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The Treatment of Bipolar Disorder

Xinyue Li *

College of Pharmaceutical Biotechnology, Chins Medical University, Shenyang, China

* Corresponding Author: 2019446704@stu.cmu.edu.cn

Abstract. As a relatively large class of neurological diseases, bipolar has always been an important object of research and exploration by scientists. When bidirectional patients develop the disease, they are aggressive and a great burden for their families. Therefore, how to treat bipolar has been a hot topic. Current treatments for bipolar include medication, psychotherapy, and physiotherapy. Drug therapy includes mood stabilizers, antidepressants, anticonvulsants, antipsychotics and so on. Psychotherapy is aimed not only at the patient, but also with his or her spouse and relatives. Treatment modalities include psychoanalytic therapy, analytic psychotherapy, cognitive behavioral therapy, suggestive therapy, and supportive therapy. However, different treatment modalities have certain limitations. For example, drugs have certain side effects and may cause complications during treatment. Psychotherapy is more limited by the patient. Physical therapy may cause memory impairment, nausea, headaches, etc. This review is about current treatment modalities for bipolar and their limitations.

Keywords: Bipolar disorder; BDNF; Treatment.

1. Introduction

Bipolar is a kind of recurrent psychiatric disorder that alternates between mania and depression of varying degrees. According to the 2013 American Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), BD is expanded into bipolar spectrum disorder and is divided into differnet types, such as type I, type II, cyclothymic disorder, substance- or drug-induced bipolar and associated disorders and so on. Bipolar disorder can occur at any age for the first time. In most patients, the average age of onset is 17.3 years [1]. Men and women both have bipolar I at roughly the same rates, although women are more likely to experience type II. Male patients mostly develop in the form of manic episodes, while women's first onset is mostly manifested as depressive episodes [2], or more depressive episodes or mixed episodes in the course of the disease, and the onset time is more likely to occur in menopause and postpartum, which may be related to factors such as endocrine system dysfunction. The incidence of bipolar disorder has been on the rise in recent years. The World Health Organization claims that the average incidence of BD worldwide is 2%-3%, and some countries or regions can be as high as 5%-7%. Factors that predispose to bipolar include genetic factors and environmental factors. In addition, childhood experiences, social environment, seasonal changes, etc. all will influence the occurrence of bipolar disorder. Bipolar has a high mortality rate, mainly due to suicide and cardiovascular disease [3], especially suicide, which is a significant problem in patients with bipolar disorder. Therefore, suicide prevention should be a focus of bipolar treatment.

Treatment of BD includes medication, psychotherapy, physical therapy. Commonly used drugs for the treatment of BD include mood stabilizers, antidepressants, anticonvulsants, classical and non-classical antipsychotics. But medication is often accompanied by certain side effects. The most typical side effects are weight gain, metabolic disorders, sedation or lethargy, and akathisia [4]. These side effects, such as weight gain and metabolic disorders, may in turn affect the therapeutic effect of the drug. Treatment of BD also includes psychotherapy. Psychotherapy includes individual, couple or group, and family therapy. Psychotherapy is given to patients from different aspects to reduce the impact of psychosocial factors on patients. However, psychotherapy should only be used as an adjunct, and if necessary, a combination of medication is a better option. Physical therapy include electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). ECT is a common

method in the treatment of BD. It is generally used in the early stages of psychotic depression or in the setting of inadequate response to medical therapy [5]. The results showed that ECT played a good role in mania and depression studies. However, ECT may cause some memory loss, and other side effects include common transient headaches, muscle pain, nausea from anesthesia and, rarely, bone and soft tissue damage, prolonged seizures, and mania-induced attacks [6]. Transcranial magnetic stimulation is an emerging treatment with fewer and milder side effects, but more trials are needed to confirm the definitive answer to the treatment of bipolar [6].

As a mental illness with high mortality and disability rates, the treatment of bipolar has always been a challenging problem. At present, the treatment of bipolar mostly adopts combination therapy, and a variety of ways are combined to solve the different effects of bipolar from different directions. Starting from the treatment methods of bipolar, this article discusses and summarizes the different treatment methods of bipolar, their disadvantages and limitations, and looks forward to the future development of bipolar treatment.

2. The pathogenesis of bipolar disorde

Factors influencing BD include environment factors and genetic factors. Among them, environment factors also include natural environment factors such as climate and season, and social environment factors such as trauma and life events. Different factors may not belong to more than one category, so their classification is also an important issue (Figure 1) [7]. The influence of genetic factors on biphasic is mainly caused by the damage caused to the nervous system. It may be related to certain genes, for example, brain-derived neurotrophic factor (BDNF) gene, neuromodulin 1 (NRG1), etc.

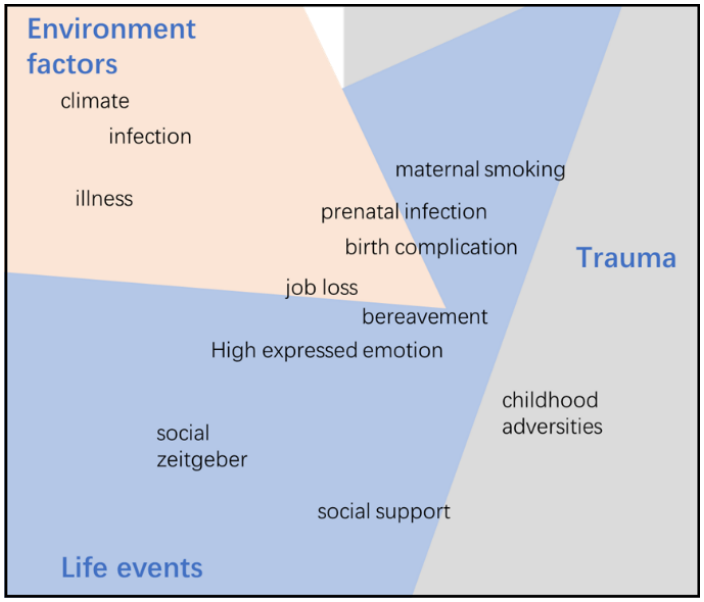

Figure 1. Environment factors of bipolar disorder [7].

2.1. Environment factor

The patients who suffer from bipolar disorder may have a history of childhood trauma. Although there is still little research on the effects of childhood trauma on bipolar, the influence of it for bipolar disorder is still certain. The effects of childhood trauma on bipolar are caused by advancing the age of onset have been confirmed by some studies [8]. Additionally, the likelihood of substance abuse, rapid cycling, the occurrence and frequency of psychosis, and suicidal thoughts and behaviors all increase because of childhood trauma, which is more common in women.

Bipolar disorder has strong seasonal characteristics, and changes in the seasons may cause changes in mood. According to surveys, manic episodes will usually occuar in spring, depressive episodes are more usual in early winter, and mixed or ambiguous episodes occur in early spring [9]. Second,

women have more features of seasonal episodes than men. In addition, climatic factors, for example, sunshine, temperature, may influence the recurrence of bipolar disorder.

A social event is any significant change in the personal and social consequences that arise in an individual's environment [7]. For example, changes in biological circadian rhythms may have an impact on emotional stability. Both positive and negative life events can trigger mania and depression. Goals, bereavement, and so on can trigger mania, and individual illnesses are more likely to lead to depression. According to investigations, the occurrence of depression has a certain relationship with the quantity of life events, but has nothing to do with the quality of life events. Post's kindling hypothesis points out that the first episode is more affected by outside factors, including life experiences, than the future episodes. At the same time, the occurrence of recurrent episodes is more independent of life events and generally autonomous [7].

Social support is a perception or experience that generally refers to various supports from outside the individual as part of the mutual support of social networks. Most surveys suggest that social support has some effect on bipolar. Social support is decreasing and is linked to relapse and rehabilitation. At the same time, there are studies that show that social support has a certain specificity, that is, it has an impact on depression, but does not affect mania [10]. In addition to social support, the course of bipolar disease is also influenced by family behavior. For example, the impact of criticism from relatives on depression and mania can cause symptoms to show more severe signs. At present, surveys of the impact of social support on bipolar use self-assessment tools, and the conclusions are influenced by subjective emotions, so the results are often variable.

2.2. Genetic factors

Bipolar disorder carries a higher genetic risk, especially in families. The lifetime rate of bipolar among relatives with pre-certification for the disorder is about: 47-70% for identical twins; First-degree relatives 5-10%; No relatives: 0.5-1.5% (Table 1) [11]. The majority of cases of bipolar disorder involve complicated genetic pathways or the interaction of several genes. Genes including BDNF, DAOA, DISC1, GRIK4, SLC6A4 and TPH2 are undergoing independent studies to prove their link to bipolar, but have not yet been confirmed [12]. However, genome-wide association analysis has successfully identified susceptibility genes for various complex diseases and suggested that DGKH, CACNA1C, and ANK3 are specific genes for BD [12].

Table 1. Approximate bipolar disorder and unipolar depression lifetime rate of different proband relatives [11].

Degree of relationship to bipolar proband	Rate of bipolar disorder (%)	Rate of unipolar depression (%)
Identical twin	40-70	15-25
First degree relative	5-10	10-20
General population	0.5-1.5	5-10

In general, adding the risk of bipolar disorder and unipolar depression in relatives gives the probability of a relative's lifetime risk of developing moderate to severe psychological disorder. However, quantifying the lifetime risk of unipolar depression in the general population is difficult, so the data in the table above are based on clinical definitions comparable to those used in genetic studies for significant depression.

How genes influence bipolar disorder, take BDNF as an example. BDNF is a protein with neurotrophic effects that is widely expressed in the nervous system. It promotes the formation and differentiation of new neurons and synapses while assisting in the survival of already existing neurons. The control of emotional control areas of the brain, such as the prefrontal cortex and hippocampus, as well as related changes in neural circuits, are inseparable from the BDNF gene. Antidepressants and neuroplasticity changes are regulated by it, thereby improving depressive symptoms. Single nucleotide polymorphisms in the BDNF gene, i.e., valine at val66met, substitute methionine, are

involved in altered transport of BDNF. When val66met mutates, BDNF expression decreases, which leads to increased Amygdala activity, which leads to depression and anxiety. Figure 2 shows the mechanism of action of BDNF [13].

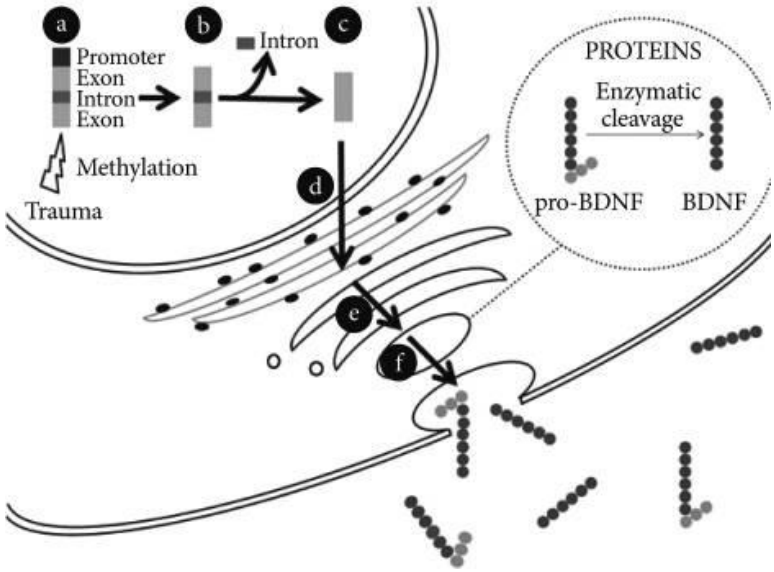

Figure 2. The mechanism of action of BDNF [13].

BDNF genes include promoters, exons, and introns, and their expression may be regulated by epigenetic mechanisms. When traumatized, BDNF gene methylation can be induced, inhibiting its transcription. Activating different promoters can produce different mRNA transcripts. Introns are removed to form processed mRNAs ready for translation. The mRNA is transferred from the nucleus into the cytoplasm and translated into proBDNF in the endoplasmic reticulum. proBDNF enters the Golgi apparatus and is cleaved by terminal proteases to form mature BDNF. The vesicles wrap BDNF and merge onto the cell membrane and release the BDNF outside the cell.

3. Treatment methods of bipolar disorder

The treatments of BD include medication, psychotherapy, and physical therapy such as electroconvulsive therapy, and transcranial magnetic stimulation. The following is a detailed discussion of the situation related to different treatment methods.

3.1. Medication

Treatment drugs used for BD include mood stabilizers, anticonvulsants, antidepressants, and atypical antipsychotics. The U.S. Food and Drug Administration (FDA) has approved several drugs for the treatment of bipolar disorder. Depending on the condition, they are approved for the treatment of different conditions, such as the treatment of manic Lithium, Valproate, Carbamazepine, Chlorpromazine, Asenapine, Cariprazine, etc.; Lithium, Lamotrigine, Aripiprazole, Ziprasidone, etc., which play a preventive maintenance role; Olanzapine, Quetiapine, Lurasidone, etc. for the treatment of bipolar depression. Among them, Carbamazepine is a sustained-release formulation; Olanzapine, Risperidone, Quetiapine and so on can increase anti-manic efficacy under the action of lithium or valproate; Olanzapine needs to be used with fluoxetine in the treatment of bipolar depression; Quetiapine and Ziprasidone need to be added with lithium or valproate for preventive maintenance; Lurasidone can be used in patients aged 10 to 17 years [14].

Depending on the bipolar patient, treatment is carried out in stages.Mood stabilizers are used as first-line agents at all stages of bipolar therapy [5]. The most commonly used mood stabilizers include lithium, valproic acid (VAP), and carbamazepine. Among them, lithium is a gold-standard mood stabilizer that can be used to fight mania, depression, and suicide. The main targets of lithium and VAP are the glycogen synthetase kinase-3 of lithium and the histone deacetylase of VAP. They

induce the transcription and expression of neurotrophic proteins, angiogenic proteins, and neuroprotective proteins for therapeutic effects. Carbamazepine is an inducer of the enzyme CYP450 3A4, which is metabolized by CYP450 3A4 in the liver. It can reduce dopamine turnover, regulate other neurotransmitters, and exert neuroprotective functions[15].

If mood stabilizers do not work or are not available, anticonvulsants will be a second option [9]. Such as lamotrigine, lorazepam, diazepam. When bipolar is first present, different drugs are generally selected for treatment depending on the initial situation [5]. For example, For the first episode of hypomania or mild depression, mood stabilizers such as lithium or divalproex are generally selected; If mixed or dysmanic disorder may use divalproex; For manic concomitant psychosis, divalproex or lithium in combination with antipsychotics may be used; For more severe depression, lithium or divalproex may be used with an antidepressant, or if delusions are also present, an atypical antipsychotic may be added; divalproex may be used if the initial onset is mania or depression with recent rapid cycling [5]. Long-term prophylactic treatment of biphasic is usually treated with lithium or divalproic acid, or a combination of both. In addition, triple therapy with valproic acid in combination with lithium and carbamazepine is also effective [5].

3.2. Psychotherapy

Medication is only one part of the treatment of BD, and its use and specific results are largely influenced by the patient's own actual situation. When patients are resistant to their own reasons, such as fear of side effects, negative emotions for treatment, etc., the decline in compliance will greatly reduce the therapeutic effect of the drug. Therefore, through psychotherapy, to alleviate the patient's negative emotions and improve the patient's compliance with the drug has become a necessary measure. To date, there have also been many studies that have shown that psychotherapy has great benefits in treating bipolar disorder.

Psychotherapy is primarily interventional, the methods of treatment involve psychoanalytic therapy, analytical psychotherapy, cognitive behavioral therapy, suggestive therapy, and supportive therapy. Through psychotherapy, reducing or eliminating negative emotions such as pain and anxiety caused by current and expected losses can not only help patients treat themselves, but also reduce the cost to families and society when patients are ill. According to the survey, individual treatment improves patients' understanding of the disease and its treatment, giving patients the opportunity to explore. Group therapy is highly feasible and does not disturb the treatment process. At the same time, it enables non-patients to correctly understand the disease and fully understand the difficulties that patients have. Couple therapy helps the spouse understand the disease, clarify the patient's attitude, and reduce stress. Family therapy has better results in women and younger patients. For older men, individual and group therapy worked better.

3.3. Electroconvulsive therapy

Electroconvulsive therapy responses rapidly and is able to show corresponding clinical effects in a short time, so it can be used in emergency situations. As for the efficacy of ECT in the treatment of BD, studies have shown that compared with the pre-ECT treatment, the number of psychiatric hospitalization days and hospitalization times of patients receiving treatment have significantly decreased [16], and most clinical experiences have shown that ECT has a significant effect in the treatment of BD. However, compared with extensive clinical experience, there is still less scientific evidence for the effect of ECT in the treatment of BD, the relevant trial samples are small, and the selected patients themselves are biased. Therefore, the research on the use of ECT in the treatment of BD is still an important issue.

3.4. Transcranial magnetic stimulation

As an emerging therapeutic method, transcranial magnetic stimulation (TMS) acts on the central nervous system through pulsed magnetic fields to provide adjuvant treatment for diseases such as central nervous system injury. TMS has been demonstrated to improve depressive symptoms by

stimulating TMS in the left prefrontal lobe [17]. At the same time, the use of TMS for treatment has few and few side effects, but there are still few trials of TMS for the treatment of BD, and it is uncertain whether it has other effects.

4. Limitations and future development of the treatment

BD treatment has been in development and there are still many limitations and drawbacks to the current treatment modalities. Medication is an unavoidable treatment, so the side effects of drugs cannot be ignored. The most basic side effects include weight gain, metabolic disorders, sedation or lethargy, and akathisia [4]. Olanzapine + fluoxetine can cause weight gain, nausea, diarrhea, and even diabetes and dyslipidemia; quetiapine can cause dizziness, sedation, fatigue, constipation, and weight gain; lurasidone may cause drowsiness, akathisia and akathisia; cariprazine can cause insomnia, nausea, sedation, dizziness and constipation, etc.; lumateperone may cause nausea, dizziness, dry mouth, sedation, etc [18].

In addition to this, the side effects of some medications may cause some complications. For example, lithium has a narrow therapeutic window, making it potentially toxic; Valproate may cause polycystic ovary syndrome; Emotion stabilizers have significant teratogenic effects; Lamotrigine may cause a rash and aseptic meningitis [4]. The side effects of the drug make it necessary to consider the actual situation of the patient during the treatment process to avoid serious consequences. As a treatment for BD, psychotherapy is an adjunct to treatment, and its use often interacts with medication. Moreover, psychotherapy is a long-term process, and it requires patients to be able to open their hearts and face their hearts. As a form of physical therapy, ECT results are positively associated with improved mood and neurocognitive impairment, but may lead to memory loss [6], as well as headaches, muscle pain, and seizures-induced mania.

Due to the complexity of BD, its treatment is often not carried out in a single way, and future research on BD treatment will also focus on multi-mode combination therapy. The specific treatment plan will also be personalized according to the actual situation of the patient, starting from different aspects, considering different situations including effects and side effects, and formulating a more appropriate treatment plan.

5. Summary

Bipolar treatment is still in the developmental stage. Combining medication with psychotherapy and physical therapy, and personalized treatment according to the different conditions of patients, is now a trend in two-way therapy. Psychotherapy is used to clarify the cause of the patient, relieve the patient's mood, and increase the compliance of treatment. Through drug treatment, alleviate and treat the patient's physiological condition to achieve the purpose of treatment. Or supplemented by physical therapy, which stimulates the patient's nervous system through physical means. However, the actual treatment should start from the patient himself, reduce the side effects of treatment, and avoid or reduce the occurrence of complications. At present, there are still many shortcomings and limitations in the treatment of bipolar. In the future, the treatment of bipolar will continue to be explored, reducing the prevalence and recurrence rate of bipolar, reducing the mortality rate of bipolar patients, and curing bipolar will be possible.

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