

# Effects of Antipsychotic Drugs and Antimanic Drugs on Bipolar Disorder

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**Abstract.** The main incidence of Bipolar is concentrated in teenagers, and the fatality rate is as high as 11% and even exceeds that of depression. There are currently 3 mainstream drug treatments, mood stabilizers, epilepsy drugs, and antipsychotics. Mood stabilizers, also known as antimanic drugs, are now the most mainstream treatment centered around lithium. Numerous studies show that mood stabilizers have a very obvious effect on bipolar. It can not only relieve the manic state but also work on the patients in a depressed state. Antipsychotic drugs, also known as strong tranquilizers, are mainly used in schizophrenia, and bipolar disorder, they are mainly used to stabilize manic states but do not work on depression. However, these methods have their limitations. The development of future treatments should take into account the biological and psychological mechanisms of the disease. This article briefly introduces the therapeutic effects of different drugs on BD from clinical data and mechanisms.

**Keywords:** Bipolar Disorder, Treatment, BDNF, Antipsychotic Drugs.

## 1. Introduction

Bipolar disorder is a mental health condition that causes extreme mood swings by emotional highs and lows, we called them mania episodes and depressive episodes [1]. Bipolar attacks are cyclical, but the specific events vary from person to person, some people may have repeated attacks within a week, while others may only have a few attacks a year. Bipolar I disorder is defined as episodes of mania for at least 7 days, while episodes of depressive states may last for more than 2 weeks. Bipolar II disorder does not have as long as the manic periods of the Bipolar I disorder but has longer periods of depression. The main incidence of Bipolar is concentrated in teenagers, and the fatality rate is as high as 11% and even exceeds that of depression. According to statistics, about 4.4% of American adults have experienced bipolar disorder in their lives. Among adolescents, the prevalence of bipolar is significantly higher in women (3.3%) than in men (2.6%). Estimates suggest that about 2.9% of adolescents have bipolar and 2.6% have a severe impairment.

Mood stabilizer treating both mania and depression has a two-way regulatory effect, and maintenance therapy can prevent relapse. Antimanic drugs (such as lithium) are effective for acute mania, depression treatment, and maintenance therapy, but less effective for mixed bipolar, rapid cycling, also one of the most commonly used drugs (toxic) Antipsychotic drugs (second generation) currently plays an important role in the treatment of the bipolar disorder, not only for the treatment of acute manic episodes but also for the depressive episodes and the maintenance therapy for bipolar disorder. This paper first introduces the relationship between Bipolar and BDNF genes, the main pathogenesis and location of Bipolar, and focuses on the effect of Antipsychotic Drugs and Antimanic Drugs.

## 2. The relationship between BDNF gene and Bipolar disorder

The bipolar disorder shows a decreased cognitive function and extreme mood changes, causing the patient to experience depressive mood, sleep disturbance, and attention deficit, all of which increase the risk of suicide and self-harm. Research data gathered from many experiments prove that there is an abnormal gene expression of BDNF and suggest that a decrease in the BDNF gene was one of the significant figures that affect the disorder and is labeled as a biomarker to distinguish bipolar disorder from other depression diseases.

BDNF gene (brain-derived neurotrophic factor gene) is a gene that is implicated in the pathogenesis of the bipolar disorder. It is in charge of encoding the protein BDNF (brain-derived neurotrophic factor), which aids in the growth, survival, and differentiation of neural cells. Most of the time finds its mRNA in the brain and cerebellum, thus correlated with the growth of human brain cells and brain activity. Moreover, the BDNF gene could be interconnected with the symptom of abnormal mood change since the cerebellum plays an important role in motor control and cognitive function like emotional control.

### 2.1. Gene mutation

BDNF Val66Met polymorphism is a missense mutation that is associated with the alteration of the signaling pathway in neurons. The presence of the Met allele may impair the ability of the Golgi body to package the BDNF and transmit them through vesicles. Since the BDNF is transmitted from dendrite to axon or either passes across the synapse to another neuron cells, the Val66Met may cause a deficit in normal BDNF expression [2]. It is thought to impair the plasticity through multiple pathways, which elects a reduction in hippocampal synaptic activity, causes memory loss, and contracts the volume of the hippocampus.

Not only does change the pathway in the hippocampus, but also increases the amygdala activity. The amygdala is a part of the brain that regulate emotion, processing memory, and decision making. However, the role of taking part in the brain's limbic system, which is a group of complexes that responds to emotion and behavior may cause an irrational reaction by the activity of the frontal lobes in the amygdala. The front lobes evaluate your emotion with anger, fear, or stress and respond to a corresponding negative limbic reaction [3]. And the series of amygdala activities are supposed to be the reason for the high risk of suicidal and self-harming behavior.

### 2.2. The reduction of Gai1 & Gai3 proteins regulated the signaling pathway of BDNF-TrkB

TrkB is one of the receptors capable of responding to the BDNF on the cell membrane. Investigation indicates that the reduction of a specific G protein component may result in a reduction in BDNF expression.

Gai1 and Gai3 are subtype members kin the class of Gi/Go in heterotrimeric G proteins. From the research, the Gai1 and Gai3 are required for BDNF to induce TrkB receptor for signaling and regulate their downstream pathways such as Akt-mTORC1 and ERK pathway. Whereas, the series of signaling pathways from dysregulation of Gai1 and Gai3 protein to the BDNF-TrkB pathway and the Akt-mTORC1 is a negative cycle caused by stress.

The research by John Marshall and his colleagues, in a stress model of depression, discover that there is a downregulation of Gai1 & Gai3 proteins in the hippocampus. Hence, the signaling pathway of BDNF-TrkB to their downstream of Akt-mTORC1 is being inhibited or reduced. A reduction in Akt-mTOR leads to cognitive impairment in the prefrontal cortex [4]. And the teams from John Marshall prove it by assessing an experiment between schizophrenia, bipolar disorder, and a control variable for testing Akt-mTOR activity in the prefrontal cortical region [5].

## 3. Serotonin

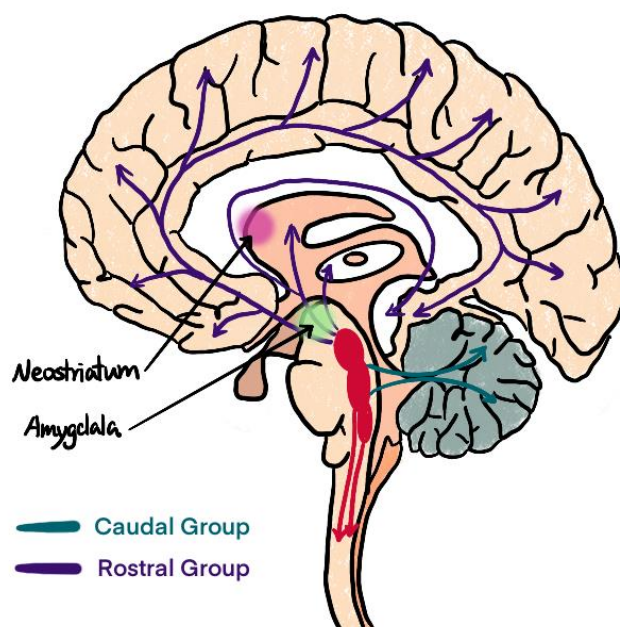
Despite the genetic factor, the research shows that the reduction of some biogenic amines such as serotonin, dopamine, and noradrenaline are all typical to observe in a bipolar disorder patient. The

BDNF level in the hippocampus is also decreased by the increasing stress. Since the BDNF plays a crucial role in brain development via the regulation of neurotrophic outgrowth, synaptogenesis, and cell survival, the concentration of serotonin was also regulated by it [6].

The lower level of BDNF is directly correlated with the decreased serotonin, thus weakening the activity in the human hippocampus and prefrontal cortex. The consequences may result in memory loss, slow thinking, and more difficulty dominating emotional responses. In addition to amygdala activity, a lower level of serotonin may increase the frequency of signaling in the amygdala and generate the emotion of anger and fear. Analyzing the mechanism of serotonin activity, the origin of serotonin is the primary key to comprehension. Firstly, the serotonin is situated at the presynaptic neuron in raphe nuclei, a cluster of nuclei that are found in the spinal column where the serotonin is produced. As a neurotransmitter, serotonin induces neuronal signaling across the synapse and is transmitted all through the brain through a serotonergic pathway (figure 1).

Although there is no exact exploration of the mechanism of how serotonin did affect the level of depression, the transmission pathway tries to explain it. Gain insight into the serotonergic pathway, it is divided into two transmission pathways including the rostral group, and the caudal group. The rostral group is transmitted through the front side of the brain and the caudal group either transmit behind the spinal column.

The particular brain stem they are used to pass through is the dorsal raphe nucleus, and they primarily project to the cerebral cortex, neostriatum, amygdala, and substantial nigra. In this case, the amygdala and neostriatum are correlated with depressed emotion. As mentioned above, the amygdala is the majority storing memory from an emotional event, and it is founded to have a high level of serotonin in the region for regular neuron transmission and function. In addition, the PDE2A in the neostriatum is proved that the most pronounced alteration in the model of bipolar disorder, a lower level of serotonin seems to cause a dysfunction of the striatum [7]. So, when people are having a low serotonin level, they get irritable since the amygdala will aggravate and amplify their emotions, whilst unable to control their feelings due to a lower prefrontal cortex activity.



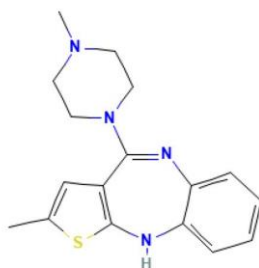
**Figure 1.** The two major pathways of the serotonergic. They are mainly distinguished by the transmission direction. The purple mark is the rostral pathway, and the green mark is the caudal pathway.

## 4. Treatment

### 4.1. Antipsychotic Drugs on Bipolar disorder

#### 4.1.1. Antipsychotics for bipolar disorder.

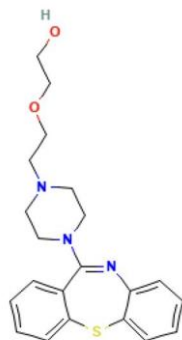
Several antipsychotics have a long history in the treatment of bipolar disorder. They help to reduce psychotic symptoms, such as hallucinations and hallucinations, but some of them show powerful curative effects in a large number of patients with bipolar disorder. At present, the most commonly used drugs for therapists are olanzapine, quetiapine, lurasidone and calipamine.



**Figure 2.** The structure of Olanzapine

Olanzapine (figure 2) is an atypical antipsychotic drug used to treat adults and adolescents aged 13 and over. It is also used to treat the symptoms of schizophrenia because it alters the activity of natural substances in the brain. Olanzapine is a synthetic derivative of thiophene and diazonium Xiping County, with antipsychotic, anti-emetic and anti-emetic properties. As a selective monoamine antagonist, olanzapine binds to the following receptors: serotonin, dopaminergic, m1-5 muscarinic, histamine H1 and  $\alpha$  1 adrenergic receptor, with GABA A, benzodiazepine and  $\beta$  the adrenergic receptor is weakly bound. The antisilencing and antiemetic effects of this drug appear to be due to serotonin blockade by both 5-HT2 and 5-HT3 receptors [8]. Although the exact mechanism underlying the role of olanzapine in schizophrenia is unknown, it has been suggested that the antipsychotic activity of olanzapine is mediated through antagonizing dopamine d2 receptors and that rapid ligand-receptor dissociation kinetics contribute to reducing extrapyramidal symptoms. Common side effects of olanzapine are weight gain, metabolic effects and dopamine blockade. Olanzapine can lead to increased appetite and Bulimia after weight gain. Another side effect of olanzapine is increased metabolic risk. Insulin sensitivity and glucose tolerance may be impaired in young people, especially in young people. Although the exact mechanism of these adverse effects is unknown, there is evidence that the Wnt signaling pathway effector protein TCF7L2 plays a key role in glucose homeostasis [9].

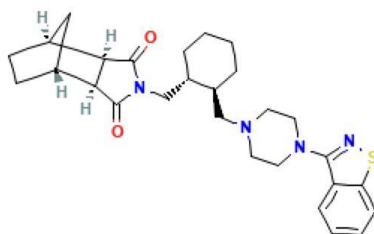
In Olanzapine's clinical trial, Olanzapine's study of patients with bipolar disorder compared the effectiveness of Olanzapine with that of a placebo. In this study, 514 participants were randomly selected from a sample of bipolar disorder aged 18 to 65. The aim of the study was to measure changes from baseline to the end point of the Asperger Syndrome, a 10-item checklist for severe depression. By the end of the study, the mean score in the olanzapine group had decreased by 14 points. Among the 26 units, the average score in the placebo group decreased by 11 points.71 units. This result shows that olanzapine is effective in the treatment of bipolar disorder.



**Figure 3.** The structure of Quetiapine

Quetiapine (figure 3) is an Atypical antipsychotic sustained-release (long-acting) tablet used to treat bipolar disorder in adults and children over 10 years of age, as well as schizophrenia and quetiapine tablets, occasionally in combination with other drPrevent bipolar disorder or depression. Quetiapine has a strong affinity for 5-ht2 receptor. Although, quetiapine has many complex mechanisms, it mainly mediates its pharmacological effects through 5ht2 antagonism. It also acts on dopamine D1 and D2 receptors. Quetiapine is an antagonist of D2 receptor and 5-HT2 receptor [10].

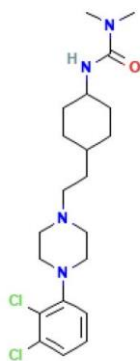
Clinical trials of Quetiapine, quetiapine for bipolar disorder and alcohol dependence, to measure the effectiveness of Quetiapine as an antipsychotic for bipolar disorder (and alcohol dependence), whereas this section only presents the results of studies on the effectiveness of Quetiapine for bipolar disorder. In this study, a total of 90 participants were randomly selected patients with bipolar disorder, aged between 18 and 65. We used the Hamilton Depression Scale (HRSD) to measure depression levels from baseline to end point. The results of this study showed that the score of quetiapine group was 0.6 less than the placebo group, indicating that quetiapine can eliminate the symptoms of bipolar disorder.



**Figure 4.** The structure of Lurasidone

Atypical antipsychotic is a drug used to treat bipolar disorder in adults (also used for schizophrenia) and children 10 years of age and older. Lurasidone is a complete antagonist of dopamine d 2 and 5-ht2a and 5-ht7 receptors (figure 4). Compared with other atypical antipsychotics, it is a part of serotonin antagonist agonists and has the highest binding affinity to serotonin antagonists. It is the blockade of D2 and 5-HT2A receptors that makes reone characteristic of atypical antipsychotics [11].

In the clinical trial of luraceone, luraceone hydrochloride-a six-week phase III study (PREVAIL3), was compared with placebo to measure the efficacy of luraceone. The study was a six week, three blind, phase III trial in which 356 participants were randomly selected from patients with bipolar disorder aged 18 to 75. The rurasidone group's average final score dropped by 11 points. Eight units, the placebo group decreased by 10 units. Four units showed that lurasidone could successfully alleviate the symptoms of bipolar disorder.



**Figure 5.** The structure of Kalizine

Kalizine (figure 5) is an atypical antipsychotic used to treat depressive episodes in patients with bipolar I. It is also used for short term treatment of manic episodes or mixed episodes in patients with Bipolar I disorder [12]. Kalizin has no age limit. Calipiprazine is an n-alkyl piperazine, which is n, N-dimethyl-N '- {trans-4 - [2 - (piperazine-1-yl) ethyl] cyclohexyl] urea, which is replaced by 2,3-dichlorophenyl at the 4 position of the piperazine ring. It functions as dopamine agonists, second-generation antipsychotics, and serotonin antagonists. As a partial agonist of D2 and D3 receptors, it is highly selective for D3 receptors, which is relatively unique because many other antipsychotics are D2 and 5-HT2A agonists [13].

When studying the efficacy of a fixed dose of kalizine versus a placebo for depression in patients with Bipolar I disorder, the efficacy of Kalizine was measured by comparing Kalizine with placebo. The study is the third phase of a fourfold cover experiment in which 493 participants were randomly selected from bipolar patients aged 18 to 65. Finally, there is one carirazine group.5 mg per day, 14 mg less. The average score was 8 units, and the other group scored 3 points. Carbazine decreased by 14 per day. The mean score was 1 unit, while that of the Placebo group dropped by 12 units. These results suggest that carazine is an effective antipsychotic against bipolar disorder.

## 4.2. Antimanic Drugs on Bipolar disorder

Antimanic drugs are one of the most common drugs in bipolar disorder, and we can also call them mood stabilizers. The two most common antimanic drugs are lithium carbonate and Depakote.

### 4.2.1 lithium carbonate

Lithium carbonate can control acute manic episodes and be used for manic relapse, not only for the treatment and prevention of bipolar depression but also for the synergistic treatment of treatment-resistant depression and the prevention of suicidal behavior in patients with mood disorders. That is to say, as long as it continues in a state, lithium carbonate is the first choice. However, it is relatively less effective in the treatment of fast-circulating, mixed attacks.

Although lithium is very effective in reducing mood swings, lithium is also been to be said a difficult and potentially dangerous drug to provide to patients. Because the therapeutic dose of lithium is almost close to its toxic dose, this means that it is uncomplicated to accidentally ingest too much lithium and become poisoned. This can lead to respiratory depression, seizures, coma, and even death. Therefore, before prescribing this bipolar drug, a series of laboratory tests, such as complete blood cell technology, serum, electrolytes, and hormones, must be performed to screen patients for lithium conditions. These tests also need to be repeated periodically during use to allow adequate monitoring of lithium blood levels. Real-time monitoring of renal function is very important in the use of lithium. Because kidney function is crucial for removing lithium from the system, if there is a problem with kidney function and the proper amount of lithium cannot be decomposed in time, lithium poisoning will likely result from accumulation. (Very close and frequent testing of blood lithium levels is required in the early stages of treatment, but as treatment stabilizes, blood testing can be gradually relaxed to every 3 to 6 months).

Normal side effects of lithium have including tremors, weight gain, excessive micturate, thirst, decreased coordination, memory concentration loss, hair loss, and others. At the same time, lithium treatment can also reduce thyroid function, which prevents the release of thyroid hormones that cause the thyroid gland to decrease function. Therefore, thyroid hormones must also be tested regularly when taking lithium. Because of that lithium's effects are not immediate, it has often been prescribed along with other bipolar medication for adjuvant therapy. It can take weeks or even months for lithium to work its full effect. On top, just because of this post-period, other drugs are often used to pre-treat the acute phase of a bipolar attack. Therefore, lithium is most often used as a prophylactic in the treatment of bipolar.

Studies have shown that controlled trials also show that lithium can significantly reduce the incidence of recurrent affective disorder. The researchers treated with low-dose, once-daily lithium, combined with antidepressants and antipsychotics when necessary. During the study year, 73% of bipolar patients had no or only minor morbidity.

#### 4.2.2 Valproic Acid

Valproic acid is frequently used to stabilize patients who are unable to tolerate lithium medication. Valproic is still more effective than placebo and approximately as effective as lithium in the short term, according to clinical trials. Valproic acid can be used as a short-term bipolar illness medication when fast mood stabilization is required, as it has a shorter duration of effect than lithium. Valproate may be more effective than lithium at treating mania, rapid cycling, and mixed states of epilepsy, but it is not as effective or long-lasting in treating depressive episodes.

The most serious adverse effects of sodium valproate are liver damage and thrombocytopenia, both of which are critical in maintaining proper blood function. Platelets are used by the liver to control blood clotting. To keep liver problems within an acceptable range, liver enzyme function analysis and whole blood cell technology should be conducted on specific patients at the start of medication and repeated on a frequent basis. Other common side effects of valproate bipolar medication include nausea, tiredness, increased hunger, weight gain, hair loss, poor concentration, and severe abdominal discomfort. It's also worth noting that valproate was first discovered to be used for epilepsy rather than bipolar disorder, therefore it's sometimes regarded as an anticonvulsant rather than a mood stabilizer.

The researchers carried out a 6-month open-label trial of safety and tolerability testing in 9-17-year-old model mania patients [14]. 109 of the 226 individuals had finished the study by the end of the trial. There was an asymptomatic increase in mean plasma ammonia levels, a drop of 12.4 on the mean Young Mania Rating Scale from baseline to last visit, and improvements in behavioral and caregiver stress levels.

#### 4.3. Combined treatment for antipsychotic medicines

The combined treatment of antipsychotic drugs

It has been using antipsychotics to treat depression for a long time. Because atypical antipsychotics have fewer side effects than typical antipsychotics, it has now been used as a monotherapy or in combination with antidepressants to treat depression with or without psychiatric symptoms. Antidepressant effects of atypical antipsychotics include the regulation of monoamines, glutamate-aminobutyric acid (GABA), cortisol, and neurotrophins.

For combination therapy, the U.S. Food and Drug Administration (USFDA) has approved quetiapine sustained-release tablets and aripiprazole [13](second generation antipsychotics), In that management and treatment of schizophrenia, bipolar disorder-related mania, irritability associate with autism spectrum disorders, dissociative treatment of major depression, and Tourette syndrome.) As an adjuvant treatment for depression, olanzapine and fluoxetine (fluoxetine is FDA certified for major depression (8 years and older), obsessive-compulsive disorder, panic disorder, bulimia, bulimia, premenstrual anxiety disorder and bipolar depression, as well as refractory depression when combined with olanzapine.) , used for the treatment of refractory depression. The pharmacological

mechanisms of atypical antipsychotics for depression are different from typical antipsychotics. Atypical antipsychotics may lead to the effects of the following antidepressants: rapid separation and reduced activity of dopamine receptors, 5-HT<sub>1A</sub> receptors, 5-HT<sub>2A</sub> / 2C receptors and  $\alpha$  2 receptor inhibitory activity decreased, norepinephrine transporter (net) blocked, glutamate or  $\gamma$ - The regulation of aminobutyric acid (GABA) system leads to the decrease of cortisol level and the increase of brain-derived neurotrophic factor (BDNF).

#### 4.4. Other treatment for Bipolar Disorder

##### 4.4.1 psychotherapy (CBT)

Although bipolar disorder is caused by the imbalance of chemical substances in the brain, in the whole course of bipolar disorder (manic depression), patients will have various psychological problems, so psychological treatment is also an important measure throughout the disease [15].

Psychotherapy programs often include psychoeducational interventions, cognitive behavioral therapy, family therapy, and interpersonal and social harmony therapy. Studies have shown that psychotherapy can make bipolar patients more aware of the problems they are facing, and can also help with medication adherence and more effective treatment with medication.

In the research, the researchers compared two groups of people who had recently been diagnosed with bipolar disorder. 1 group received standard care, including medication and support from community groups, psychiatrists, or general practitioners [16]. The other group received standard care and CBT. The researchers found that the latter group achieved better and longer-lasting recovery than the group that did not receive CBT.

##### 4.4.2 Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is usually only used as the most extreme last resort [17]. For the treatment of manic and depressive episodes. It mainly uses vagus nerve stimulation and deep brain stimulation to improve extreme mood, but because it is an irreversible invasive treatment, doctors often use it cautiously.

## 5. Conclusion

Bipolar disorder affects 45 million people worldwide, with an estimated 1.1 million adolescents suffering from the disorder. It is crucial to face and resolve the disease of bipolar, not only to rescue those sufferers, but also to stabilize the public security. The drugs currently on the market are mainly focused on antipsychotics and antimanic drugs. To treat in an antipsychotic way, it is most used by therapists with olanzapine, quetiapine, lurasidone, and cariprazine. Cause the antipsychotic drugs are effective to correct the dysfunction of serotonin levels and serotonin receptors including 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>7</sub> suits the remedy to the case. In the Antimanic way, lithium was the primary choice, and valproic acid are the alternative one. It is useful in stabilizing depression mood and can subside manic emotions and suicidal ideas. Furthermore, declare that the regular circadian rhythm and exercising were all available in the recovery, by the increase of oxidative stress and balance signaling activity. Although there are several methods to treat bipolar disorder, what needs to be improved is the public perception of the disorder. From the data, only about 25% of bipolar patients are correctly receiving treatment, and the rest of the patients might be unaware or with wrong cognition of the disease. Therefore, to prevent the high risk of being diagnosed with bipolar disorder and reduce the suicidal rate, accurate advocacy, and communication are necessary.

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