Proceedings of the 3rd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/24/20231106

The mechanism and the therapeutics of Major Depressive Disorder

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Abstract. Major Depressive Disorder (MDD) is currently a common and significant disorder. More young people are being diagnosed each day. Decades of research have been done and have provided us with the ability to manage the illness in terms of treatments and the neurobiology behind it. However, it is universally acknowledged that some of the problems still remain. The complete mechanism which processes in the brain of a patient of MDD is not fully revealed and in some cases, treatments such as evidence-based psychological psychotherapy and antidepressants lacked effectiveness. For patients who do experience a reduced level of depressive symptoms, repeated episodes happens often and recurrent remains at high chances. In this review, human knowledge of MDD in the current state will be summarized, including the two most commonly believed pathophysiology pathway. In addition, different types of treatments that tackles distinct aspects of the disorder are highlighted. Prevention programs and intervention methods which have been applied are discussed. They range from small actions, such as practicing meditation and mindfulness, to large movement, such as taking a psycho-educational program with a therapist. Lastly, this review points out the inadequate in human understanding towards MDD and outlines the some of the therapeutical prospects in research and investigation of depression that are able to give rise to a more successful and effectual treatment system option in the future.

Keywords: Major depressive disorder, antidepressant, selective norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitor.

1. Introduction

Clinical Depression is a type of mental disorder which is growing more and more common, having a lifetime incidence of up to 20 percent in women and 12 percent in man. It can interfere with someone's day-to-day life by developing symptoms such as low mood, lacking energy, glumness, insomnia, and an inability to enjoy life. Without proper treatment, depression may deteriorate, the patient may be diagnosed as Major Depressive Disorder (MDD) also known as unipolar depression. Mood disorders affect up to 20 percent of American population, involving 6.7 percent for MDD. The pathophysiology involves a decrease in number of neurotransmitters which leads to disregulation, it is complex and varies within different scenarios [1].

MDD can be diagnosed using a system made up of five criteria called: Diagnostic and Statistical Manual of Mental Disorders- Fifth edition (DSM-5), which consists of five major criteria that only if most criteria are met, the patient can be diagnosed as MDD. Treatment of MDD can be approached from

DOI: 10.54254/2753-8818/24/20231106

different aspects, including evidence-based drug treatments using antidepressant, physical treatments with Electroconvulsive Therapy (ECT) and psychological treatments such as Psychotherapy Cognitive Behaviour therapy (CBT) and interpersonal psychotherapy (IPT). However, recent research reveals there is a lack of satisfactory therapeutic outcome for treatments of MDD. Therefore, this article aims to focus on the relevant aspects of MDD, including details of its mechanism, diagnosing methods, therapeutic conductions and Prevention.

2. Mechanism

The exact mechanism of depression is not fully revealed, but there are two most believed pathophysiology which logically explains the mechanism inside the brain during depression.

The first hypothesis states that the mechanism is associated with the decreased brain level of monoamine neurotransmitters: Serotonin (SHT), 5-hydroxytrytamine (5-HT), y-Aminobutyric acid (GABA), Norepinephrine and dopamine (DA). Studies have suggested that 5-HT receptors are often reduced in the brain of patients with medial temporal lobe epilepsy, while in the brain of patients with panic disorder, both 5-HT and GABA receptors have

experienced a decline. In addition, in the PET imaging study of patients with medial temporal lobe epilepsy and serve anxiety, the decrease of 5-HT1A receptor was found in the hippocampus and its connecting Limbic lobe and Dentate gyrus. Furthermore, inflammatory factors and over-stimulation of neuronal activity leads to a decrease in formation of new neurons (neurogenesis) in brain, which can contribute to depression. Research have also shown over-secretion of cortisol when stressed, to an extend that the brain can no longer suppress the release can also cause decrease in neogenesis [2].

The second theory suggests that the activation of the panic loop is related to Amygdala (fear experience) and hippocampus (fear recurrence). By transferring excessive discharge of Amygdala neurons through the hypothalamus and the midbrain Periaqueductal gray, fear experience, autonomic nerve escape behaviors and endocrine response escape behaviors can occur. The activation of panic loop is related to the hippocampus fear recurrence. The activation of panic loop is a reasonable hypothesis, while it similar to the excessive discharge of epileptic neurons as they can be treated by inhibiting the excessive transmission [2].

3. Diagnose

Depression can be diagnosed while utilizing the DSM-5 criteria which consists of 5 criteria: A, B, C, D and E [3].

Criteria A is the basic one and has to be met for the least; patient have to experience a two-weeks long period feeling depressed, anxiety or a loss of pleasure. The depressive mood should be designated by official reports or from observations made by a third-person perspective. A loss of pleasure should only be designated when patients have been found displeased in most daily events. To meet criteria A, patients will still have to meet at least three or four of the following sub-features of criteria A to be diagnosed as MDD. Those include losing or gaining more than five percent of total body mass monthly in a non-dieting or weight-gaining condition. Similarly, a daily increase or decrease of the person's appetite with unknown reasonings also accounts for the symptom. Another is any type of regular sleep disturbance. Next is a frequent psychomotor perturbation of slowing down which can be noticeable by people around. Two further symptoms may include fatigue or low energy and feelings of valuelessness, emptiness, or excessive inappropriate culpability. Lastly, a diminishing ability of thought processing and a daily irresolution, recurring thoughts of suicide are some criteria as well. In terms of suicidality, suicidal ideation can be either with or without previous planning. Following one criteria A, there comes B, C, D, and E criteria to be met.

B criteria indicates any symptoms that significantly hinder social, vocational, or other critical areas of functioning or produce clinically substantial distress.

C criteria states that the event cannot be attributed to a drug's physiological effects or to another illness.

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D criteria declares that other diseases such schizoaffective disorder, schizophreniform disorder, delusional disorder, or other specified schizophrenia spectrum and other psychotic disorders should not be able to explain the occurrence of the major depressive symptoms better.

Subsequently, E criteria notes that for MDD, neither a manic nor a hypomanic episode should ever occur, if episodes present, the patient will be diagnosed as bipolar type either one or two.

To sum up, for a person to be diagnosed MDD, all five out of the five criteria in DSM-5 should be considered and met. For doctor's support, 'M SIGECAPS (Mood low, Sleep Disturbances, Interest loss, Guilt, Energy low, Concentration difficulties, Appetite changes, Psychomotor retardation, Suicidality)' is used. Patients must meet up to at least five or more of the letters to be diagnosed [3].

4. Therapies

4.1. Antidepressant

Some treatment strategies currently include evidence-based drug, physical, and psychological treatment for anxiety related depression. The CANMAT Guidelines for the Management of Adult Depression (2016) recommends that Antidepressant with broad indications to be used in patients of depression, including Paroxetine, Sertraline and Escitalopram in 5-hydroxytryptamine Reuptake inhibitor (SSRIs), and Venlafaxine and Duloxetine in serotonin and Norepinephrine reuptake inhibitor (SNRIs) [4].

SSRIs, as the second generation of Antidepressant are used for first-line treatment of depression. Research shows that SSRIs (fluoxetine, sertraline, paroxetine, citalopram and escitalopram) have clear effects on treating depression and are recommended as first-line drugs. SNRIs (venlafaxine and duloxetine) are also considered as first-line drugs for depression; clinical cure rate of Venlafaxine excels above that of Fluoxetine in SSRIs. Norepinephrine and specific serotonergic antidepressants (NaSSA) like Mirtazapine is a first-line treatment drug for depression. However there lacked high-level clinical research evidence, therefore it is recommended as a second-line drug. Combined-drug treatment, including Venlafaxine and Mirtazapine, is often used as second step intervention plan for poor single drug treatment, but due to the high dose used, it is easy to lead to more adverse reactions, therefore combined-drug treatment of antidepressant remains to be further studied and is not recommended at present. Although antidepressants are commonly used in treating depression, improvement in symptoms does not turn prominent until weeks after receiving therapy. Long-term use of antidepressants can gradually reverse some of the effects of chronic stress, including upregulating neurotrophin expression and reactivating hippocampal plasticity. Antidepressant can help by increasing concentration of neurotransmitters such as SHT, DA and NE instantly, however the long delay in effectiveness is due to the network dysregulation which can take weeks as it includes gene transcriptions. Therefore, many antidepressants are aiming to restore efficient regulation instead of increasing neurotransmitter concentrations. Apart from that, some drugs can prevent, or reverse damage caused by increasing cortisol release, over-stimulation or inflammation in brain. A neurotrophic factor, bdnf, acts to stimulate dendritic sprouting, and promoting new neuron growth [5].

An 8-week study was carried out at the Beijing Anding hospital (a psychiatric hospital in Beijing) from April 2013 to September 2017 to compare the superiority of SNRIs and SSRIs. The trial was randomized and single-blinded. The primary results were judged by the improving depressive symptoms using Hamilton Depression Rating Scale (HAMD-24) score. Effects in HAMD-24 depression feature score and Clinical Global Impressions-Improvement (CGI-I) were obtained to measure the secondary outcomes. The efficacy was analyzed utilizing the Full Analysis Set (FAS) and the modified intention-to-treat (mITT) principle [6].

Study included a total of 184 postmenopausal women diagnosed MDD. 172 of them took part in the FAS, among which 82 were treated with venlafaxine (a SNRI) and 90 were given fluoxetine (a SSRI). In terms of result, both groups showed a significant decline in the HAMD-24 score, although a larger reduced was saw in the venlafaxine group. In addition, in the venlafaxine-treated group, the CGI-I response rate appeared to be higher compared to the fluoxetine-treated group. There was no discernible

DOI: 10.54254/2753-8818/24/20231106

difference between the two groups with regards to adverse effects. The trials have shown that venlafaxine is better adapted and has a better effect on the treatment of postmenopausal MDD [6].

4.2. Non-chemical treatments

Non-chemical treatments for depression are some physical therapies including Electroconvulsive Therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) Neuroregulatory techniques such as magnetic seizure therapy (MST) have gradually been applied to the treatment of depression for acute patients. Currently, rTMS has become a first-line treatment, while ECT is mentioned as a second-line treatment as a result of some of its side effects. After comprehensive consideration of relevant research evidence, Antidepressant together with rTMS are recommended as first-line treatment and with ECT, makeup a second-line treatment. Other physical therapies are insufficient in clinical evidence, so are not recommended at all [7].

4.3. Psychotherapy Cognitive Behaviour therapy (CBT) and interpersonal psychotherapy (IPT)

Psychotherapy Cognitive Behaviour therapy (CBT) and interpersonal psychotherapy (IPT) are first-line treatment options for depression and can be used as an alternative or supplement to antidepressant drug therapy. Research shows that CBT enhances the treatment of anxiety related depression, with a clinical cure rate of around 30% [3]. IPT also has a symptomatic improvement effect on depression and anxiety. It is recommended CBT as the choice for first line, and IPT adjuvant therapy as the second line of treatment.

However, some studies have shown that with evidence-based psychotherapy (CBT and IPT) alone, only small benefits on treating depression are seen. A study was carried out to investigate the effectiveness of evidence-based psychological depression psychotherapy, 83 randomized controlled trials of psychotherapy interventions (CBT and IPT) were studied. In the medium-term follow-up (about 12 months), 32 of trials consisting of 5965 partakers had depression diagnosis as their primary outcome. And 73 of trials with 13829 contributors had a self-rated primary outcome of depression diagnosed. There is still not enough evidence proving that just by treatment of psychotherapy of depression itself, MDD can be fully treated. Going further, there are limitations to the study. The control group that considers the non-specific elements is the attention placebo comparison group. Some of non-specific elements are the attention or involvement in a trial of researchers) showed that the treatments had no effect when being compared [8].

5. Prevention

There are multiple ways for preventing MDD, they range from small, such as practicing meditation and mindfulness, to large, such as taking a psycho-educational program with a therapist. Prevention programs includes manualised psychological, psycho-educational programs and computerised interventions like CBT, IPT, wellbeing therapy (WBT) and mindfulness-based cognitive therapy (MBCT). It is possible to avoid 22 percent of new cases of MDD annually due to evidence of the effectiveness of depression. Some prevention programs have even been introduced to schools [9].

Cognitive behavioral therapy (CBT) acts positively among individuals who are at risk of depression. It focuses on the link between feelings, beliefs, and behaviours and is an evidence-based theraoy based on clinical competence and scientific investigations. During a CBT, positive language is used to refute and rephrase irrational and negative terms. CBT is effective in preventing patients to approach things in their life in a negative manner by helping people to realise their unproductive thoughts and to refocused them towards problem-solving techniques [5].

Interpersonal Psychotherapy (IPT) can be effective in both treating and preventing stages of the mental illnesses. Several meta-analyses have proven the efficacy of IPT and it is used commonly in the past decade. More than 1000 intervention trials have been carried out by psychotherapy researchers. Other than reducing depression rating of an individual, it also contributes to increasing self-esteem, overall functioning and social functioning of the individual. For elderly patients, IPT improves their

DOI: 10.54254/2753-8818/24/20231106

response to pharmacotherapy. IPT is also effective when applied to bulimia nervosa and bipolar disorder. Compared to standard clinical management, IPT has shown to be better at maintaining patient's euthymic state [5].

MBCT and WBT are other types of psychosocial approaches that are group based and take 8 weeks. During MBCT and WBT, people will learn about how to recognize early warning symptoms of MDD. Through mindfulness training and cognitive-behavioral exercises, clients are able to stop and come out of the old pattern of thoughts that triggers depression [10].

Schools provide an ideal environment to deliver prevention programs to young people, as it is a place where young people can be taught to manage their emotional difficulties with the help from adults and their partners. There are two types of school-based prevention approaches: Universal approaches and Targeted approaches. Universal approaches are delivered to all individuals regardless of their risk of depression. Therefore, universal programs will be aimed at a large proportion of students in the school. Whereas Targeted approaches target only those individuals who have a higher risk profile for MDD, such as those with familial risk factors. Investigations carried out in middle schools of Chile and Iceland shows less pupil were affected by MDD or any mental disorder in schools that have used targeted approaches. The experiments also suggests that prevention programs are more effective in the earlier stage when pupil are still developing than later when fixed behavioral and cognitive habits have already been demonstrated [4].

6. Therapeutic prospect

For many years, research has been done based on the monoamine deficit hypothesis of depression, however the treatments based on the idea have only been found to be moderately successful. Therefore, with only just the understanding of monoamine deficiency hypothesis is not enough.

As shown in animal models, neurogenesis has saw an increase in rate when given long term antidepressant within the hippocampus, this shows different region of the brain have different implications in MDD, also suggesting that there may be antidepressants which performs site-specific functions. Future research may go into such details to be able to synthesis specific drugs targeting only the specific region in the human brain [11].

Early research has suggested MDD patients respond differently to different functional medications. For example, some patients seem to respond better to medications that just affect 5-HT function, others to medications that affect both NE and 5-HT function, while still others appear to only benefit from medications that affect all three monoamine systems. Due to this sign, there are now some pharmaceutical companies that are working on developing a "triple" monoamine reuptake inhibitor [11].

Further, some functional imaging studies can help to understand the depressive monoaminergic dysfunction anatomy. As an example, monoamine depletion techniques and PET imaging can be used together to better understand the neuroanatomy of depression relapse with depleted monoamines. In addition, radioligands which binds to particular monoamine transporters and receptors may be informative as it works to tell in which region of the brain and to what extend are these systems abnormal in a patient of MDD [11, 12].

Lastly, the continuous discovery of new drugs can help reduce symptoms of MDD. Ketamine has been demonstrated to produce short-term antidepressant effects in rodent models as well as in individuals with depression. The discovery of the mechanisms involves active research; Ketamine inhibits a certain form of synaptic transmission, which activates several signalling pathways and increases the expression of neurotrophins. The prefrontal cortex and hippocampus become more malleable as a result of these molecular alterations, which most likely contribute to the behavioural effects of ketamine [13].

7. Conclusion

MDD still remains prevalent in the current state, affecting more individuals and families. Up until now most of the relevant research are based on only the monoamine deficiency hypothesis mechanism. In spite the lack of complete understanding of its full mechanism several treatments have been applied and

DOI: 10.54254/2753-8818/24/20231106

used, some showing great effect while others do not. More studies are still being carried out to investigate more about the mechanism in each specific region of the brain in patient with MDD. Further research will need to be conducted in the future to increase to effectiveness and the efficiency of treatments and methods of prevention toward MDD. Some research directions aim to advance understanding of the scientific hypotheses underlying MDD and are likely to aid in the development of novel antidepressant medications. In addition to the monoamine shortage concept, several potential therapies include medications that target the neuromodulatory system and targeted brain stimulation techniques that specifically target the neuronal networks involved in depression. New and important developments in MDD therapy and understanding are anticipated throughout the coming years.

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