

Advances in the Mechanism and Treatment of Major Depression Disorder

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Abstract. Recently, as a common psychological disease in contemporary people, depression has gradually attracted people's attention. The treatment of depression has gradually developed from single drug treatment to multiple treatment methods. However, due to the lack of professional knowledge, most people still do not know much about depression and its treatment methods. Therefore, this article mainly introduces the current situation of depression and its treatment methods which includes anti-depressants, psychotherapy and physical therapy, in the hope that psychological diseases such as depression will be paid more attention and patients will be treated correctly.

Keywords: Depression, Anti-depressant, Psychotherapy, Physical Therapy.

1. Introduction

Depression, which is also called Major depressive disorder (MDD), is now one of the most common psychological diseases with continuous and long-term low mood as the main clinical features. Normally, it can happen at any age, typically begins in adulthood.

According to the survey from World Health Organization (WHO) in 2012, there are about 350 million people with depression worldwide. Besides, a mental health survey conducted in 17 countries found that one in every 20 people has had or is currently suffering from depression in average.

The annual prevalence of depression is 1.5 % and the lifetime prevalence reaches 3.1 %. According to investigation, depression has affected 20% of the total population. Though there might be some differences in the incidence of depression in different countries and regions, it still includes lots of patients suffering from depression. For example, severe depression's annual prevalence is about 7 % in the United States, 2 % to 5 % in Europe, 1 % to 7 % in Africa, and about 2.1 % in China.

Moreover, with the development and progress of economy and society, the pace of social life is accelerating, which leads to the increasing of competitive pressure. Thus, people's psychological and behavioral problems are becoming increasingly prominent. However, the problems specifically reflecting not only in the increasing number, but also in depression gradually become younger. For example, the incidence of mental and psychological disorders in college students is as high as 25 % [1] and adolescent students tend to have impulsive suicide due to depression. Therefore, people now attach great importance to depression because of its status as one of the biggest modern psychological disease.

2. Reasons and affecting factors of depression

Unfortunately, the reason which could cause depression is not clear at present. Recently, most of the scientists believe that the factor might lead to depression is a combination of genetic, environmental, psychological and biological factors. For example, if someone suffered from stress of major life changes or trauma, the possibility of he/ she gets depression might be higher. Besides, depression might occur on patients who suffering from other serious medical illnesses, such as diabetes, cancer, heart disease, or Parkinson's disease. Moreover, imbalance in neurotransmitter involved in mood, such as dopamine, 5HT, NA and etc, might also lead to depression.

And according to some research, if a family has a patient with depression, then the family members are at higher risk of the disease, which may be a genetic cause of increased susceptibility to depression. Among which bipolar depression is more hereditary. However, this finding not means that anyone

who has a family history of depression will certainly suffer from it, and not every depression patients has a family history of depression, which suggesting that inheritance is not the only determinant.

3. Different treatment methods of depression

Although we do not have a clear reason of why people are suffering from depression, we do have some effective ways to treat depression. At present, the treatment of depression mainly includes anti-depressants, psychotherapy and physical therapy. The latter mainly includes electroconvulsive therapy, transcranial magnetic stimulation and vagus nerve stimulation.

3.1. Anti- depressants

At present, most of the methods for the treatment of depression need to be combined with anti-depressants therapy. Therefore, anti- depressants are playing important roles in depression treatments. The main mechanisms of anti- depressants can be divided, for example, into enhancing NE function, enhancing 5-HT function and simultaneously enhancing NE and 5-HT function. This part mainly provides an introduction of four common types of anti- depressants that showed its importance in clinical practice.

3.1.1. Monoamine oxidase inhibitors and reversible selective monoamine oxidase inhibitors (MAOI)

Monoamine oxidase inhibitors are a class of anti- depressants used earlier in clinical practice. Its representative drugs are isopropylhydrazine, safazine, phenylethylhydrazine, and etc. Of which isopropylhydrazine is the first drug used to treat depression[2]. However, there are many adverse reactions, such as toxic liver injury, hypertension crisis and so on. Besides, the efficacy is far less than that of the later tricyclic drugs. Therefore, it has become a secondary drug for the treatment of depression.

In recent years, a new selective monoamine oxidase A inhibitor (MAOI) has been developed. It is a kind of drug that enhances both the NE and 5-HT systems. Moclobemide is the only representative of MAOI anti- depressants. Unlike previous drugs, moclobemide has fewer side effects and is easy to tolerate. But it still has some adverse reactions such as nausea, orthostatic hypotension, and occasional hypertension. Its pharmacological action is selective inhibition of MAO - A[3].

MAO-A is the main metabolic enzyme of central norepinephrine (NE) and 5-HT. The use of moclobemide can increase the concentration of the above neurotransmitters in the synaptic cleft, so that it will improve mood and decrease depressive symptoms. And the inhibition is reversible, so there will be no cholinergic receptor blocking effect. Therefore, we can see that it not only retains the antidepressant effect, but abandons the traditional MAOI adverse reactions and TCA anticholinergic adverse reactions.

3.1.2. Tricyclic Antidepressants (TCAs)

TCAs are early clinical NE and 5-HT function enhancers, the main mechanism is achieved by inhibiting 5-hydroxytryptamine(5-HT) and norepinephrine(NE) reuptake. Representative drugs include imipramine, clomipramine, clomipramine, doxepin amitriptyline and etc. TCAs have been used to treat depression for half a century and always are considered to be as a classic and effective anti- depressant.

TCAs sometimes have more than one mechanism. For instance, clomipramine is a kind of TCAs, which approved by the US Food and Drug Administration(FDA) as a drug for the treatment of obsessive-compulsive disorder (OCD). It is also used as an antidepressant in many countries. The inhibition of 5-HT reuptake is not the only mechanism, because its metabolites also inhibit the reuptake of NE. Therefore, its antidepressant effect may be the common result of these two effects. Treatment inhibition of clomipramine found in several clinical trials.

The reason why patients prefer TCAs including the effect was significantly. According to Yi Chai et al's experiment which conducted within- and between-person comparisons of self-harm risks in

people aged 40 years or older across five antidepressant classes错误!未找到引用源。 , we can see the results that show a phenomenon that TCAs had a lower short-term risk of self-harm compared to SNRIs and SSRIs. Generally, TCAs are given to patients who suffer from more severe depression conditions. “One possible explanation was that TCAs are associated with greater toxicity compared to SNRIs, NaSSAs, and SSRIs regarding self-poisoning, and therefore, the prescription of TCAs for those considered at high risk of self-harm is avoided[4].” explained by Yi Chai et al.

However, TCAs might also cause wide range adverse reactions, of which can be extremely serious. Such as dry mouth, constipation, blurred vision, elevated intraocular pressure and other anticholinergic side effects. Besides, after taking TCAs patients might sometimes suffer from as well as cardiovascular adverse reactions such as arrhythmia, orthostatic hypotension, and conduction block. In addition, the drug onset is slow, needed to be administered multiple times a day, but lost of patients have poor tolerance and adherence to drugs. Moreover, excessive TCAs can even cause death. Therefore TCAs were gradually replaced by new antidepressants after the 1990s.

3.1.3. Tetracyclic antidepressants

The mechanism of tetracyclic antidepressants is similar to TCAs, mostly by inhibiting NE reuptake, selectively blocking NE reuptake and increasing the activity of NE in the central system, thereby improving the patients' mood. The representative drugs are maprotiline, reboxetine, mianserin and etc. Besides, it usually has a rapid onset and often take effect after 3 to 4 months, and with qualities of good tolerance, small anticholinergic effect and low cardiotoxicity. Tetracyclic antidepressants with a wide range of antidepressant effects which is effective for various types of depression such as reactive and neurotic depression, and has obvious anti-anxiety and sedative effects. Common adverse reactions include dry mouth, constipation, urinary retention, postural hypotension. After taking tetracyclic antidepressants, few patients might appear symptom of epileptic seizures. However, similar to tricyclic antidepressants, these two anti-depressants are currently less clinically used.

3.1.4. Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) is a new type of anti-depressant drugs. The main mechanism of action of SSRIs is acting on the presynaptic membrane of 5-HT highly selective reuptake inhibition. It has light impact on other neurotransmitters, mainly reflected in almost none impact on NE or the recovery of dopamine (DA). Compared with traditional drugs, such as TCAs, SSRIs have better efficacy and tolerance, higher safety, and less impact during patients' life and work. As the result of these drugs have a clear antidepressant effect and fewer adverse reactions than tricyclic antidepressants (TCAs), the NICE guideline, therefore, recommends SSRIs as the first choice for pharmacological treatment of depression错误!未找到引用源。 .

Zimelidine was a kind of SSRIs used in clinical practice at first, which was later eliminated due to its toxic effects. The representative drugs at present are fluoxetine, paroxetine, citalopram, sertraline and fluvoxamine.

However, when combined with MAOIs, such drugs can easily lead to toxic 5-HT hyperfunction symptoms, mainly manifested as mental disorders, hyperactivity, high fever, diarrhea, disturbance of consciousness, and even death. Therefore, when changing the medication strategy for patients taking MAOIs, if SSRIs are to be used, they must be taken after 2-5 weeks of stopping MAOIs. In addition, SSRIs have less cardiotoxicity than TCAs, and have no anticholinergic effect and sedation, accompanied by adverse reactions such as insomnia, headache, dizziness, and extrapyramidal reactions.

According to the results of the recent report, the current clinical side effects are mainly reflected in : patients with depression due to the long-term using of SSRI antidepressant drugs, are suffered from abnormal blood lipid levels and glucose metabolism disorders. Because depression patients are more likely to have diabetes than normal people, and the prevalence of depression in diabetic patients is about 3-4 times that of normal people.

Chen's[6] experiment indicate a link between blood glucose level and SSRIs: Before treatment, blood glucose levels in both groups were in the normal range, and the depression group was

significantly higher than the control group. After taking SSRI anti-depressants for 30 days, the blood glucose level decreased significantly and was in the normal range. This result indicating that patients with depression could significantly reduce the blood glucose level after using SSRI drugs. Therefore, patients with depression should check their blood glucose and blood lipid levels in time during the long-term use of SSRI antidepressants, so as to detect and treat as soon as possible.

3.2. Psychotherapy

Psychotherapy is a new mode of clinical treatment of depression. Based on the psychological characteristics of patients, physicians determine appropriate interventions, and promote their recovery by correcting patients' wrong cognition and behavior.

Except from the general psychotherapy, it also includes behavior therapy, hypnosis and teletherapeutics, biofeedback therapy, music therapy, art therapy and Morita therapy.

Since depression is a highly recurrent mental illness, the recurrence rate of patients after initial cure is as high as 50 %, so for most of patients, their treatment period is long. However, considered the side effects of anti-depressants, generally, in the late drug treatment will combined with psychological treatment. According to Zhang et al's experiment[7], reducing drug strategy combined with psychotherapy can not only achieve the same effect as low-dose drug maintenance therapy, but also help to reduce the incidence of adverse reactions for patients who with high risk of recurrence of depression.

Most of people have a thought that psychotherapy is totally safe, nevertheless, it also has some side effect. Such as suicide attempt, drug abuse, on-compliance with treatment, tension in treatment relations and excessive dependence on therapists.

Therefore, patients who want to seek psychological intervention or psychotherapy need to be careful. It is necessary to ensure that doctors have permission to carry out the treatment, otherwise they will face a series of above side effects or even more serious ones.

3.3. Electroconvulsive therapy

Electroconvulsive therapy, also known as ECT, is a treatment method that uses a certain amount of current to pass through the brain, causing epileptic discharges in the central nervous system and generating generalized seizures. The treatment mechanism is by making the cerebral cortex discharge widely, to increase the body norepinephrine synthesis and uptake, and by improving the sensitivity of 5-hydroxytryptamine neurons to achieve the therapeutic effect.

Because cognitive behavioral therapy and drug therapy are ineffective for nearly 30 % of patients who suffered from depression, and the above two methods usually work slowly. Therefore neither of them are suitable for patients with suicidal behavior who need to quickly relieve depressive symptoms. So for these patients, electroconvulsive therapy is a more effective and efficient antidepressant. And according to experiments ~~错误!未找到引用源。~~, 48 % of patients who are ineffective in drug treatment are effective in ECT treatment.

At present, ECT is considered to be one of the most effective anti-depressant therapy, widely used in the treatment of depression. Especially in use of major depression, bipolar disorder, depressive episodes and refractory depression. Unlike drug therapy which only has 10 % to 40 % remission rate, the remission rate of ECT can be as high as 50 % to 60 %.

However, there are few cases of clinical application of ECT. Firstly, the main reason is that this method also has some side effect, which may cause cognitive impairment in patients, including retrograde amnesia, anterograde amnesia, acute disorientation, executive dysfunction and other symptoms. There are many factors that affect cognitive impairment during treatment, including patient age, cognitive function status before treatment, placement of treatment electrodes, and current waveforms. This cognitive function may be restored within one month after treatment, but there is no consensus on the natural recovery of ECT-related cognitive impairment.

In addition, the reasons of why patients prefer other treatments more than choosing ECT treatment are likely from the related research on ECT smear and its expensive treatment costs. For example, an

ECT in the United States costs \$ 300 to \$ 1,000 per time, and it takes about 700 RMB each time in China. However, a course of treatment requires at least 6 to 12 times of ECT.

In general, ECT is one of the most effective methods for the treatment of depression. However, due to uncontrollable side effects and high treatment costs, most patients and their families are discouraged and having misunderstanding of this treatment. Nevertheless, scientists are improving ECT to optimize and innovate ECT programs, thereby improving its antidepressant effects and reducing side effects such as cognitive impairment.

3.4. Cranial electrotherapy stimulation (CES)

The therapeutic mechanism of Cranial electrotherapy stimulation (CES) is to stimulate the brain through low-intensity micro-current, change the abnormal brain waves of patients, and promote the brain to secrete a series of neurotransmitters and hormones which are thought to be closely related to anxiety, depression, insomnia and other diseases, so as to achieve the treatment of these diseases. And compared with drug therapy, this treatment has no side effects.

At present, CES treatment has a certain effect, but it has not been applied in clinical practice on a large scale. The benefit of patients may be due to the placebo effect. Although CES still has some problems and controversies in the treatment of many diseases, especially mental illness, it is undeniable that compared with drug therapy, CES provides new ideas for the treatment of mental illness such as depression, anxiety and insomnia.

According to the research results of Yixin Chen et al[8], the treatment of mixed anxiety and depression disorders in children with CES technology is effective and has no serious adverse reactions.

Thus, if patients are worried about the sequela of drug treatment, or some patients who cannot tolerate drugs, as well as children and pregnant female, CES therapy should be considered as their first choice. At the same time, for ordinary patients, CES therapy can also be used as an auxiliary method to cooperate with drug therapy to reduce the dosage of drugs and reduce adverse reactions.

3.5. Vagus nerve stimulation

The vagus nerve stimulation technique was originally an implantable vagus nerve stimulation. This method not only showed certain results in the clinical treatment of depression, but also achieved expected results in the treatment and intervention of epilepsy, primary headache and other diseases. However, as the result of the treatment is invasive surgery, the treatment equipment needs to be implanted into the patient's body, so the treatment fee is expensive and may have chance to cause some side effects.

With the advancement and development of science and technology, vagus nerve stimulation has ushered in innovation. The current vagus nerve stimulation technology has been transformed into Transcutaneous vagus nerve stimulation technology. It is a new, safe and non-invasive brain nerve stimulation regulation technology. According to Badran's research ^{错误!未找到引用源。}, the basic working principle of tVNS is to apply intermittent pulsed electrical stimulation to the vagus nerve branches in the external ear of the human body, so that the electrical signal is non-invasively transmitted to the brain through the vagus nerve pathway to induce changes in cerebral cortex activity and related neurobiochemical markers, thereby achieving the goal of neuromodulation.

In addition, researchers generally believe that its main mechanism of action is to activate the cholinergic anti-inflammatory pathway by regulating the concentration of acetylcholine and promote the secretion of neurotransmitters such as norepinephrine and γ -aminobutyric acid in cognitive function-related brain regions, thereby promoting the improvement of cognitive functions such as memory, attention and executive function. However, the above experiments are all indirect measurements. The role and influence of vagus nerve technology have not been fully grasped, but its positive effect on the treatment of diseases is beyond doubt.

4. Conclusion

In summary, there are many ways to treat depression, but the most widely used methods in clinical practice are still drug therapy and psychotherapy. That's mainly because of people lacking knowledge of depression. We need to realize that not all patients with depression are suitable for a certain method of treatment. The specific treatment method cannot be determined by the patient's own likes and dislikes. Patients with different symptoms should ask the doctor to develop a special treatment plan after understanding their own condition.

Beside of that, this phenomenon also shows that people still have conventional ideas about the way to treat psychological and mental diseases, and it is difficult to accept new treatments, which also reflects the necessity of improving high-tech treatment methods, by reducing its sequelae and side effects, so that to benefit more patients and their families, and to encourage people to pay more attention to the social problem of mental health.

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