The Function of TPH2 in Bipolar Disorder and Related Treatment Mechanisms

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Abstract: Bipolar disorder, known as a mental health condition, that features extreme mood swings, is classified into three types: Bipolar I, II, and cyclothymic disorder. Bipolar I patients experience at least one manic or mixed episode, and several depressive episodes. Bipolar II patients experience at least one hypomania or mix episode, and several depressive episodes. Cyclothymic patients experience relatively mild hypomania and depressive episodes, but they suffer from a higher number of mixed episodes. The diagnosis of bipolar disorder is to follow the standard criteria from the DSM-5. However, the determination is relatively subjective. On the other hand, genetic mutations also con-tribute to the occurrence of bipolar. A variety of gene mutations or single nucleotide polymorphisms (SNPs) are ex-perimentally shown to be associated with bipolar disorder. Amongst them, one of the most significant gene poly-morphisms is TPH2 polymorphism. A specific variant of S41Y functions by disrupting the downstream signalling pathways leading to abnormal levels of serotonin release. Drug treatment of bipolar primarily includes lithium and second-generation antipsychotics (SGAs), where lithium mediates bipolar symptoms at psychological, neuronal, and cellular levels. SGAs target both dopaminergic and serotonergic pathways to relieve these symptoms. However, the advent of other novel treatment methods challenges traditional treatments. Details of functional pathways are wait-ing to be further explored in the future. This review provides our current knowledge on the curr ent genetics and treatment of bipolar.

1 INTRODUCTION

Bipolar disorder is a mood disorder that affects 1% of the total population (Almeida et al 2009). It was first identified by the French psychiatrist Jean-Pierre Falret in 1851. He described this disorder as circular madness in which patients' moods change between depression and mania (Angst 1998). Later in 1921, a German psychiatrist, Emil Kraepelin, further studied mental illness and differentiated bipolar disorder from schizophrenia. He stated that bipolar disorder belongs to the manic-depressive insanity group and mentioned the term "mixed states", in which mania and depression occur one after another (Angst, Sellaro 2000). Eventually, in 1980, bipolar disorder was formally identified in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3) (Benazzi 2007). In this book, standardized diagnostic criteria are described to distinguish bipolar disorder from other mental illnesses. In addition, it is the first time that bipolar disorder is separated into three subtypes. Now this book has its fifth edition (DSM-5). It specifically describes the characteristics and diagnostic criteria of the three types of bipolar disorder, bipolar I disorder bipolar II disorder, and cyclothymic disorder (Benazzi 2007).

Bipolar disorder is a mental disorder that reduces patients' quality of life and affects their health. It is a

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chronic and recurrent mood disorder that could last lifelong (Carbon, Hsieh, Kane, Correll 2017). The common onset age is in adolescence or early adulthood. Patients with it experience different levels of mania, depression, and mix moods. Bipolar disorder is hard to treat. Currently, there is no cure for it. Moreover, it is very challenging for patients to manage due to the fluctuation of the mood state. Thus, bipolar patients' quality of life is affected to a great extent. A large number of bipolar patients feel their lives are negatively affected, especially in the aspect of education, vocation, and work functions as well as their social relationships (Carkaci-Salli, et al 2014). Their health-related quality of life (HRQOL) score, the perception of an individual's wellbeing, physical, psychological, and social functioning is lower compared to normal people (Escamilla, Zavala 2008). The suicide risk for bipolar patients is 20-30 times higher than the general population (Frye, et al. 2015).

However, we only know little about bipolar disorder, including its pathology and treatments. With the development of genetic technology, more research has been conducted to understand this disease and its genetic causes. Therefore, in this review, we present the symptom and diagnosis methods for three different types of bipolar disorder, including bipolar I, bipolar II, and cyclothymic disorder. The mutations that lead to bipolar disorder are concluded as well. Finally, pre-existing treatments are described, and emerging future therapy is proposed. Together, this review provides a summarization for bipolar disorder. More importantly, it states the apparent limitations for both diagnosis and treatments and provides directions for future research to better understand and treat bipolar disorder.

2 SYMPTOM

2.1 Bipolar I Disorder

Bipolar I disorder is known as manic-depressive disorder. Patients with bipolar I disorder are averagely symptomatically ill for half of the time after the diagnosis, and the onset age is 23.5 (Geddes, Miklowitz 2013). Patients experience at least one manic episode, in which they will suffer from an unusually elevated mood and energy such as increased activity and decreased need for sleep. In addition, it is also possible that patients exhibit catatonic behaviour and undergo the onset of postpartum. Except for manic episodes, patients may experience a major depressive episode (Grande, Berk, Birmaher, Vieta 2016). The result from the paper, Lewis et al. report that it is 3 times more common for bipolar I disorder patients to have depressive symptoms than manic symptoms (Geddes, Miklowitz 2013). During a depressive episode, patients show symptoms such as depressed mood and loss of pleasure (Hoffman). In addition to separately manic and depressive symptoms, bipolar I disorder patients may also suffer from the mixed episode, in which manic symptoms and depressive symptoms occur one after another. More than half of the patients undergo a mania and depression cycle once a year. Few of them undergo a mood cycle more than 10 times per year (Geddes, Miklowitz 2013).

The symptoms described above could be mild, server but show no psychotic features, or server and show psychotic features for bipolar I patients. Although half of the bipolar I disorder patients show psychotic symptoms, the lasting time is relatively short (Grande, Berk, Birmaher, Vieta 2016). Bipolar I disorder is known for patients to experience manic and major depressive episodes, but during the ill time, subsyndromal, minor depressive, and hypomanic are more common symptoms. The data collected from 146 bipolar I disorder patients indicates that subsyndromal, minor depression, and hypomania take up 74.0% of the total ill time. In contrast, mania and the major depressive episode take up only 12.3% of the total ill time (Geddes, Miklowitz 2013).

2.2 Bipolar II Disorder

Bipolar II disorder is a relatively mild manic-depressive disorder in which patients are in a euthymia state most of the time. The onset age for bipolar II disorder patients is around 31 years old (IsHak, Brown, Aye, Kahloon, Mobaraki, Hanna 2012). While they are symptomatically ill, they also suffer from a mood cycle that undergoes manic and major depressive episodes (Jann 2014). However, compared to bipolar I disorder, bipolar II disorder patients experience less severe mania, called hypomania (Jauhar, Young 2019). Its symptoms include increased physical activity, more self-confidence, and more irritability (Judd, et al. 2002). The symptoms of hypomania are very similar to mania, but the mood instability in hypomanic episodes is not severe enough to cause significant behavioural impairment (Jauhar, Young 2019).

For bipolar II patients, it is more common to have depression compared to hypomania. A mixed episode is relatively rare to occur, and the lasting time is very short (Grande, Berk, Birmaher, Vieta 2016).

Although bipolar II disorder is less severe than bipolar, I type, the patient still shows some level of cognitive dysfunction even under euthymia state (IsHak, Brown, Aye, Kahloon, Mobaraki, Hanna 2012).

2.3 Cyclothymic Disorder

Cyclothymic disorder is the mildest disorder compared to bipolar I and II (Lee, et al 2021). For cyclothymic patients, the main symptom is mild hypomania and depression, where patients experience low and high moods. Both hypomanic and depressive episodes are not server enough to diagnose as bipolar disorder. However, the changing of mood states varies among patients. Patients who normally undergo depressive episodes may shift to hypomania for a few days. It is also possible that the mood switch occurs several times a day.

Except for the typical symptoms, some cyclothymic patients risk developing comorbid psychiatric disorders. On average, cyclothymic patients show a higher number of moods shift despite the mood circulation styles are different. In addition, the early onset age, and the late diagnosis due to mild ill symptoms also contribute as a factor for comorbidity (Lee, et al 2021).

Table 1. Symptoms of Bipolar disorders.

Category	Symptoms
Bipolar I Disorder	At least one manic or mixed episode and several depressive episodes.
Bipolar II Disorder	At least one hypomanic (mild mania) episode. Depressive episode is very common whereas mix episode rarely occurs.
Cyclothymic Disorder	Hypomanic and depressive episode are not server enough to diagnose as hypomania or depression. Mix episodes occur frequently.

3 DIAGNOSIS

The current diagnosis method is to follow the criteria from the DSM-5 (Judd, et al. 2002). Patients who experience at least one manic episode and depression episodes are identified as bipolar I disorder. Patients who experience at least one hypomanic episode and depression episodes are identified as bipolar II disorder. Patients who experience cycling between mild hypomania and depression are identified with the cyclothymic disorder (Lin, et al 2007).

The traditional diagnosis method has been used since 20 century, but this method is very subjective, so it is very difficult to correctly diagnose this mental disorder. As mentioned above, depression is more common compared to mania and hypomania. The problem is, mental diseases such as major depressive disorder and unipolar disorder also display depressive symptoms (Lin, et al 2007). Therefore, bipolar disorder is easy to be diagnosed as other mental disorders. There are total three types of bipolar disorder. Amongst them, bipolar II disorder is characterized by the display of hypomania, in which a full-blown mania is excluded. Thus, without a clear manic symptom, bipolar II disorder can be misdiagnosed as a unipolar disorder. The third type, cyclothymic disorder, is also very challenging for diagnosis since the symptoms are so mild that the patients seldom seek for help. Moreover, the hypomania symptoms usually result in pleasant feelings, so when they think they are ill, it's normal when they are depressive. This cause cyclothymic disorder has a chance to be diagnosed as depression as well (Lin, et al 2007). The challenges for bipolar diagnosis mean that more accurate methods should be provided to avoid misdiagnosis. Neuroimages and biomarkers are investigated as two novel methods.

Neuroimages of bipolar and unipolar patients are analysed. The result indicates that compared to the unipolar patient, depressed bipolar patients show decreased fractional anisotropy (FA), which plays a role in mood regulation in the right frontal-temporal regions. Their white matter that connects key prefrontal and subcortical neural regions, which plays a role in emotion processing and the regulation of neural circuitry, is also different from unipolar patients (Macritchie, 0 et al 2010). Moreover, during emotion processing, the amygdala activity, and its connectivity to the prefrontal cortical show different patterns between bipolar patients and unipolar patients (Maina, Bertetto, Boccolini, Salvo, Rosso, Bogetto 2013). These distinct characteristics between

bipolar and unipolar patients can help to differentiate these two disorders, especially when patients are under a depressive episode.

In addition to neuroimages, biomarkers are investigated to use as diagnostic indicators as well. Plasma proteins analysis between bipolar patients and healthy individuals reveals that the protein level of growth differentiation factor 15 (GDF-15), hemopexin (HPX), hepsin (HPN), matrix metalloproteinase-7 (MMP-7), retinol-binding protein 4 (RBP-4), and transthyretin (TTR) are higher for bipolar I disorder patients compare to bipolar II disorder patients and healthy individuals (Malhi, Tanious, Das, Coulston, Berk 2013). Proteins such as proprotein convertase subtilisin/kexin type 9 (PCSK9), carbonic anhydrase 1 (CA-1), and peroxiredoxin 2 (PRDX2) are found upregulated in bipolar II patients compared to healthy individuals (Mason, Brown, Croarkin, 2016). These proteins are suggested as potential biomarkers for bipolar disorder diagnosis.

4 MUTATION

4.1 Genetic Mutation and Its Relation to Bipolar

Many neurological disorders are considered to be related to genetic mutations. Many researches have connected the cause of the bipolar disorder (BD) to different biological processes. Such mechanisms include variants like neurotransmitters, receptors, enzymes, and co-factors. Genetic factors code these variants, and certain genetic mutations will affect genetic transcription/translation, protein expression, neurological signalling cascade, enzyme activity, and eventually lead to bipolar disorder (Mayo Clinic Staff). Current drug therapy for most neurological disorders is non-specific and can only treat certain common conditions like headache and seizure (Michalak, Yatham, Kolesar, Lam 2006). To trace the disease's cause back to its root, treatment targeting the genetic mutations considered causal for BD should be most effective and promising. However, it is important to point out that it is very difficult to identify certain genetic mutations responsive to medication and therapy. Therefore, clinical research in this area is challenging. We will talk about such potential yet complicated genetic treatment in section IV.

Studies suggest that a number of genes are correlated to this disorder. Some of their mutations are shown to be present in most of the bipolar patients' conditions. Dense genetic maps have been used to identify specific genes and their role in the neurological pathway, and the knockout effect of such genes has been studied (Müller-Oerlinghausen, Berghöfer, Bauer 2002). Numerous candidate genes have been studied thoroughly, and the following section talks about one of the most critical genes involved in BD.

4.2 The Role TPH2 Polymorphism Plays in Bipolar

The neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) is responsible for modulating appetite, aggression, sleep, and mood. It has a significant effect on both human peripheral and central nervous systems. Many neurological disorders have been associated with dysfunction of the serotonin signalling cascades and processes. Tryptophan hydroxylase 2 (TPH2) is the first and rate-limiting enzyme in the biosynthesis of serotonin. TPH2 enzyme is expressed abundantly in serotonergic neurons of the brain. Studies have shown that TPH2 polymorphism is associated with many neuropsychiatric disorders, including bipolar disorder, major depression, schizophrenia, autism, suicidal behaviour, and aggression (Mayo Clinic Staff). Over 500 single nucleotide polymorphisms (SNPs) have been identified in the TPH2 gene, and about 300 of them are found in humans. Zhang, X. et al. (Mayo Clinic Staff) summarized 6 coding non-synonymous SNPs and 3 coding synonymous SNPs. To determine the biological importance of a specific SNP and its effect on the serotonergic pathway, the location of which the genetic variant occurs is critical (e.g., intron, exon, promoter region, 3'UTR/5'UTR). Different mutated locations of the TPH2 gene imply different consequences: dysfunction of gene transcription/translation, alternative splicing, protein misfolding, enzyme inactivation, or dysfunction of a post-translational modification. The functional consequences are unclear if the mutation occurred in a noncoding region (e.g., intron/promoter region).

4.3 TPH2 SNP - S41Y

In overview, one specific SNP we will talk about in this review is tyrosine for serine at position 41 (S41Y) in the regulatory domain of the enzyme TPH2. Studies have associated the S41Y SNP with bipolar disorder and depression in the Han Chinese population. Most of the bipolar disorder patients at clinic research express S41Y SNP, which is

evidential for its relevance to bipolar (Phillips, Kupfer 2013, Pompili, et al 2013).

Carkaci-Salli, N. et al. (Phillips, Kupfer 2013) expressed TPH2 human protein in bacteria and PC12 cells and discovered that S41Y TPH2 expressed increased Vmax and in vitro stability decreased by 28 minutes at 37 degrees Celsius. Contradictorily, S41Y bacteria have increased enzyme activity but decreased serotonin production, suggesting that decreased enzyme stability is more critical than activity in serotonergic biosynthesis. S41Y SNP decreased cyclic AMP-dependent protein kinase A (cAMP PKA) phosphorylation by 50 percent compared to wild type, which leads to the disruption of post-translational regulation of TPH2, and reduced serotonin production, which may lead to bipolar disorder.

We have compared the nucleotide sequence of TPH2 among humans, mice, zebrafish, and fruit flies, and the amino acid is not conserved at position 41 among these four species. However, the polar property is conserved between humans and zebrafish. Suggesting that zebrafish could be a potential animal model for studying SNPs at position 41 of TPH2.

5 BIPOLAR TREATMENT

5.1 Treatment Methods

The treatment of the bipolar disorder is diverse, ranging from drug treatment to clinical therapies. Primarily, drug treatment is one of the most effective treatment methods of bipolar disorder because its targeting often involves neurological pathways directly responsible for causing bipolar disorder. Two main types of drug treatment are emphasized: Lithium treatment and Second-Generation Antipsychotics (SGAs) (Torrent, et al 2006). Lithium is considered a gold standard bipolar treatment in the past century after it was introduced 60 years ago. Research into its mechanisms is conducted at multiple levels. Lithium mono therapy is the best option to relieve acute mania and depression in bipolar symptoms. Lithium contributes to both pre and post-synaptic modulations at the neuronal level, where chronic lithium administration can stabilize glutamate neurotransmission and increase glutamate re-uptake to achieve mood stabilization effects. It also increases the level of GABA in plasma and downregulates the effects of NMDA receptors as well (Zhang, Beaulieu, Gainetdinov, Ca-ron 2006). Neuroimaging techniques are used for bipolar disorder diagnosis, which can effectively identify the changes in brain area with lithium use, such as the increase in the volume of brain grey matter, hippocampus, left amygdala, and striatum. In addition, lithium is beneficial to bipolar individuals, but it can cause harmful side effects on normal individuals due to its selectivity of action (Zhang, Beaulieu, Gainetdinov, Ca-ron 2006).

Another important type of drug treatment is named second-generation antipsychotics, also known as SGAs. Antipsychotics, known as medications for treating psychological disorders, are divided into first-generation antipsychotics (typical) and second-generation antipsychotics (atypical). The first generation of antipsychotics functions only in blocking dopaminergic receptors (D2). However, SGAs act on blocking both dopaminergic and serotonergic receptors (5HT2A). Another advantage of the SGAs is the decreased percentage of causing moving disorders than first-generation antipsychotics, and the side effects are milder. For instance, a meta-analysis from 2017 demonstrated a significant difference in tardive dyskinesia between classes (Rajput 1975). A significant feature of bipolar disorder is the abnormally high level of excitation caused by excessive dopamine and serotonin signaling. SGAs, as heterogeneous molecules, can reduce the high level of excitation by acting on receptor antagonists of dopaminergic receptors (D2) and serotonergic receptors (5HT2A), in which they block the specific functional pathways of dopaminergic and serotonergic receptors. Although they have less affinity for the D2 receptor than first-generation antipsychotics and higher affinity for 5HT2A receptors, these molecules can still block both pathways. This process leads to a lower level of dopamine and serotonin transmission, therefore reducing the abnormal excitation level caused by bipolar. The approved antipsychotics include aripiprazole, olanzapine, quetiapine, and ziprasidone, which all serve as receptor antagonists of D2/5HT2A or both (Van Meter, Youngstrom, Findling 2012).

5.2 Challenges of Traditional Treatments

Lithium and second-generation antipsychotics are both considered traditional treatments for bipolar disorder. However, these methods also have potential limitations and challenges. Limitations of lithium treatment include difficulties in identifying compensatory responses that are distinct from the bipolar-caused primary dysfunctions. In addition, the process of neurotransmission involves many convoluted mechanisms in multiple different

pathways. Under these circumstances, identifying common targets across different bipolar stages or phases is very challenging due to the different personal responses of individual patients and the various mood states. Also, most of the current findings of lithium use in bipolar treatments involve preclinical in vitro or in vitro studies, which use higher than the therapeutical level of lithium concentrations (Zhang, Beaulieu, Gainetdinov, Caron 2006). Therefore, these studies require further examinations and may not be easily applied for human studies because different lithium concentrations may render different neurobiological effects under various concentrations and doses of lithium treatment.

Second-generation antipsychotics (SGAs) also have shortcomings that significantly influence their functions. Include a variety of adverse or side effects of using the molecule to treat bipolar disorder. These side effects include weight gain, abnormal glucose, cholesterol metabolism, and dysfunction in sexual behaviours. For instance, the use of antipsychotics in maintenance treatment in BD from the clinical care of people presenting with first-episode mania in the first episode psychosis (FEP) service features the controversies of SGAs treatment. Treatment with SGAs, in this case leading to more weight gain and more severe metabolic dysfunctions. Another limitation of SGAs is that it only functions well in bipolar patients with no treatment adherence problems (Van Meter, Youngstrom, Findling 2012).

5.3 Future Directions

For Lithium treatment, the potential mechanisms proposed are waiting to be further explored in detail for understanding the underlying interconnections of different neurological pathways. Further research may involve longitudinal studies to determine whether the underlying mechanisms of neuroprotective properties and mood stabilization effects of lithium are mutually intercorrelated. Multi-modal approaches can also be applied to examine the part of neuroimaging and genetic studies of bipolar disorder and the advent of more advanced technologies.

The use of SGAs treatment for therapeutic purposes of bipolar disorder is seen as increasingly important in both the cases of monotherapy and adjunctive therapy. There are different considerations of pharmacological properties, efficacy, and tolerability in bipolar disorder for SGAs use. Maintenance treatment with SGAs can be used in the circumstance of patients who have lithium intolerance or adherence problems in conjunction with newer digital technologies for early relapse signs and monitoring individualized health care systems. Longer-term trials with various compounds and focusing on treatments acting on differing poles of illness can be conducted in the future.

6 CONCLUSION

Bipolar disorder is a mental health condition classified into three types: Bipolar I, II, and cyclothymic disorder. The diagnosis of bipolar in current days is by following DSM-5. Novel methods such as using neuroimaging and biomarker are proposed. Genetic mutation is one of the causes for bipolar disorder, in which a specific type of TPH2 gene polymorphism named S41Y plays a role in affecting TPH2 gene expression and further disrupts the downstream signalling pathways. To treat this condition, drug treatments are considered effective treatment methods. Lithium is one of the treatment methods targeting glutamate stabilization and increasing GABA signalling to reduce the excitation level in bipolar patients. Second-generation antipsychotics (SGAs) are also able to reduce excitation by blocking dopaminergic and serotonergic receptors to prevent further downstream effects. Bipolar disorder is a mental disorder that can seriously affect patients' health. However, currently, the diagnosis, genetic causes and treatments of bipolar disorder are not well studied. The diagnosis of bipolar in current days is by following DSM-5, which is relatively subjective.

Bipolar treatments in which lithium use is difficult to target common pathways in different stages of bipolar disorder. SGAs may render side effects such as weight gain, abnormal glucose, cholesterol metabolism, and dysfunction in sexual behaviours. Moreover, the signalling pathways and the role of specific genetic factors in gene polymorphism targeting may also be further explored. Therefore, more studies are required to better understand the pathology of bipolar disorder. In addition, the validation of bipolar neuroimaging patterns and biomarkers may serve as future diagnosis method. Novel technologies such as CRSIPR and other genetic editing tools, are considered very effective and may be able to cure bipolar patients by correcting genetic mutations and applying gene repair mechanisms.

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