

# Diagnosis, Mechanism, and Current Treatment of Depression: Current Situation and Future Directions

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**Abstract**—Depression has become one of the most concerning disease in the world and is projected to be the most serve global burden of disease by 2030. Its high morbidity, high relapse and high mortality features have caused millions of deaths and exerted impact on societies all over the world. Although researchers have been trying to address this problem for decades, there are still no proper solutions. This review concludes two major diagnostic systems, current progress of depression's mechanisms, and available treatments on the market. Moreover, it specifically adds animal models and corresponding behavioral tests, and evaluates their pros and cons, aiming to help future researchers better conduct their experiments.

**Index Terms**—depression, mechanism, treatment

## I. INTRODUCTION

Due to the global pandemic and social distancing, there are more and more depression patients. According to an epidemic research, there are 4.7% of people all over the world are suffering from depression which means depression has damaged hundreds of millions of people's health [1]. Besides, depressive patients demonstrated a higher suicidal intention than patients of other diseases. There are researches suggesting that about 2%~7% depressive patients died from suicide [2]. Based on researches from WHO, depression will become the second global burden of disease by 2020 [3] and top the list by 2030 [4]. Based on the facts, depression is a widespread mental disease featuring with high morbidity, high relapse rate and high mortality rate. However, there are no effective therapies of depression. Therefore, this paper is written to raise people's concern about depression and provides reference for future researchers. The author includes diagnosis of depression, the major hypothesizes of depression's mechanism, animal model of depression and their protocols, and current treatments for depression, with the purpose of giving the readers a comprehensive overview.

## II. MECHANISM OF DEPRESSION

Unfortunately, researchers have not been able to specialize a certain pathology for major depressive

disorders. Currently, major depressive disorders could be explained by many hypothesizes.

### A. The Monoamine Hypothesis

Dopamine (DA), Noradrenaline (NE), 5-hydroxytryptamine (5-HT) and so on affect human biological functions widely. They are involved in many reactions in central nervous system such as emotion reactions, mental activities, body temperature control and sleep, etc. The monoamine hypothesis is relatively wide acknowledged in the discussion of depression's mechanism [5]. The hypothesis is based on the viewpoint that the lack of concentration or function of monoamine in synaptic clefts of central nervous system is the biology basis of depression [6]. In last century 50s, researchers have suspected that the mechanism of depression is a failure of monoamine's function in synaptic clefts, and they further presumed that increasing the concentration of neurotransmitter in synaptic clefts is the ultimate access to cure depression. 5-HT is a major central neurotransmitter. According to researches, a failure of 5-HT not only could trigger emotion disorders such as depression and anxiety, but also could affect other neurotransmitter thus triggering depression [7]. Using drugs that deplete 5-HT (reserpine) can induce depression [8]. In addition, Randrup proposed that in certain patients' DA function decreased [8]. The loss of NE's concentration is also closely related to triggering depression [9]. Using drugs that deplete NE, such as reserpine and tyrosine hydroxylase inhibitor (AMPT) can also induce depression [10].

### B. Hypothalamic-Pituitary-Adrenal Axis Changes

The content of corticotropin released in the cerebrospinal fluid of depression patients is higher than normal. After antidepressant treatment, the level of corticotropin released will tend to be normal, the depression will be reduced as well [11]. Hypothalamus releases CRH which functions at hypophysis, stimulating hypophysis to release Adreno-Corticotrophic Hormone (ACTH). ACTH further functions at paranephros stimulating it to release Adreno-corticotrophic. And Adreno-corticotrophic could serve as feedback to regulate HPA axis [12]. Clinical studies demonstrate that about 50% depression patients have distinct changes in diurnal

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rhythm meaning that depressed mood is aggravated in the morning and alleviated in the evening. In this case, HPA axis could adjust appetite, sleep and reactions towards stimulations, and are largely attributed to depression [5].

### C. Inflammation

According to recent researches, depression patients have their cellular immunity damaged by suppressing their helper T cells and activating their inhibitory T cells. The mechanism of such changes may relate to the activation of cytokines and other inflammations in their immunity system. Specifically, MDD patients were in general characterized by an impaired maturation of Th2 cells, Th17 cells, and NK cells and by decreased serum levels of IL-7 and sCD25 [11]. Meanwhile, depression is often found in patients with immunity system failure such as arthritis and stroke. Depressive symptoms related to these diseases are rarely resulted by pain, depressive mood caused by physical diseases, but are directly attributed to immunity activation and cytokines release [13].

### D. Structural and Functional Brain Changes

Hippocampus is an important structure in limbic system, and it has a lot of effects in regulating emotion, study, memory. Chronic stress could damage hippocampus, causing its structure and function change [14]. 15 women with recurrent MDD (rMDD) in remission and 15 healthy women were scanned with a 3T Siemens MR scanner. The neutral and negative (stress-evoking) stimuli were observed at the same time, while their blood samples were obtained before. Besides, HPA-axis hormone levels were measured during and after the scanning. Compared to the 15 healthy women, women with rMDD demonstrated hyperactivation in the amygdala and hippocampus, which is negatively related to the cortisol changes and positively associated with the duration of remission [15]. Brain-derived neurotrophic factor, BDNF, is necessary in sustaining neurons' function. Autopsies revealed that the BDNF concentration in depression patient's hippocampus is noticeably reduced. Also, in animal mood experiments, chronic stress factor could lead to the loss of BDNF positive neurons of mice, and additional BDNF injected by researchers could reverse the depressive behaviors demonstrated in animals. BDNF has the ability to protect neurons from depression by activating MAPK pathway [16].

### E. Genes

Researchers all over the world have conducted a massive amount of experiments regarding to finding genes' efforts in causing depression mechanism. All the mechanisms stressed above are all related to genes in some ways. There are increasingly more evidences showing heredity largely relates to causing and development of depression. Till now, the relative genes with depression are still veiled, people merely spotted limited gene sequences holding attribution to MDD (major depressive disorder). For example, Ortiz et al. found that compared with the control group, the

expression of NR3C1 gene of MDD suicide patients was lower [17]. Gray *et al.* observed that compared with non-suicide patients with MDD, all MDD patients who died by suicide had a higher level of GRIN2B gene expression. This indicates that the mRNA level of GRIN2B may be a biological marker of suicide [18]. Gene sequences about coding synthesis, release, intake and metabolism of compound related depression are becoming the alternative gene sequences for further depression researches [19].

### F. Environmental Milieu

A lot of research has validated that the incidence of depression is related to the external environment. For example, researchers tested mice with depression in the early mother-infant separation and found that the methylation level of the NR3C1 gene in the prefrontal cortex and hippocampus of the mice were both increased [20]. The expression of NR3C1 gene affects the level of GR and the function of HPA axis, which is closely related to depression [21]. The interaction between gene and environment is first brought up in a research regarding to 5-HT [21]. 5-HTTLPR, the gene sequences of 5-HT transporter, may affect the impact of stressful events have on depression. Exposed to the equivalent stressful situation, individuals with S allele are found with a higher depression morbidity and suicide rate than individuals with L allele [22]. Recently, a Meta-analysis revealed that the interaction between 5-HTTLPR gene and stress factors could increase the risk of getting a depression [23].

### G. Epigenetics

With the development of gene-environment interaction in the last decade, researchers are equipped with the ability to study the mechanism in a brand-new perspective. Epigenetics may reveal a new possible way by indicating that environmental factors have the capacity of modifying brain neurobiology [24]. For example, in the study of the association between SLC6A4 promoter methylation and changes in brain structure and function, researchers used positron emission tomography and found that the reduction of 5-HT in the prefrontal lobe in the body is associated with the methylation of the SLC6A4 promoter [25]. Whereas, this hypothesis is confronted with serious challenges, even if it is ground-breaking. Because researchers have to be clear with its therapeutic approaches first, then, it is accessible to develop clinical studies [26].

## III. DIAGNOSIS

Depression is mostly demonstrated as major depressive disorder which is featured with recurrent depressive episodes. To distinct major depressive disorder from unhappiness and sadness, there are strict indicators to follow [26]. Firstly, as shown in Fig. 1, patients must show five or more specified symptoms nearly every day during a two-week episode, and there must be differences between the symptoms and the

patient's previous behaviors. Moreover, depressed mood or anhedonia are necessary in diagnosing a depressive episode [27]. Secondly, symptoms must cause clinical suffrage or damage in major functioning such as sociability or profession. Thirdly, symptoms cannot be attributed to physiological effects triggered by some medicines [28]. Fourthly, all the presents of major depressive disorder can not be explained by other psychiatric diseases [26].

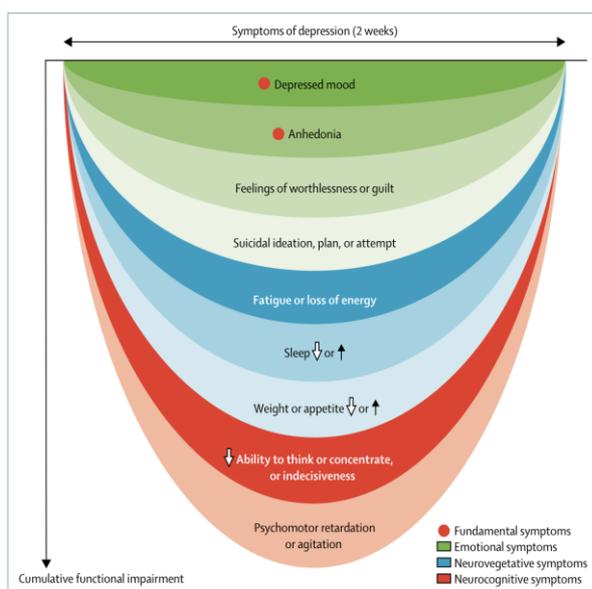


Figure 1. Defining major depressive disorders.

Currently, there are two major diagnostic systems—DSM (Diagnostic and Statistical Manual of Mental Disorders) [27] and ICD (International Classification of Diseases)[29]—whose results are based on the identification of a number of symptoms: depressed mood, anhedonia, feelings of worthless or guilt, suicidal ideation or attempt, fatigue or loss of energy, increase or decrease of sleep, increase or decrease of appetite or weight, loss of ability to concentrate or indecisiveness, psychomotor retardation or agitation.

However, both of the systems have flaws in diagnosing depression, considering the fact that depression shares some common symptoms with other psychiatric and medical diseases. Symptoms such as lack of ability to enjoy pleasure, diurnal variation and feelings of worthless or guilt are more specific to depression. While other symptoms such as fatigue or loss of energy and insomnia can be commonly found in other medical diseases [30]. Besides, to rate the severity of depression, screening tools are designed to fit into different clinical settings including face-to-face therapy and online self-report [31]. However, there are some limitations needed to be considered. One of the limitations is screening lacks hierarchy among the range of symptoms spanning emotional, cognitive and neurovegetative [26]. When it comes to practice, the absence of hierarchy could mess up the result by cataloging largely different depressive presentations into seemingly equivalent severity [32].

## IV. CURRENT TREATMENT

### A. Psychological Therapies

Psychological therapies include cognitive behavioral therapy, interpersonal therapy, acceptance and commitment therapy and mindfulness-based cognitive therapy [26]. Those therapies all have some certain effects in treating depression. There is some research indicating that the effect of cognitive behavioral therapy shares similarities with that of second-generation antidepressant, but its side-effect is less noticeable. Besides, in the short run, there is no significant difference between pharmacotherapy and psychological treatment. However, in the long-run, psychotherapy is more advantageous [33]. Psychotherapy may have a stronger effect on patient satisfaction and social function or other aspects of well-being than medication, which cannot be measured by the improvement of depression scores [34].

Therefore, although the second-generation antidepressants are usually used for initial treatments for patients, cognitive behavioral test still could be the proper measure for initial treatment. Moreover, the combination of pharmacotherapy and psychological treatments shows a stronger effect than either of them alone [34].

### B. Pharmacotherapy

- 1) TCA. The commonly used TCAs are Mipamine, Amitriptyline, and Doxepin, and so on. The antidepressant efficacy of TCAs is based on their ability to modulate norepinephrine and serotonin (5-HT) synaptic transmission to differing extents [35]. TCA is fat-soluble and well absorbed by oral administration. The plasma protein binding rate of TCA is 90% ~ 95%. It is widely distributed in various tissues of the body. TCA is metabolized in the liver and many of its metabolites are also bioactive. But half-life of TCA in blood plasma is long. So, it needs 1~3 weeks to reach steady blood concentration. TCA can block acetylcholine M receptor, histamine H1 receptor and norepinephrine  $\alpha$  1 receptor, thus leading to drug adverse reactions [36].
- 2) SSRIs has a similar effect with TCAs and have dominated treatment over the last decade. SSRI performs its effect by controlling 5-HT selectively and reuptaking the presynapse from the synaptic cleft. Since SSRIs demonstrate little or no affinity for  $\alpha$ -adrenoceptors, muscarinic cholinergic, or histamine receptors, SSRIs have better overall safety and tolerability than TCAs [37]. The types of SSRI currently being applied in clinical uses are fluoxetine, fluoxamine, paroxetine, sertraline, and citalopram. Fluxetine not only can help depression patients, but also have considerable effects for patent with obsessive-compulsive disorder and patent with phobia. However, it could lead to side-effects such as nausea, emesis, headache and so on [38].
- 3) Venlafaxine is an antidepressant medication of the Serotonin-Norepinephrine Reuptake Inhibitor

(SNRI) class [39]. Venlafaxine is different from the other antidepressants which has a unique chemical structure and neuro pharmacology. Since SNRI demonstrate little or no affinity for  $\alpha$ -adrenoceptors, muscarinic cholinergic, or histamine receptors, it has a stronger effect and less side-effect than TCA [39].

- 4) Monoamine Oxidase Inhibitors (MAOIs) are a class of drugs that inhibit the activity of one or both monoamine oxidase enzymes. 5-HT and norepinephrine are metabolized by mitochondrial monoamine oxidase. MAOIs produce an elevation in the extracellular (synaptic) concentrations of monoamines, such as 5-HT, norepinephrine, and dopamine, which accounts for their antidepressant activity [35]. The Food and Drug Administration (FDA) has approved MAOIs to treat depression, including Isocarboxazid (Marplan), Phenelzine (Nardil), Selegiline (Emsam), Tranylcypromine (Parnate). MAOIs are associated with the potential for hypertension and hazardous food and drug interactions, and, consequently, are not widely used [40]. Tyramine and other sympathomimetic amines that are generally present in fermented foods (such as cheese) will enter the circulatory system, and then release norepinephrine to strengthen the activities of the sympathetic nerves and cardiovascular systems, eventually leading to hypertensive crisis [41].

## V. CONCLUSION

As previous research analyzed, depression is already a severe disease in the world, and the on-going global pandemic makes it even worse. Although researchers have been raised many hypotheses, the mechanism of depression is still remained uncertain. Nevertheless, the latest research on gene effects opened up a new way to figure out the mechanism of depression. But for now, all the antidepressants that are available in the market have flaws such as severe side-effects or high prices. To bring out an ideal antidepressant, the key is to conduct more effective animal models without violating animals' rights. A successful animal model and corresponding behavioral tests could not only indicate the uncertain side-effects on human, but also study the mechanism of depression by observing animals' behaviors and test their chemicals. Therefore, there is still a large amount of work need to be done in the future.

## CONFLICT OF INTEREST

The author declare no conflict of interest.

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