016/j.genhosppsych.2015.01.005
25. Bao AM, Swaab DF (2018) The human hypothalamus in mood disorders: The HPA axis in the center. IBRO Rep 6:45-53. doi: 10.1016/j.ibror.2018.11.008

26. Dean J, Keshavan M (2017) The neurobiology of depression: An integrated view. Asian J Psychiatr 27:101-111.
doi: 10.1016/j.ajp.2017.01.025
27. Gerritsen L, Milaneschi Y, Vinkers CH, et al (2017) HPA Axis Genes, and Their Interaction with Childhood Maltreatment, are Related to Cortisol Levels and Stress-Related Phenotypes. Neuropsychopharmacology 42(12):2446-2455. doi:10.1038/npp.2017.118
28. Mikulska J, Juszczyk G, Gawrońska-Grzywacz M, Herbet M (2021) HPA Axis in the Pathomechanism of Depression and Schizophrenia: New Therapeutic Strategies Based on Its Participation. Brain Sci 11(10):1298.
doi:10.3390/brainsci11101298
29. Menke A (2019). Is the HPA Axis as Target for Depression Outdated, or Is There a New Hope? Frontiers in psychiatry 10: 101.
doi:10.3389/fpsyt.2019.00101
30. Keller J, Gomez R, Williams G, et al (2017) HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry 22(4):527-536.
doi:10.1038/mp.2016.120
31. Delgado PL (2000) Depression: the case for a monoamine deficiency. J Clin Psychiatry 61(6):7-11.
32. Sharma A, Dhingra D, Dutt R (2020) Syringic acid reversed depression-resembling behaviour induced by chronic unpredictable mild stress paradigm in mice. International Journal of Pharmaceutical Sciences and Drug Research 13(06):651-660. doi:10.25004/ijpsdr.2021.130608
33. Cowen PJ, Browning M (2015) What has serotonin to do with depression? World Psychiatry 14(2):158-160.
doi:10.1002/wps.20229
34. Rihmer Z, Dome P, Katona C (2022) Serotonin and depression - a riposte to Moncrieff et al. (2022). Neuropsychopharmacol Hung 24(3):120-125.
35. Daniele A, Divella R, Paradiso A, et al (2011) Serotonin transporter polymorphism in major depressive disorder (MDD), psychiatric disorders, and in MDD in response to stressful life events: causes and treatment with antidepressant. In Vivo 25(6):895-901.
36. Marathe SV, D'almeida PL, Virmani G, Bathini P, Alberi L (2018) Effects of Monoamines and Antidepressants on Astrocyte Physiology: Implications for Monoamine Hypothesis of Depression. *J Exp Neurosci* 12:1179069518789149.
doi:10.1177/1179069518789149
37. Delgado PL, Moreno FA (2000) Role of norepinephrine in depression. J Clin Psychiatry 61(1):5-12.
38. Grace AA (2016) Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat Rev Neurosci 17(8):524-532. doi:10.1038/nrn.2016.57
39. Delva NC, Stanwood GD (2021) Dysregulation of brain dopamine systems in major depressive disorder. Exp Biol Med (Maywood) 246(9):1084-1093.
doi:10.1177/1535370221991830

40. Belujon P, Grace AA (2017) Dopamine System Dysregulation in Major Depressive Disorders. Int J Neuropsychopharmacol 20(12):1036-1046. doi:10.1093/ijnp/pyx056
41. Wachowska K, Gałecki P (2021) Inflammation and Cognition in Depression: A Narrative Review. J Clin Med 10(24):5859. doi:10.3390/jcm10245859
42. Catena-Dell'Osso M, Rotella F, Dell'Osso A, Fagiolini A, Marazziti D (2013) Inflammation, serotonin and major depression. Curr Drug Targets 14(5):571-577. doi:10.2174/1389450111 3149990154
43. Lee CH, Giuliani F (2019) The Role of Inflammation in Depression and Fatigue. Front Immunol 10:1696. Published 2019 Jul 19. doi:10.3389/fimmu.2019.01696
44. Dantzer R (2004) Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur J Pharmacol 500(1-3):399-411. doi: 10.1016/j.ejphar.2004.07.040
45. Shadrina M, Bondarenko EA, Slominsky PA (2018) Genetics Factors in Major Depression Disease. Front Psychiatry 9:334. doi:10.3389/fpsyt.2018.00334
46. Pitsillou E, Bresnehan SM, Kagarakis EA, et al (2020) The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. Mol Biol Rep 47(1):753-770. doi:10.1007/s11033-019-05129-3
47. Landgraf D, McCarthy MJ, Welsh DK (2014) The role of the circadian clock in animal models of mood disorders. Behav Neurosci 128(3):344-359. doi:10.1037/a0036029
48. Sato S, Sassone-Corsi P (2021) Linking Depression to Epigenetics: Role of the Circadian Clock. Adv Exp Med Biol 1344:43-53. doi:10.1007/978-3-030-81147-1_3
49. Claudio A, Fagiolini A (2022) Circadian neuromarkers of mood disorders. Journal of Affective Disorders Reports 10:100384. doi: 10.1016/j.jadr.2022.100384
50. Konstantakopoulos G, Dimitrakopoulos S, Michalopoulou PG (2020) The preclinical discovery and development of agomelatine for the treatment of depression. Expert Opin Drug Discov 15(10):1121-1132. doi:10.1080/17460441.2020.1781087
51. Spadoni G, Bedini A, Rivara S, Mor M (2011) Melatonin receptor agonists: new options for insomnia and depression treatment. CNS Neurosci Ther 17(6):733-741. doi:10.1111/j.1755-5949.2010. 00197.x
52. Bhatt S, Kanoujia J, Mohana Lakshmi S, et al (2023) Role of Brain-Gut-Microbiota Axis in Depression: Emerging Therapeutic Avenues. CNS Neurol Disord Drug Targets 22(2):276-288. doi:10.2174/1871527321666220329140804
53. Vadnie CA, McClung CA (2017) Circadian Rhythm Disturbances in Mood Disorders: Insights into the Role of the Suprachiasmatic Nucleus. Neural Plast 2017:1504507.

doi:10.1155/2017/1504507

54. Mendoza J, Vanotti G (2019) Circadian neurogenetics of mood disorders. Cell Tissue Res 377(1):81-94.
doi:10.1007/s00441-019-03033-7
55. Moon E, Partonen T, Beaulieu S, Linnaranta O (2022) Melatonergic agents influence the sleep-wake and circadian rhythms in healthy and psychiatric participants: a systematic review and meta-analysis of randomized controlled trials. Neuropsychopharmacology 47(8):1523-1536.
doi:10.1038/s41386-022-01278-5
56. Boiko DI, Shkodina AD, Hasan MM, et al (2022) Melatonergic Receptors (Mt1/Mt2) as a Potential Additional Target of Novel Drugs for Depression. Neurochem Res 47(10):2909-2924.
doi:10.1007/s11064-022-03646-5
57. Łoniewski I, Misera A, Skonieczna-Żydecka K, et al (2021) Major Depressive Disorder and gut microbiota - Association not causation. A scoping review. Prog Neuropsychopharmacol Biol Psychiatry 106:110111.
doi: 10.1016/j.pnpbp.2020.110111
58. Knudsen JK, Bundgaard-Nielsen C, Hjerrild S, Nielsen RE, Leutscher P, Sørensen S (2021) Gut microbiota variations in patients diagnosed with major depressive disorder-A systematic review. Brain Behav 11(7):e02177.
doi:10.1002/brb3.2177
59. Chang L, Wei Y, Hashimoto K (2022) Brain-gut-microbiota axis in depression: A historical overview and future directions. Brain Res Bull 182: 44-56.
doi: 10.1016/j.brainresbull.2022.02.004
60. Jiang H, Ling Z, Zhang Y, et al (2015) Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 48:186-194.
doi: 10.1016/j.bbi.2015.03.016
61. Mayer EA, Nance K, Chen S (2022) The Gut-Brain Axis. Annu Rev Med 73: 439-453.
doi:10.1146/annurev-med-042320-014032
62. Wu M, Tian T, Mao Q, et al (2020) Associations between disordered gut microbiota and changes of neurotransmitters and short-chain fatty acids in depressed mice. Transl Psychiatry 10(1):350.
doi:10.1038/s41398-020-01038-3
63. Jianguo L, Xueyang J, Cui W, Changxin W, Xuemei Q (2019) Correction: Altered gut metabolome contributes to depression-like behaviors in rats exposed to chronic unpredictable mild stress. Transl Psychiatry 9(1):275.
doi:10.1038/s41398-019-0645-9
64. Caramia M, Romanov RA, Sideromenos S, et al (2023) Neuronal diversity of neuropeptide signaling, including galanin, in the mouse locus coeruleus. Proc Natl Acad Sci U S A 120(31): e2222095120.
doi:10.1073/pnas.2222095120
65. Tillage RP, Sciolino NR, Plummer NW, et al (2020) Elimination of galanin synthesis in noradrenergic neurons reduces galanin in select brain areas and promotes active coping behaviors. Brain Struct Funct 225(2):785-803.

doi:10.1007/s00429-020-02035-4

66. Tillage RP, Foster SL, Lustberg D, Liles LC, McCann KE, Weinshenker D (2021) Co-released norepinephrine and galanin act on different timescales to promote stress-induced anxiety-like behavior. Neuropsychopharmacology 46(8):1535-1543. doi:10.1038/s41386-021-01011-8
67. Flores-Burgess A, Millón C, Gago B, et al (2022) Galanin (1-15) Enhances the Behavioral Effects of Fluoxetine in the Olfactory Bulbectomy Rat, Suggesting a New Augmentation Strategy in Depression. Int J Neuropsychopharmacol 25(4):307-318. doi:10.1093/ijnp/pyab089
68. Narváez M, Borroto-Escuela DO, Millón C, et al (2016) Galanin receptor 2-neuropeptide Y Y1 receptor interactions in the dentate gyrus are related with antidepressant-like effects. Brain Struct Funct 221(8):4129-4139. doi:10.1007/s00429-015-1153-1
69. Domin H (2021) Neuropeptide Y Y2 and Y5 receptors as potential targets for neuroprotective and antidepressant therapies: Evidence from preclinical studies. Prog Neuropsychopharmacol Biol Psychiatry 111:110349. doi: 10.1016/j.pnpbp.2021.110349
70. Shende P, Desai D (2020) Physiological and Therapeutic Roles of Neuropeptide Y on Biological Functions. Adv Exp Med Biol 1237:37-47. doi:10.1007/5584_2019_427
71. Gupta S, Gautam M, Prasoon P, Kumar R, Ray SB, Kaler Jhajhria S (2018) Involvement of Neuropeptide Y in Post-Incisional Nociception in Rats. Ann Neurosci 25(4):268-276. doi:10.1159/000495130
72. Gołyszny M, Obuchowicz E (2019) Are neuropeptides relevant for the mechanism of action of SSRIs? Neuropeptides 75:1-17. doi: 10.1016/j.npep.2019.02.002
73. Martins J, Elvas F, Brudzewsky D, et al (2015) Activation of Neuropeptide Y Receptors Modulates Retinal Ganglion Cell Physiology and Exerts Neuroprotective Actions In Vitro. ASN Neuro 7(4). doi:1177/1759091415598292
74. Hillard CJ, Liu QS (2014) Endocannabinoid signaling in the etiology and treatment of major depressive illness. Curr Pharm Des 20(23):3795-3811. doi:10.2174/13816128113196660735
75. Huang WJ, Chen WW, Zhang X (2016) Endocannabinoid system: Role in depression, reward and pain control (Review). Mol Med Rep 14(4):2899-2903. doi:10.3892/mmr.2016.5585
76. Bright U, Akirav I (2022) Modulation of Endocannabinoid System Components in Depression: Pre-Clinical and Clinical Evidence. Int J Mol Sci 23(10):5526. doi:10.3390/ijms23105526
77. Hasbi A, Madras BK, George SR (2023) Endocannabinoid System and Exogenous Cannabinoids in Depression and Anxiety: A Review. Brain Sci 13(2):325. doi:10.3390/brainsci13020325
78. Sarris J, Sinclair J, Karamacoska D, Davidson M, Firth J (2020) Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry 20(1):24.

doi:10.1186/s12888-019-2409-8

79. Gallego-Landin I, García-Baos A, Castro-Zavala A, Valverde O (2021) Reviewing the Role of the Endocannabinoid System in the Pathophysiology of Depression. Front Pharmacol 12:762738.
doi:10.3389/fphar.2021.762738
80. Morena M, Patel S, Bains JS, Hill MN (2016) Neurobiological Interactions Between Stress and the Endocannabinoid System. Neuropsychopharmacology 41(1):80-102. doi:10.1038/npp.2015.166
81. Lu HC, Mackie K (2021) Review of the Endocannabinoid System. Biol Psychiatry Cogn Neurosci Neuroimaging 6(6):607-615.
doi: 10.1016/j.bpsc.2020.07.016
82. Hu SS, Mackie K (2015) Distribution of the Endocannabinoid System in the Central Nervous System. Handb Exp Pharmacol 231: 59-93.
doi:10.1007/978-3-319-20825-1_3
83. Shen CJ, Zheng D, Li KX, et al (2019) Cannabinoid CB_1 receptors in the amygdalar cholecystokinin glutamatergic afferents to nucleus accumbens modulate depressive-like behavior. Nat Med 25(2):337-349.
doi:10.1038/s41591-018-0299-9
84. Valverde O, Torrens M (2012) CB1 receptor-deficient mice as a model for depression. Neuroscience 204:193-206.
doi: 10.1016/j.neuroscience.2011.09.031
85. Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F (2013) Endocannabinoid system and mood disorders: priming a target for new therapies. Pharmacol Ther 138(1):18-37.
doi: 10.1016/j.pharmthera.2012.12.002
86. Quraishi SA, Paladini CA (2016) A Central Move for CB2 Receptors. Neuron 90(4):670-671.
doi: 10.1016/j.neuron.2016.05.012
87. Ishiguro H, Horiuchi Y, Tabata K, Liu QR, Arinami T, Onaivi ES (2018) Cannabinoid CB2 Receptor Gene and Environmental Interaction in the Development of Psychiatric Disorders. Molecules 23(8):1836.
doi:10.3390/molecules23081836
88. Ishiguro H, Iwasaki S, Teasenfitz L, et al (2007) Involvement of cannabinoid CB2 receptor in alcohol preference in mice and alcoholism in humans. Pharmacogenomics J 7(6):380-385.
doi: 10.1038/sj.tpj.6500431
89. Ortega-Alvaro A, Aracil-Fernández A, García-Gutiérrez MS, Navarrete F, Manzanares J (2011) Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors in mice. Neuropsychopharmacology 36(7):1489-1504.
doi:10.1038/npp.2011.34
90. Barna I, Zelena D, Arszovszki AC, Ledent C (2004) The role of endogenous cannabinoids in the hypothalamo-pituitary-adrenal axis regulation: in vivo and in vitro studies in CB1 receptor knockout mice. Life Sci 75(24):2959-2970.
doi: 10.1016/j.lfs.2004.06.006

91. Duman RS, Sanacora G, Krystal JH (2019) Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. Neuron 102(1):75-90.
doi: 10.1016/j.neuron.2019.03.013
92. Luscher B, Maguire JL, Rudolph U, Sibille E (2023) $GABA_A$ receptors as targets for treating affective and cognitive symptoms of depression. Trends Pharmacol Sci 44(9):586-600.
doi: 10.1016/j.tips.2023.06.009
93. Khoodoruth MAS, Estudillo-Guerra MA, Pacheco-Barrios K, Nyundo A, Chapa-Koloffon G, Ouanes S (2022) Glutamatergic System in Depression and Its Role in Neuromodulatory Techniques Optimization. Front Psychiatry 13:886918. doi:10.3389/fpsyt.2022.886918
94. Duman RS, Aghajanian GK, Sanacora G, Krystal JH (2016) Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 22(3):238-249.
doi:10.1038/nm.4050
95. Musazzi L, Racagni G, Popoli M (2011) Stress, glucocorticoids and glutamate release: effects of antidepressant drugs. Neurochem Int 59(2):138-149.
doi: 10.1016/j.neuint.2011.05.002
96. Moriguchi S, Takamiya A, Noda Y, et al (2019) Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. Mol Psychiatry 24(7):952-964.
doi:10.1038/s41380-018-0252-9
97. Lener MS, Niciu MJ, Ballard ED, et al (2017) Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine. Biol Psychiatry 81(10):886-897.
doi: 10.1016/j.biopsych.2016.05.005
98. Kositsyn YM, de Abreu MS, Kolesnikova TO, et al (2023) Towards Novel Potential Molecular Targets for Antidepressant and Antipsychotic Pharmacotherapies. Int J Mol Sci 24(11):9482.
doi:10.3390/ijms24119482
99. McOmish CE, Pavey G, Gibbons A, et al (2016) Lower [3H]LY341495 binding to mGlu2/3 receptors in the anterior cingulate of subjects with major depressive disorder but not bipolar disorder or schizophrenia. J Affect Disord 190: 241-248.
doi: 10.1016/j.jad.2015.10.004
100. Matosin N, Fernandez-Enright F, Frank E, et al (2014) Metabotropic glutamate receptor mGluR2/3 and mGluR5 binding in the anterior cingulate cortex in psychotic and nonpsychotic depression, bipolar disorder and schizophrenia: implications for novel mGluR-based therapeutics. J Psychiatry Neurosci 39(6):407-416. doi:10.1503/jpn.130242
101. Lee PH, Perlis RH, Jung JY, et al (2012) Multi-locus genome-wide association analysis supports the role of glutamatergic synaptic transmission in the etiology of major depressive disorder. Transl Psychiatry 2(11): e184.

doi:10.1038/tp.2012.95

102. Ghosal S, Hare B, Duman RS (2017) Prefrontal Cortex GABAergic Deficits and Circuit Dysfunction in the Pathophysiology and Treatment of Chronic Stress and Depression. Curr Opin Behav Sci 14:1-8.
doi: 10.1016/j.cobeha.2016.09.012
103. Luscher B, Fuchs T (2015) GABAergic control of depression-related brain states. Adv Pharmacol 73:97-144.
doi: 10.1016/bs.apha.2014.11.003
104. Douillard-Guilloux G, Lewis D, Seney ML, Sibille E (2017) Decrease in somatostatin-positive cell density in the amygdala of females with major depression. Depress Anxiety 34(1):68-78.
doi:10.1002/da.22549
105. Varga Z, Csabai D, Miseta A, Wiborg O, Czéh B (2017) Chronic stress affects the number of GABAergic neurons in the orbitofrontal cortex of rats. Behav Brain Res 316: 104-114.
doi: 10.1016/j.bbr.2016.08.030
106. Kolata S, Nakao K, Jeevakumar V, et al (2017) Neuropsychiatric phenotypes produced by GABA reduction in mouse cortex and hippocampus. Neuropsychopharmacology 43(6):1445-1456.
doi:10.1038/npp.2017.296
107. Jacobson ML, Browne CA, Lucki I (2020) Kappa Opioid Receptor Antagonists as Potential Therapeutics for Stress-Related Disorders. Annu Rev Pharmacol Toxicol 60: 615-636.
doi:10.1146/annurev-pharmtox-010919-023317
108. Taylor GT, Manzella F (2016) Kappa Opioids, Salvinorin A and Major Depressive Disorder. Curr Neuropharmacol 14(2):165-176. doi:10.2174/1570159x13666150727220944
109. Bailey SJ, Husbands SM (2018) Targeting opioid receptor signaling in depression: do we need selective κ opioid receptor antagonists?. Neuronal Signal 2(2):NS20170145. doi:10.1042/NS20170145
110. Adzic M, Lukic I, Mitic M, Glavonic E, Dragicevic N, Ivkovic S (2023) Contribution of the opioid system to depression and to the therapeutic effects of classical antidepressants and ketamine. Life Sci 326:121803.
doi: 10.1016/j.lfs.2023.121803
111. Jelen LA, Stone JM, Young AH, Mehta MA (2022) The opioid system in depression. Neurosci Biobehav Rev 140:104800.
doi: 10.1016/j.neubiorev.2022.104800
112. Browne CA, Jacobson ML, Lucki I (2020) Novel Targets to Treat Depression: Opioid-Based Therapeutics. Harv Rev Psychiatry 28(1):40-59. doi:10.1097/HRP.0000000000000242
113. Browne CA, Wulf H, Lucki I (2021). Kappa Opioid Receptors in the Pathology and Treatment of Major Depressive Disorder. In: Liu-Chen LY, Inan S (eds) The Kappa Opioid Receptor. Handbook of Experimental Pharmacology, vol 271. Springer, Cham.

114. Browne CA, Lucki I (2019) Targeting opioid dysregulation in depression for the development of novel therapeutics. Pharmacol Ther 201:51-76. doi: 10.1016/j.pharmthera.2019.04.009
115. Nakamoto K, Taniguchi A, Tokuyama S (2020) Changes in opioid receptors, opioid peptides and morphine antinociception in mice subjected to early life stress. Eur J Pharmacol 881:173173. doi: 10.1016/j.ejphar.2020.173173
116. Penner-Goeke S, Binder EB. Epigenetics and depression (2019) Dialogues Clin Neurosci. 21(4):397-405. doi:10.31887/DCNS.2019.21.4/ebinder
117. Klengel T, Binder EB (2015) Epigenetics of Stress-Related Psychiatric Disorders and Gene × Environment Interactions. Neuron. 2015;86(6):1343-1357. doi: 10.1016/j.neuron.2015.05.036
118. Portela A, Esteller M. Epigenetic modifications and human disease (2010) Nat Biotechnol 28(10):1057-1068. doi:10.1038/nbt.1685
119. Bagot RC, Labonté B, Peña CJ, Nestler EJ (2014) Epigenetic signaling in psychiatric disorders: stress and depression. Dialogues Clin Neurosci 16(3):281-295. doi:10.31887/DCNS.2014.16.3/rbagot
120. Pishva E, Rutten BPF, van den Hove D (2017) DNA Methylation in Major Depressive Disorder. Adv Exp Med Biol 978:185-196. doi:10.1007/978-3-319-53889-1_10
121. Fuchikami M, Yamamoto S, Morinobu S, Okada S, Yamawaki Y, Yamawaki S (2016) The potential use of histone deacetylase inhibitors in the treatment of depression. Prog Neuropsychopharmacol Biol Psychiatry 64:320-324. doi: 10.1016/j.pnpbp.2015.03.010
122. Wu MS, Li XJ, Liu CY, et al (2022) Effects of Histone Modification in Major Depressive Disorder. Curr Neuropharmacol 20(7):1261-1277. doi:10.2174/1570159X19666210922150043
123. Robison AJ, Vialou V, Sun HS, et al (2014) Fluoxetine epigenetically alters the CaMKIIα promoter in nucleus accumbens to regulate ΔFosB binding and antidepressant effects. Neuropsychopharmacology 39(5):1178-1186. doi:10.1038/npp.2013.319
124. Kenworthy CA, Sengupta A, Luz SM, et al (2014) social defeat induces changes in histone acetylation and expression of histone modifying enzymes in the ventral hippocampus, prefrontal cortex, and dorsal raphe nucleus. Neuroscience 264:88-98. doi: 10.1016/j.neuroscience.2013.01.024
125. Deussing JM, Jakovcevski M (2017) Histone Modifications in Major Depressive Disorder and Related Rodent Models. Adv Exp Med Biol 978:169-183. doi:10.1007/978-3-319-53889-1_9
126. Liu W, Ge T, Leng Y, et al (2017) The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex. Neural Plast 2017:6871089. doi:10.1155/2017/6871089

127. Cavaleri D, Moretti F, Bartoccetti A, et al (2023) The role of BDNF in major depressive disorder, related clinical features, and antidepressant treatment: Insight from meta-analyses. Neurosci Biobehav Rev 149:105159. doi: 10.1016/j.neubiorev.2023.105159
128. Kishi T, Yoshimura R, Ikuta T, Iwata N (2018) Brain-Derived Neurotrophic Factor and Major Depressive Disorder: Evidence from Meta-Analyses. Front Psychiatry 8:308. doi:10.3389/fpsyt.2017.00308
129. Cohen S, Levi-Montalcini R, Hamburger V (1954) A nerve growth-stimulating factor isolated from sarcom as 37 and 180. Proc Natl Acad Sci U S A 40(10):1014-1018. doi:10.1073/pnas.40.10.1014
130. Barde YA, Edgar D, Thoenen H (1982) Purification of a new neurotrophic factor from mammalian brain. EMBO J 1(5):549-553. doi:10.1002/j.1460-2075. 1982.tb01207.x
131. Yang T, Nie Z, Shu H, et al (2020) The Role of BDNF on Neural Plasticity in Depression. Front Cell Neurosci 14:82. doi:10.3389/fncel.2020.00082
132. Arosio B, Guerini FR, Voshaar RCO, Aprahamian I (2021) Blood Brain-Derived Neurotrophic Factor (BDNF) and Major Depression: Do We Have a Translational Perspective? Front Behav Neurosci 15:626906. doi:10.3389/fnbeh.2021.626906
133. Castrén E, Kojima M (2017) Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. Neurobiol Dis 97(Pt B):119-126. doi: 10.1016/j.nbd.2016.07.010
134. da Silva SK, Wiener C, Ghisleni G, et al (2018) Effects of cognitive-behavioral therapy on neurotrophic factors in patients with major depressive disorder. Braz J Psychiatry 40(4):361-366. doi:10.1590/1516-4446-2017-2357
135. Porter GA, O'Connor JC (2022) Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime?. World J Psychiatry 12(1):77-97. doi:10.5498/wjp.v12.i1.77
136. Hsieh MT, Lin CC, Lee CT, Huang TL (2019) Abnormal Brain-Derived Neurotrophic Factor Exon IX Promoter Methylation, Protein, and mRNA Levels in Patients with Major Depressive Disorder. J Clin Med 8(5):568. doi:10.3390/jcm8050568
137. Schröter K, Brum M, Brunkhorst-Kanaan N, et al (2020) Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci 270(2):169-181. doi:10.1007/s00406-019-01007-y
138. Taliaz D, Stall N, Dar DE, Zangen A (2010) Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Mol Psychiatry 15(1):80-92. doi:10.1038/mp.2009.67
139. Tornese P, Sala N, Bonini D, et al (2019) Chronic mild stress induces anhedonic behavior and changes in glutamate release, BDNF trafficking and dendrite morphology

only in stress vulnerable rats. The rapid restorative action of ketamine. Neurobiology of Stress 10:100160.
doi: 10.1016/j.ynstr.2019.100160

140. Tsai SJ (2007) The P11, tPA/plasminogen system and brain-derived neurotrophic factor: Implications for the pathogenesis of major depression and the therapeutic mechanism of antidepressants. Med Hypotheses 68(1):180-183.
doi: 10.1016/j.mehy.2006.06.005
141. Luo T, Tian H, Song H, et al (2020) Possible Involvement of Tissue Plasminogen Activator/Brain-Derived Neurotrophic Factor Pathway in Anti-Depressant Effects of Electroacupuncture in Chronic Unpredictable Mild Stress-Induced Depression in Rats. Front Psychiatry 11:63.
doi:10.3389/fpsyt.2020.00063
142. Melchor JP, Strickland S (2005) Tissue plasminogen activator in central nervous system physiology and pathology. Thromb Haemost 93(4):655-660.
doi:10.1160/TH04-12-0838
143. Bahi A, Dreyer JL (2012) Hippocampus-specific deletion of tissue plasminogen activator "tPA" in adult mice impairs depression- and anxiety-like behaviours. European Neuropsychopharmacology 22(9):672-682.
doi: 10.1016/j.euroneuro.2012.01.008
144. Dong H, Qin YQ, Sun YC, et al (2021) Electroacupuncture Ameliorates Depressive-Like Behaviours in Poststroke Rats via Activating the tPA/BDNF/TrkB Pathway. Neuropsychiatr Dis Treat 17:1057-1067.
doi:10.2147/NDT.S298540
145. Party H, Dujarrier C, Hébert M, et al (2019) Plasminogen Activator Inhibitor-1 (PAI-1) deficiency predisposes to depression and resistance to treatments. Acta Neuropathol Commun 7(1):153. doi:10.1186/s40478-019-0807-2
146. Elias E, Zhang AY, Manners MT. Novel Pharmacological Approaches to the Treatment of Depression. Life (Basel). 2022 Jan 28;12(2):196.
doi: 10.3390/life12020196.
147. Deyama S, Minami M, Kaneda K (2021) Resolvins as potential candidates for the treatment of major depressive disorder. J Pharmacol Sci 147(1):33-39.
doi: 10.1016/j.jphs.2021.05.002
148. Deyama S (2020) Nihon Yakurigaku Zasshi 155(6):381-385.
doi:10.1254/fpj.20044
149. Deyama S, Kaneda K, Minami M (2022) Resolution of depression: antidepressant actions of resolvins [published online ahead of print, 2022 Oct 19]. Neurosci Res S0168-0102(22)00266-8.
doi: 10.1016/j.neures.2022.10.006
150. Ishikawa Y, Deyama S, Shimoda K, et al (2017) Rapid and sustained antidepressant effects of resolvin D1 and D2 in a chronic unpredictable stress model. Behav Brain Res 332:233-236.
doi: 10.1016/j.bbr.2017.06.010