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Progress on the Pathogenesis and Treatment of OCD, AD and Depression

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Abstract

Background: Obsessive-compulsive, anxiety disorder, and depression are the most common negative emotions. The incidence rate is high and spread across all age groups. With the rapid development of the world economy and the increasing competition in social life, the incidence rate has also increased rapidly, more and more young suffer from these three kinds of mental illnesses. Many studies have been carried out to investigate the pathogenesis and therapeutic method. It is necessary to summarize the progress for references to further research and treatment. **Method**: Based on a series of literature, the studies on the pathogenesis and therapeutic method of the three kinds of illnesses are summarized and analyzed. The points and results either of West medicine (WM) or traditional Chinese medicine (TCM) are collected and compared to find the best tendency of study and the best therapeutic method. **Results**: Obsessive-compulsive disorder, anxiety disorder and depression are common in recent years and severely affect people's lives. In view of WM. These three kinds of illnesses are all related to the changes or damage of part of brain and nervous system. While TCM thinks that they are due to Qi stagnation or deficiency of heart Yin. Many methods of treatment have been presented and used clinically, but the effect is limited. **Conclusion**: The most promising and effective methods are those combining WM and TCM.

Keywords

Obsessive-Compulsive, Anxiety Disorder, Depression, Combined Treatment of TCM and WM

1. Introduction

Obsessive-compulsive disorder (OCD) is a common clinical mental disorder

with a prolonged course and difficult to cure. Anxiety disorder (AD), a kind of neurosis mainly manifested by anxiety, is listed as one of the top ten disabling diseases by the World Health Organization. It is often manifested as worry without obvious cause and fixed content, accompanied by obvious autonomic nervous dysfunction. Depression (or Major depressive disorder, MDD) is an affective disorder with a high incidence rate and serious harm to human physical and mental health. The occurrence of depression will lead to the disorder of normal sleep mechanism to a certain extent, while insomnia may have symptoms of depression and mania. Depression is the fourth largest disease in the world. It is expected to become the second largest disease by 2030. Generally, OCD, AD and depression are the most common negative emotions.

OCD, AD and depression are closely related, transforming, interdependent and restraining each other. For example, OCD generally does not occur alone. Most OCD patients are accompanied by anxiety, a few are accompanied by depression, and some OCD patients are mixed with AD and depression together. The three kinds of illnesses are all caused by the impairment of the function of serotonin, a neurotransmitter. More precisely, the patient's serotonin system is defective. Therefore, the basic idea of treating OCD is the same as that of treating depression. The difference is that the dosage is larger and mixed drugs are needed for OCD. People have carried out long-term research on these three diseases and have a certain understanding of the pathogenesis. On this basis, a variety of treatment schemes have been put forward, especially the combining treatment of TCM and WM is more promising.

On the above viewpoints, this paper summarizes and analyzes the research progress on the pathogenesis and treatment methods of these three diseases, in order to provide help for the future research direction of pathogenesis and treatment methods.

2. Pathogenesis and Diagnosis

OCD is characterized by excessive monitoring of errors and behaviors and the abnormal increase of error related negative wave amplitude in EEG indexes. In terms of brain function, it is characterized by excessive activation of prefrontal lobe and anterior cingulate gyrus. Error processing hyperfunction is considered to be a specific intraphenotype of OCD [1].

AD is a neurosis characterized by anxiety. Clinically, it is divided into panic disorde (PD) and generalized anxiety disorder (GAD). GAD, also known as chronic anxiety or floating anxiety, is the most common form, accounting for 75% of AD. The symptoms of patients are extensive and persistent anxiety. They often feel inexplicable panic. The overall mood is irritable, restless, and anxious. They often feel that something unfortunate will happen immediately and can't concentrate on doing something, which is unbearable but can't get rid of. The symptoms includes palpitation, palpitation, timidity, sweating, chest tightness, irritability, shortness of breath, forgetfulness, dry mouth, insomnia, constipa-

tion, diarrhea, skin flushing or pallor, and in serious cases, lip tremor and limb trembling, which seriously affect the life and work of patients [2].

AD is widespread among college students (about 20%). Some doctoral students are in a sub-health state due to great mental pressure. Depression and AD are common psychological diseases among doctoral students also, and the incidence rate is high. Many students can't graduate on schedule, and even delay as long as 5 - 10 years or longer. Some escape academic research halfway. The weak relationship with tutors is a common feature of most graduate students experiencing depression and/or AD [3]. Univariate analysis shows that the common potential risk factors for depression and AD of doctorial students are professional title promotion pressure, frequency of meeting with tutors, unpleasant experience with tutors, type of tutors, difficulty in meeting the requirements of paper publishing, meaningful perception of doctoral reading, expected graduation time, balance among work, family and difficulty. Assistance for tutors in applying for projects or applying for awards, assisting in guiding thesis writing, and participating in tutor projects are unique risk factors for depression of doctorial students. Raising children and the number of doctoral students under the guidance of tutors are unique risk factors for the occurrence of AD. Teacher-student relationship is the greatest influencing factor of depressive symptom. The influence of factors of anxiety symptom of doctorial students in order of contribution are as follows: teacher-student relationship, difficulty in publishing papers, difficulty in balancing work, family and doctoral study, scientific research self-efficacy, graduation expectation, frequency of meeting, significance of doctoral projects, frequency of meeting, feeling of economic pressure and whether or not you are working in clinical practice.

The neural mechanism of OCD is mainly related to the prefrontal brain regions including orbital frontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), as well as subcortical brain structures such as ventral striatum, thalamus, insula. A large number of studies on the neural mechanism of OCD agree that the dysfunction of cortico striato thalamo cortical circuits (CSTC) is closely related to the pathophysiological mechanism of OCD [4] [5].

The cognitive psychology model of OCD proposed by Schwartz mainly focuses on the error related risk identification system. The key to the formation of obsessive-compulsive concept is the persistent and excessive cognitive monitoring of errors or errors in a specific behavior situation, and so constant formation of the subjective impression that "something is wrong". When the relief of tension or anxiety associated with obsessive-compulsive behavior may be experienced as a form of reward, then there will be a pathological cycle pattern of obsessive—compulsive thinking—emotional tension—reward motivation—obsessive—compulsive behavior [6]. The reason for OCD patients always trying to correct something due to their suspection of the correctness is that the generation of inappropriate "false risk awareness" cognitive signals results from the over-activation of the error monitoring system. The evidences are found from the perspectives

of behavior, EEG, functional imaging and so on.

Depression is an affective disorder mental disease, which is mainly manifested by long-term depression. At the same time, it also has symptoms such as lack of pleasure and slow thinking. Depression seriously endangers human physical and mental health.

There are three main points on the pathogenesis of depression in reinforcement learning: 1) The activities of dopamine system in basal ganglia and midbrain respond to internal and external false signals decrease, and false information causes the phase reduction of dopamine system activities; 2) The phase decrease of dopamine system activity relieves the inhibition of ACC and medial frontal lobe, and the activity of ACC and medial frontal lobe increase; 3) ERN or FRN, as a reinforcement learning signal from depression activity to ACC, is conducive to adjusting the next step of behavior. Depression has an important impact on people's decision-making behavior through reinforcement learning signals such as ERN or FRN. Among them, learning from "mistakes" through external feedback is an important way for people to adapt to the environment and develop themselves.

It is shown that intestinal flora may play an important role in the occurrence, development, prevention and treatment of depression by acting on the neuroendocrine system, autonomic nerve and immune pathways [7] [8] [9] [10]. The number of lactobacillus and bifidobacterium in the feces of patients with depression is significantly lower than that of healthy volunteers [11]. The relative abundance of prevobacteriaceae in patients with depression is significantly higher than that in healthy volunteers. The contents of rumen cocci and fecal bacilli in the genus level are significantly reduced, while the abundance of prevobacteriaceae is significantly increased, suggesting that patients with depression are also accompanied by abnormal intestinal flora [12]. The intestinal flora affects the central nervous system through the "gut brain" axis. The abnormality of the intestinal flora gut brain axis can participate in the occurrence of depression through neural, immune, endocrine and other mechanisms [13].

A variety of intestinal flora can produce neuromodulatory substances and may affect brain development, especially synaptogenesis and maturation. The changes in the expression of brain derived neurotrophic factor (BDNF), mRNA and protein in hippocampus are related to the intestinal brain axis. The level of BDNF mRNA in the brain of sterile animals is different from that of animals parasitic on normal flora. After intestinal inflammation caused by whipworm infection, mice show anxiety-like behavior, which is related to the decrease in the expression of BDNF mRNA in hippocampus. After improvement of abnormal behavior by probiotics, BDNF expression level returned to normal level [14]. Inflammatory markers (such as tumor necrosis factor α(TNF-α)), interleukin 6 (IL-6) and C-reactive protein in the serum of patients with depression are often higher than normal levels.

The classic hypothesis of depression—monoamine hypothesis believes that the reduction of 5-HT, dopamine (DA) and norepinephrine (NE) released in the

central nervous system will lead to the decrease of the content of neurotransmitters above the synapse [15]. When the body is in a state of psychological stress for a long time, it is easy to cause stress injury and abnormal function of the "gut brain" axis, leading to the decline of 5-HT level, and inducing depression.

More than 50% of DA in the body comes from the intestine. DA includes the receptors of D_1, D_2, D_3, D_4 and D_5. D_1, D_3 and D_5 exist not only in the nerve endings of the intestinal wall, but also in the intestinal mucosa. D_3 is a key factor involved in the reward circuit of the midbrain limbic dopamine system and is closely related to the 5-HT energy of the central nervous system. D_2 exists only in the nerve endings of the intestinal wall and is involved in regulating the mesencephalic limbic reward pathway, and six loci have been found to be closely related to the pathogenesis of depression. D_4 exists only in the intestinal mucosa [16].

Norepinephrine (NE) neurons are located in the locus coeruleus of the brain and communicate through NE. They are divided into α and β receptors, where the increase of the activity of subtypes of receptors $\alpha 2$ can lead to the decrease of NE release and the aggravation of depressive symptoms.

The occurrence of epilepsy, depression and many other neuropsychiatric diseases are related with GABA (γ-Aminobutyric acid). Functional defect, abnormal level and receptor dysfunction of GABA can all induce depression.

Short chain fatty acids (SCFA), includes formic acid, acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid, valeric acid, etc., are the metabolites of intestinal flora and important energy source of intestinal epithelial cells. It can affect intestinal mucosal barrier, induce T cell differentiation, and play immune regulation and anti-inflammatory functions [17]. The production of SCFA changes with flora structure. It can enter the brain through the blood-brain barrier and is an important signal molecule connecting the function of intestinal flora-intestinal-brain axis. It can increase the release of sympathetic NE, stimulate intestinal chromaffin cells to produce 5-HT, and regulate GABA and Glu [18]. Intestinal flora can be combined with intestinal endocrine cells through vagal afferent fibers, and then transmitted to the nucleus tractus solitarius, thalamus, locus coeruleus, amygdala and periaqueductal gray, thereby change the level of neurotransmitters in the brain [19] [20].

The frontal lobe structure of patients with depression will change, including the frontal lobe volume, cortical thickness and surface area, cortical folding coefficient. The volume of prefrontal lobe in patients with depression decreases significantly, especially the volume of dorsomedial and lateral prefrontal lobe [21]. Because the thickness of frontal cortex changes in different parts, the thickness of frontal pole, paracentral gyrus and right medial orbital frontal lobe in patients with depression will increase, and the thickness of left anterior central gyrus will decrease [22].

At rest, patients with depression have abnormal brain activity. Liu *et al.* [23] found that the Cohe-ReHo values of the left medial prefrontal lobe and the left inferior parietal lobule in patients with depression are higher than those in the

control group. The fMRI multimodal scan shows that in the depression group, the Cohe-ReHo values of bilateral striatum, bilateral medial prefrontal lobe and right thalamus increase, while the Cohe-ReHo values of left middle frontal gyrus, anterior cingulate gyrus, hippocampus and right amygdala decrease [24].

However, the current study still has some limitations in the study and diagnose based on imaging technology: 1) for brain structure imaging study, most of them focus on brain area/volume, and few studies are on other variables, such as cortical thickness, surface area, folding coefficient and so on. But the study of these variables may improve the study of brain structural abnormalities and comprehensively reflect the characteristics of brain structure in patients with depression. 2) The study on brain structure, function and metabolism is relatively independent. We should avoid distinguishing too much in study. As a whole, we can explore the connections of important brain regions in structure, function and metabolism, and find key therapeutic targets. 3) At present, there are few studies on the imaging differences of brain structure, brain function and brain metabolism between patients with and without refractory depression, and most of them are cross-sectional studies, which urgently need developmental study of large samples.

3. Therapeutic Method

3.1. Treatment of AD and OCD

GAD is a kind of neurosis mainly manifested by anxiety, accompanied by obvious autonomic nervous dysfunction. Patients often complain of sleep disorder, often or continuously have tension without clear object or fixed content, excessive worry about things, often accompanied by neurological symptoms such as depression and mental weakness [25]. Compared with decades ago, the GAD patients are no longer mainly with liver depression and Qi stagnation, but caused by mental tension and excessive thinking in the viewpoints of TCM. Excessive thinking, insufficient blood and loss of mental health can all lead to mental disorders and anxiety. AD can also cause the lack of heart Yin, hyperactivity, hot flashes, night sweats, five heart upset heat, dizziness, tinnitus, pulse count and other symptoms. Based on the above pathogenesis, Tianwang Buxin Dan is often selected to treat generalized anxiety due to heart Yin deficiency.

At present, the main drug for the first-line treatment of GAD is benzodiazepines, but this drug has great side effects. Most patients are highly dependent on this drug, and will develop resistance to it, with poor compliance. Other drugs such as serotonin inhibitors, adrenergic receptor blockers are not only expensive, but also have many side effects. Buspirone type drugs have no obvious side effects, but they take effect slowly and have selectivity in the treatment of AD. People have to look for other more safe and effective drug, which provides a broad space for giving play to the advantages of TCM in the treatment of AD. Modified Wendan Decoction can improve the behavior of either AD or depression, and its antidepressant effect may be better than that of anti AD.

TCM, such as wild jujube kernel, cypress kernel, ophiopogon japonicus, angelica sinensis, radix scrophulariae, salvia miltiorrhiza, codonopsis pilosula, schisandra chinensis, polygala, poria, cauliflower, rhizoma cyperi, acacia flower, rose generation flower, raw dragon tooth, pearl powder, are found to have good curative effect when used for treatment of GAD.

Except for treatment by using drug, comprehensive nursing intervention for anxiety patients can reduce anxiety scores and improve sleep quality, which is conducive to the improvement of comprehensive quality [26]. Cognitive behavioral therapy and psychosocial support combined with paroxetine can alleviate the anxiety level of anxiety and depression patients, improve mindfulness and psychological elasticity, and improve the quality of life of patients [27].

OCD often occurs companying with AD. Sometimes OCD patients suffer from AD and depression at the same time. So the treatment scheme of these illnesses is similar. The drugs often used for OCD are serotonin reuptake inhibitors (SRI), including fluoxetine and serotonin reuptake inhibitors (SSRI) such as paroxetine, sertraline, citalopram and escitalopram, similar to that for AD and depression. However, the OCD usually needs to take large doses of drugs in the treatment relative to AD and depression, so not only side effects are more, but also drug resistance is easier to happen. The efficiency is not more than 60% and easy to relapse. Therefore, psychotherapy (such as cognitive behavioral therapy, Mindfulness cognitive therapy, Morita therapy, psychoanalysis) or psychotherapy combined with drugs are often used for treatment of OCD. In recent years, the surgical methods such as anterior cingulate gyrus destruction, internal capsule forelimb destruction, vagus nerve stimulation and deep brain electrical stimulation are used to treat OCD. Many regulating drugs of glutamate system are used in the treatment of refractory OCD, such as N-methyl-D-aspartate receptor (NMDAR) antagonists and NMDAR agonists, and some of them show significant effects.

3.2. Treatment of Depression

Metformin is a first-line drug for the treatment of T2DM (type 2 diabetes). It is safe and can play an antidepressant role through anti diabetes, anti-inflammatory, anti-oxidation, direct repair of damaged hippocampal formation and other mechanisms. The reactivity of metformin in the treatment of depression is closely related to gender. The dose of metformin used to improve depression is equivalent to that used to treat T2DM, but the sample size of the current study is small, and no large cohort study of antidepressant by metformin has been carried out in China [28].

Drugs traditionally used in clinical treatment of depression include selective 5-hydroxytryptamine (5-HT) reuptake inhibitors, 5-HT and norepinephrine reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors [29]. However, these antidepressants have some limitations in clinical treatment. For example, monoamine drugs will take weeks or even months to produce a therapeutic response. Studies have shown that glutamatergic drugs (such as la-

motrigine and riluzole) can produce faster and more lasting antidepressant effects, but the efficacy of these drugs is limited, and drug resistance will appear in 20% - 30% of patients with depression [30]. In addition, long-term use of antidepressants is likely to lead to metabolic abnormalities in patients (such as increased body mass, hyperglycemia, high abdominal blood glucose, hyperinsulinemia, insulin resistance (IR) and lipid metabolism disorders), which may aggravate GAD or induce diabetes [31].

TCM can protect nerve cells by inhibiting the activation of NLRP3, so as to reduce depression [32]. TCM classifies depression as "depression syndrome". At first, Qi stagnation is the main cause of depression, then the pathogenesis slowly transforms to actual symptom such as fire, blood stasis, phlegm, food stagnation, dampness stagnation, and so on. At this moment, damage of the function of viscera (heart, spleen, kidney) will occur due to long illness. It is found that one of the mechanisms of antidepressant effect of TCM is due to the oligomeric domain of binding nucleotides, leucine rich repeats and inflammatory signal pathway containing pyridine domain 3 (NOD like receptor 3, NLRP3).

As the main active component of cinnamon, trans cinnamaldehyde has the anti-inflammatory, hypoglycemic and neurological functions. Trans cinnamaldehyde can inhibit activation of NLRP3 pathway and NF-κB pathway in the prefrontal cortex and hippocampus [33].

Many TCMs are developed to treat depression. The mechanism for treatment has been studied detailed. Shugan Jianpi Recipe can promote NLRP3 to enter cells to separate the Caspase-1 from ASC complex, and release IL-1β. The proportion of myeloid suppressor cells will decrease based on TLR4/NF-κB inflammatory pathway and then affects the immunosuppressive microenvironment. It is thought that this may be the main mechanism of Shugan Jianpi Recipe on the apoptosis of depression [34]. It is found that Chaihu Shugan powder can inhibit the inflammatory response of liver and prefrontal cortexmediate by regulating the activation of NLRP3 pathway and mediating the routing of TLR4/NF-κB. It is the mechanism that Chaihu Shugan powder improves depression [35]. Mahuang Fuzi Xixin decoction can alleviate depression by regulating NLRP3 pathway and enhancing neurogenesis pathway [36]. Banxia Houpu Decoction can play an role in antidepressant by regulating NLRP3 pathway in liver, hypothalamus, hippocampus and prefrontal cortex [37]. Xiaoyao Powder can regulate NLRP3 pathway and reduce caspase-1 and IL-1 β to protect cortical cells and improve depression [38].

Suanzaoren Decoction is often used to treat patients with depression. According to the research results, there are 309 active ingredients in Suanzaoren Decoction and 111 action targets to depression. The main active ingredients are saponins. There are 1496 intersection targets between insomnia and depression. Suanzaoren Decoction and depression and insomnia have a total of 42 targets. By using the integrated pharmacology platform, it is found that the three (Suanzaoren Decoction, depression and insomnia) work together on 6 key targets: HTR1A, HTR2A, DRD2, CYP2D6, GABRA1 and GABRB2. Suanzaoren Decoc-

tion regulates the signal transmission of nervous system and endocrine system by stimulating these six key targets, such as serotonin receptor pathway and dopamine receptor pathway, so as to regulate neurotransmitters in the brain and achieve the effects of calming nerves and antidepressant. Therefore, Suanzaoren Decoction can prevent insomnia and depression through multiple ways, multiple targets and multiple links [39].

The key to the pathogenesis of depression is that the Qi is disordered due to excessive worry, or uncontrollable joy and anger, or depressed mood for a long time. The brain activity is suppressed and so it cannot play its corresponding integration and regulation role, resulting in the occurrence of depression. That means, the location of the pathogenesis of depression is in the brain [40]. In patients of first-episode depression, the functional connection between the posterior cingulate gyrus or precuneus of the throat of DMN and other brain regions decreases when the patients do not receive drug treatment.

Exercise can effectively regulate the formation of specific parts of the central nervous system, the concentration of neurotrophic factors, the level of glucocorticoids and the release of proinflammatory cytokines, and induce hippocampal neurogenesis in the central nervous system, so as to effectively stimulate the central nervous system and alleviate the symptoms of depression. Therefore, it is suggested to take exercise as an effective intervention to alleviate depression [41].

Bupleurum Liver-Soothing Powder is composed of Frigid Extremities Powder removing Zhishi (Fmctus Aurantu Immatu-rus) but plus Chenpi (Pericarpium Citri Reticulatae), Zhiqiao (Fructus Auraraii), Xiangfu (Rhizoma Cyperi) and Chuanxiong (Rhizoma Chuanxiong). It has the effects of soothing the liver, moving Qi and promoting blood circulation and relieving pain. In this formula, Chaihu (Radix Bupleuri), Baishao (Radix Paeoniae Alba), Zhiqiao (Fructus Aurantii), and Xiangfu (Rhizoma Cyperi) all have certain anti-depressant effects. Combined with these four herbs, the simplified formula of Bupleurum Liver-Soothing Powder is used to intervene in depression-like rats. It is found that it can effectively improve the state of depression through a variety of ways [42].

Melatonin (MT), also known as pineal hormone or melatonin, is an indole heterocyclic compound secreted by the brain pineal gland. After synthesis, MT is stored in the pineal gland and released by sympathetic excitation. MT is an endogenous hormone which can regulate circadian rhythm, neuroendocrine, immune function and synaptic plasticity, and is closely related to the pathogenesis of depression. Clinical trials find that the level of serum MT in patients with depression is significantly increased. The antidepressant mechanism of MT involves the regulation of hypothalamic-pituitary-adrenal (HPA) axis, cytokines, synaptic plasticity and monoamine neurotransmitters. Compared with MT, its receptor agonist has the characteristics of long half-life, high absorption rate and more obvious curative effect. Therefore, MT receptor agonists, as a drug that can effectively treat depression and sleep disorders with relatively small adverse

reactions, have received extensive attention in recent years. Agomelatine (AGO) is an agonist of MT1 and MT2 receptors. High fat diet will produce oxidative stress on the central nervous system, which is easy to cause mood disorders and neuroinflammation. Agomelatine treatment can reverse depressive symptoms and reduce the levels of cytokines TNFα, IL6 and IL1β and restore the levels of BDNF and the activities of catalase and glutathione peroxidase. GW117 is a derivative compound of agomelatine, a new serotonin receptor antagonist and MT1 and MT2 receptor agonist. Compared with agomelatine, it has better antidepressant effect. Ramelteon (RMT) is an MT1/MT2 agonist and has a significant clinical improvement effect on patients. Compared with healthy people, the content of BDNF, NGF and other neurotrophic factors in patients' serum is reduced, while the levels of inflammatory factors such as IL6 and IL1β increase significantly. RMT treatment can normalize the levels of serum neurotrophic factors and cytokines [43].

3.2.1. Treatment of Depression from Microorganism Gut Brain Axis

Viable bacteria refer to living microorganisms that can have beneficial effects on human health when taken in sufficient quantities. This beneficial effect is not limited to the gastrointestinal tract, but may also include the entire microbial gut-brain axis, in which probiotics that can improve behavior and mental state are called mental probiotics. Taking psycho probiotics can increase the level of key neurotransmitters in the pathogenesis of depression. However, the number of bacteria that can be used as probiotics is small, and the disturbance of intestinal microbiota may limit the improvement of depression.

Fecal microbiota transplantation is to clean up the intestinal microbiota of patients with depression and transplant a new human intestinal microbiota at one time, which will greatly improve the curative effect and maintain the therapeutic effect for a long time. This treatment can provide a relatively large number and diversity of bacteria, but fecal microbiota transplantation also has adverse reactions, including abdominal discomfort, spasm, abdominal distension, hiccups, nausea, vomiting and diarrhea. Eating and drinking is particularly important for improving the health of intestinal microorganisms. In areas with low socio-economic level, the consumption of probiotics and fermented food is less, so the degree of depression is higher [44].

The primary motor cortex (M1) of patients with depression has a tendency to be damaged and its plasticity decreases. M1 area is involved in physical activity and muscle control, and also plays a role in cognitive process. The key symptom of depression, loss of pleasure, is considered to be related to the dysfunction of dopaminergic nervous system, because this area holds the reward system closely related to pleasure. Dopaminergic nervous system dysfunction is also closely related to depression with insomnia. Insomnia in patients with depression is usually manifested in difficulty in falling asleep, easy to wake up and early awakening. Their sleep EEG usually shows the reduction of slow wave sleep (SWS) and the extension of rapid eye movement sleep time (REM).

Depression is closely related to respiratory diseases. It shows that not only respiratory diseases can often be complicated with depression, but also the severity of depression affects the prognosis and outcome of respiratory diseases, which brings certain difficulties to clinical diagnosis and treatment. The reason is not only that lung disease is painful and difficult to heal, which brings psychological pressure and economic burden to patients, but also has a certain molecular theoretical basis. For example, chronic obstructive pulmonary disease (COPD), a common chronic disease in the elderly, has been confirmed by many studies to have a concurrent relationship with depression. COPD patients' lung tissue produces a large number of inflammatory factors such as IL-8, IL-6 and TNF-*α*. It can not only stimulate inflammatory response and promote airway changes, but also act on the nervous system through the blood-brain barrier, affecting the release of neurotransmitters and emotional regulation disorders, leading to depression [45].

Patients with depression often have autonomic nerve dysfunction, which is manifested by abnormal sympathetic excitation and parasympathetic inhibition. Sympathetic nerve excitability continues to increase, and the content of catecholamine in blood increases, which becomes a risk factor for coronary heart disease, arrhythmia and other circulatory system diseases. Patients with depression often have gastrointestinal dysfunction, such as gastroesophageal reflux disease (GERD), functional dyspepsia (FD), irritable bowel syndrome (IBS) and gastric ulcer. Many patients with depression often go to the hospital with gastrointestinal symptoms as the primary reason. When evaluating the depression scale for patients with refractory gastrointestinal diseases, it is found that more than half of them are in a depressed state, which suggests that depression has a great impact on the function of the digestive system [18]. In clinical diagnosis and treatment, it is easy to find that many patients with depression have symptoms of frequent urination, urgency or leakage of urine, which are most common in elderly women, and are considered to be related to overactive bladder (OAB). Depression and OAB usually affect each other. Patients with depression reduce social interaction due to the embarrassing situation of frequent urination or urine leakage, which aggravates their condition. OAB is more difficult to cure because of patients' negative attitude and low mood. Some scholars have found that the abnormal function of prefrontal cortex (PFC) in patients with depression weakens its inhibitory effect on the occurrence of stress-related depression, leading to the over activation of HPA axis and promoting the occurrence of depression. Bone mineral density (BMD) of most patients with depression is lower than normal level, often accompanied by osteoporosis. A considerable number of patients with brittle fracture in orthopedics department are accompanied by depression, which suggests that depression is also a risk factor for BMD reduction and fracture. Some scholars measured the BMD of the left femoral neck, greater trochanter and ward triangle in patients with depression, and found that BMD in all parts was lower than normal, and women were even lower than men. BMD level was negatively correlated with the degree of depression and the course of

disease. The reason may be as following: the content of testosterone and estradiol and other sex hormones in patients with depression decreases, and they are both directly involved in the formation of bone and the inhibition of osteoclast function. HPA axis disorder leads to the increase of glucocorticoid release and inhibits osteoblast formation and promotes osteocyte apoptosis. Leptin (LEP) levels in patients with depression are reduced. LEP can not only directly act on osteoblasts and promote their differentiation, but also act on the central nervous system and gonads, indirectly affecting bone formation [33]. More and more researchers find that the occurrence and development of depression are synchronized with the occurrence of immune inflammatory response, suggesting that there is an interactive relationship between depression and the immune system. A large number of clinical experiments show that the activation of inflammatory factors such as CRP, IL-1, IL-6, TNF-α is a key factor affecting the progression of depression.

3.2.2. Other Methods of Treatment

Except for the treatment of depression by drugs, there are other methods of TCM.

Acupuncture therapy: Acupuncture therapy can treat this disease by regulating the whole body's meridians and Qi. Through statistical analysis of the acupoint selection mentioned in the clinical reports of acupuncture for post-stroke depression, it is concluded that all acupoints are ranked according to the total frequency of use, among which the top ten acupoints are Baihui, Taichong, Neiguan, Sanyinjiao, Shenmen, Zusanli, Sishencong, Hegu, Yintang, shenting. In conclusion, acupuncture alone can improve the depressive symptoms of patients [46].

Electroacupuncture therapy: Electroacupuncture therapy is a treatment method in which a trace current wave of human bioelectricity is applied to the needle after acupuncture to get Qi. Study shows that the total effective rate of treating depression by using electroacupuncture therapy is 90% (Baihui, Yintang, Sishencong points supplemented by acupuncture), significantly higher than the WM.

Moxibustion treatment: Moxibustion can significantly improve the symptoms of patients with depression with less adverse reactions. Moxibustion is simple to operate, and patients can treat themselves at home. So doctors can guide patients to carry out moxibustion treatment by themselves in home.

Massage therapy: Guided by the theory of TCM and combined with the relevant knowledge of WM, massage acts on specific parts of the body surface with manipulation to regulate the body and achieve the purpose of physiotherapy.

Ear acupoint therapy: "The ear is gathered by the imperial veins", so clinically, it can achieve the effect of treating diseases by stimulating the acupoints on the ear [12]. The auricular points were needled and stimulated by electroacupuncture. The auricular points were selected as Shenmen, brain stem, heart, liver and kidney. The results showed that the treatment effects is significant and the adverse reactions is less.

Acupoint application therapy: Acupoint application therapy is to select appropriate TCM according to different TCM syndrome types. For depression, four specific acupoints of Xinshu, Ganshu, Pishu and Shenshu are often selected for application. The clinic trials indicates that acupoint application of TCM has a good effect on depression.

Cupping therapy: For cupping, the acupoints on the dorsal governor vessel and bladder meridian are mainly used. In the point of TCM, Qi stagnation is mostly responsible for depression. The acupoints on the Du Meridian and bladder meridian can stimulate Yang through cupping stimulation, which plays a role in warming Yang and transforming Qi and regulating consciousness.

Acupoint catgut embedding therapy: According to the theory of TCM, acupoint catgut embedding is to embed absorbable surgical thread into acupoints to stimulate acupoints and regulate the body. Depression, as a disease requiring long-term treatment, is difficult for patients to adhere to acupuncture treatment for many reasons. Acupoint catgut embedding provides an alternative.

3.2.3. Combined Treatment of TCM and WM

Combined treatment of TCM and WM can shorten the onset time, alleviate physical symptoms and prevent adverse reactions. Mild depression can be treated with TCM or acupuncture alone; Moderate and severe depression requires antidepressants as the main treatment and TCM as the auxiliary treatment; Severe depression caused by mental trauma needs WM combined with acupoint stimulation and regulation [47].

In the combined treatment of TCM and WM, we should first reasonably use the psychological evaluation scale to correctly evaluate the condition of the disease, so as to provide a basis for the determination of the treatment plan. Antidepressant WM is the most common method of mainstream medicine to treat depression, but its curative effect is often relatively slow, and the effective rate is less than 50%. Because of the uniqueness of TCM and a relatively systematic theoretical understanding and rich diagnosis and the accumulated treatment experiences in the perennial clinical practice of depression syndrome, TCM can play an active role in the prevention and treatment of depression. The advantages of TCM in the treatment of depression are more reflected in the consolidation and maintenance treatment of mild to moderate depression and depression. The combination of the two can achieve the effect of complementing each other and is often better than that of a single method. For example, the effect of Shugan Jieyu capsule combined with scitalopram oxalate or Jieyu Decoction combined with electroacupuncture Baihui, Sishencong, and combined acupuncture and medicine is more ideal. According to the specific condition of patients, the reasonable use of integrated TCM and WM can significantly improve the cure rate and quality of life of patients [48] [49].

4. Conclusions

Through the comprehensive analysis of the current research and treatment

progress of OCD, AD and depression, it is found that there is a basic consensus on the pathogenesis of these diseases. Only with treatment, although people have put forward a variety of treatment schemes, there are advantages and disadvantages to any existing treatment methods, such as WM has relatively fast effect but large side effects, as for TCM, though the side effects are small, liver and kidney damage can occur after long-term use, acupuncture and moxibustion have a downward trend in long-term treatment. The effect of combined treatment of TCM and WM is more ideal, which can not only effectively improve the mental state of patients, but also will not cause serious adverse reactions.

Due to the heterogeneity of such mental disorders, individualized treatment is the best choice, and TCM syndrome differentiation is the paradigm of individualized diagnosis and treatment. Therefore, it can be considered that the prevention and combined treatment of TCM and WM will play an important role in the future diagnosis and treatment. Of course, there are still many problems in the combined treatment of TCM and WM, such as the lack of integration of the guiding ideology of TCM and the theoretical system of WM; There are many classifications of TCM syndromes, which makes the comparability and repeatability of clinical research obviously insufficient. At the same time, doctors often use drugs based on clinical experience, and the dosage is not fixed, which cannot be quantified and difficult to repeat verification; the evaluation scale is easy to be subjectively guided by doctors and lacks specific objective indicators. Therefore, there is still a lot of work to be done in the diagnosis and treatment of this kind of disease, especially in the combined treatment of TCM and WM.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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