INDONESIAN JOURNAL OF LIFE SCIENCES

Volume 5, No. 2, September 2023

REVIEW ARTICLE

Molecular Biomarkers and Pathophysiology Specific to Bipolar Disorder: Potential Diagnosis and Treatment Targets

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A B S T R A C T

Bipolar disorder (BD) is an episodic neuropsychiatric disorder characterized by fluctuations between manic and depressive phases according to their types (BDI/BDII/cyclothymic). The disorder contributes to the decreased quality of life due to the impairment of cognitive abilities, hence necessitating early detection for proper treatment. However, the gold standard structured clinical interview for DSM-V often results in misdiagnosis due to its inability to distinguish BD from other neuropsychiatric disorders. Therefore, diagnosis through molecular biomarkers can be performed to accurately distinguish BD from other neuropsychiatric disorders. This review aims to elaborate the evidence of molecular biomarkers in BD patients from recent studies, which may be fundamental in clinical practices for accurate diagnosis. Proteomic studies provide evidence for the differentially expressed proteins, namely brain-derived neurotrophic factors, which can differentiate BD from major depressive disorder and schizophrenia. Moreover, genetic alterations from genomic and transcriptomic studies found that CACNA1C, ANK3, FADS2, and other genes may predispose an individual to BD. Some of these genes are closely related to BD pathophysiology occurrences, including impaired oxidative phosphorylation, imbalance in calcium homeostasis, and neuroinflammation: All of which arise due to mitochondrial dysfunction. These pathophysiologies can be alleviated by proper administration of mood stabilizers, antipsychotics, and anticonvulsants, but novel treatments targeting specific pathophysiology and biomarkers of BD are required for better treatment effectiveness.

K E Y W O R D S

Bipolar disorder, Mania/depression, Molecular biomarker, Mitochondrial dysfunction, Pharmacotherapies

H I G H L I G H T S

- Misdiagnosis of bipolar disorder (BD) commonly occurs due to the inability of diagnostic tools to distinguish BD from other neuropsychiatric disorder.
- Molecular biomarkers, such as brain-derived neurotrophic factors (BDNF) levels, can differentiate BD from schizophrenic and major depressive disorder patients.
- Alterations in gene expression related to BD pathophysiology may also act as a sensitive and specific diagnostic target.
- Molecular pathways can be utilized as targets for novel treatments to effectively treat BD phenotypes.

INTRODUCTION

Bipolar disorder (BD) is defined as a lifelong episodic neuropsychiatric disorder closely associated with compromised quality of life and high levels of cognitive/functional disabilities (Blanco et al., 2017; Culpepper, 2014; Jain & Mitra, 2022). BD is characterized by fluctuations between biphasic moods of mania and depression, which differ according to energy levels and behavior (Grande et al., 2016; Vieta et al., 2018). The Global Burden of Disease (GBD) study showed that BD was included in the top 20 primary causes of disabilities (Ferrari et al., 2016), with a total of 24.8 million cases being reported in 1990, increasing to 39.55 million by 2019 (Institute for Health Metrics and Evaluation, 2019). The increase in number of cases is thought to arise from improvements in diagnosis methods, diagnosis criteria, and sample sizes (Jung et al., 2020).

Despite the high prevalence, significant limitations in the diagnosis of BD are still present. The gold standard and most common techniques for the diagnosis of BD are the structured clinical interview for DSM-V (SCID) and mood disorders questionnaire (MDQ) (Konuk et al., 2022; Shabani et al., 2021). However, the latter yielded a relatively low sensitivity (75%) and specificity (74%) upon comparison to SCID, in which post-traumatic stress disorder and history of abuse contributed to false positive results (Paterniti & Biserbe, 2018). Both SCID and MDQ are also unable to differentiate between neuropsychiatric disorders and similar manifestations, such as BD from major depressive disorder (MDD), contributing to the inaccuracy of treatments. This is proven by an analysis done by Shen et al. (2018), where it was found that the misdiagnosis percentage of BD was as high as 76.8%, with the major diagnosis being unipolar depression/MDD and schizophrenia, despite the patients having met the diagnostic criteria for SCID. Misdiagnosis is not well reported after performing MDQ, but a higher number of MDQ items may be obtained by patients during acute episodes, altering the results of MDQ screening (Gervasoni et al., 2009). In addition, SCID is time-intensive and complex, therefore hindering its usage in clinical applications (Paterniti & Bisserbe, 2018).

Consequently, this review aims to analyze the current standings in BD studies from the molecular perspective, in order to provide sufficient evidence regarding molecular biomarkers in BD patients. It is expected that the biomarkers elaborated in this review can be fundamental and essential targets in neuropsychiatric clinical practices for accurate diagnosis and treatment specific to BD patients. Therefore, this review aims to summarize the genomic, transcriptomic, and proteomic findings in BD, as well as their implications in BD molecular pathophysiology and treatments.

THE DIFFERENT TYPES OF BIPOLAR DISORDER

The classification of BD patients is fundamental to be understood by healthcare professionals in order to properly administer accurate treatment strategies to the patients due to the differences in clinical manifestations. The American Psychiatric Association classifies BD into bipolar I- (BDI), bipolar II- (BDII), and cyclothymic disorder, depending on the manic/hypomanic or depressive episodes and their severity (Figure 1) (American Psychiatric Association, 2013; Vieta et al., 2018). Hypomanic episodes refer to the stage where psychotic features are absent, thus marked by less severe and shorter symptom durations (American Psychiatric Association, 2013; Guzman-Parra et al., 2021).

BDI is characterized by the presence of one or more manic episodes, which can be followed by a hypomanic episode. This type of BD commonly manifests as talkativeness, increased mood, decreased need for sleep, psychotic symptoms, overconfidence, impulsivity, and irritability (Carvalho et al., 2020; Mohammadi et al., 2017). The higher occurrence of psychotic symptoms (hallucinations and reckless behavior) in BDI compared to BDII may contribute to the need for hospitalizations in BDI patients. Therefore, it is arguable that BDI is more clinically severe in both episodes (Guzman-Parra et al., 2021). The lifetime prevalence of BDI is found to be 0.6%, with a higher occurrence in male patients (Merikangas et al., 2011).

In BDII, an individual typically has at least one hypomanic episode followed by one major depressive episode, with the absence of manic episodes (Carvalho et al., 2020). Compared to BDI, the lifetime prevalence of BDII patients is lower, being 0.4%. Interestingly, the majority of BDII patients are females, without any specific correlation elucidated (Merikangas et al., 2011). Cyclothymic disorder is diagnosed by observing the presence of hypomanic symptoms and depressive symptoms, both of which do not fall into the diagnostic threshold for both episodes. This disorder lasts for at least 2 years, with the symptoms occurring numerous times (Carvalho et al., 2020; Grande et al., 2016; McIntyre et al., 2020). Regardless of the clinical subtypes, the forms are persistent throughout their lives (Culpepper, 2014).

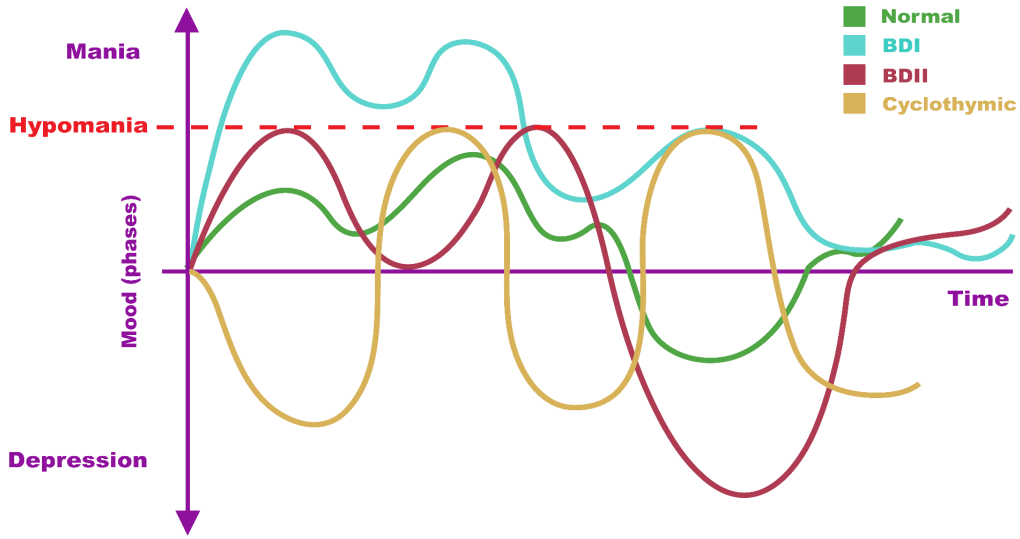

Figure 1. Graph illustrating the mood fluctuations according to the duration in BDI (blue), BDII (red), and cyclothymic (yellow) patients in comparison to non-BD individuals (green).

THE ETIOLOGY OF BIPOLAR DISORDER

The occurrence of BD and its clinical manifestations may arise due to several biological and psychosocial factors. As such, it can be said that BD is a complex multifactorial disease contributing to the high prevalence of misdiagnosis (Stahl et al., 2019; Vieta et al., 2018).

Biological Factors

Genetic factors significantly contribute to the development of BD through inheritance, in which first-degree relatives of BD patients have up to 7.6 times increased risk of predisposition to the disorder with a heritability rate of 0.62% (Song et al., 2015; Wray & Gottesman, 2012). Recent genome-wide association studies also suggests that several genes are closely associated with the etiology of BD (Li et al., 2021a; Mullins et al., 2021; Stahl et al., 2019). One of the best-supported susceptibility genes known to be closely associated with the etiology of BD is CACNA1C, which encodes for L-type voltage-gated calcium channels (Smedler et al., 2022).

Other than genetic predisposition, alterations in neuroanatomy may also result in BD manifestations. The brain structural changes induced during the manic phase include decreased activation in the left dorsolateral prefrontal cortex (DLPFC), which is involved in decision making and memory management (Alonso-Lana et al., 2019). The left hippocampal gray matter volume related to altered executive function and emotional processing were also found to be reduced (Brosch et al., 2022). Additionally, elevated levels of pro-inflammatory cytokines (such as IL-6, TNF-α and IFN-γ) were linked with BD through the dysregulation

of the hypothalamus-pituitary-adrenal (HPA) axis and altering of the monoaminergic systems, which was further shown to be strongly correlated with the severity of mood changes (Becking et al., 2015; Benedetti et al., 2020).

Psychosocial Factors

External factors may also play a key role in BD etiology. Childhood trauma is hypothesized to predispose an individual to BD and can increase mania severity (Agnew-Blais & Danese, 2016). Additionally, history of childhood emotional abuse, physical abuse, and sexual abuse is associated with decreased psychosocial function, self-harm, and increased phase changes, respectively (Larsson et al., 2013). At least one of these childhood traumas is significantly associated with an earlier onset of illness and increased depressive phases (Etain et al., 2013). Moreover, verbal abuse during childhood may also increase the susceptibility of BD patients towards anxiety, substance abuse, and rapid phase changes (Post et al., 2015). Altogether, it can be deduced that early exposure to environmental stressors may increase the risk of early BD onset.

MOLECULAR PATHOPHYSIOLOGY

The main hypotheses that explain the pathophysiology in BD patients encompass impaired oxidative phosphorylation/OXPHOS (Kim, Santos, Gage, & Marchetto, 2017), with neuroinflammation (and imbalance in calcium homeostasis being the downstream effects (Benedetti et al., 2020; Kato, 2017). These are the consequence of mitochondrial dysfunction, influencing neuronal bioenergetic demands and synaptic transmission (Picard & McEwen, 2014), such as increased mitochondrial biogenesis in manic phase and vice versa in depressive phase (Giménez-Palomo et al., 2021). The study of prefrontal cortex of post-mortem BD patients has revealed that there was decreased activity of electron transport chain (ETC) complex I and the NDUFS7 subunit due to impaired OXPHOS, resulting in increased electrons leakage and their subsequent interaction with molecular oxygen to form reactive oxygen species (ROS) (Kim et al., 2016). ROS accumulation leads to oxidative damage, which in turn might cause mutations or deletions in the mtDNA due to the lack of histones (Torell et al., 2013). This explains the low number of mtDNA copy numbers in BD patients or lipid peroxidation in the proteins involved in neuronal membrane maintenance and neurotransmitter uptake (Akarsu et al., 2018; Tsujii et al., 2019). Other than that, decreased activity of complex I may decrease intracellular and extracellular levels of brain-derived neurotrophic factors (BDNF) (Kim et al., 2015), a protein involved in the development and maintenance of new neurons (Muneer, 2020).

Neuroinflammation

ROS accumulation triggers the formation of NLRP3 inflammasome in the mitochondria as well as the activation of its downstream signaling pathways in the frontal cortex, eventually leading to the activation of IL-1β (Kim, Andreazza, Elmi, Chen, & Young, 2016). The activation and elevation of IL-1β will in turn decrease the structural connectivity of the ventromedial prefrontal cortex (Felger et al., 2016), as the production of cytokines affects synaptic transmission regulation and promotion of neuroinflammatory signaling pathways (Lotrich et al., 2014; Strenn et al., 2021). IL-1β genetic polymorphisms in BD patients is also associated with an increase in putamen volume, a basal ganglia substructure important for selection of purposeful actions, impairing its surrounding brain areas with functions in cognitive and emotional responses (Altinay et al., 2016; Strenn et al., 2021).

The neuroinflammation markers in BD also include the elevation of serum IL-6 and IL-8 in depressive and manic phases (Lu et al., 2019), with the manic phase also exhibiting higher TNF-α levels (Skibińska et al., 2022), which is hypothesized to be due to the activation of microglial cells (Sigitova et al., 2017). These

excessive pro-inflammatory cytokines can lead to brain tissue damage and dysfunction of synaptic transmission/plasticity, exacerbating the biphasic moods due to an imbalance in the level of cytokines (Panaccione et al., 2015; Watkins et al., 2014). In addition, pro-inflammatory cytokines elevations can cause white matter tissue injury through the destruction of myelin sheath integrity in brain anterior, altering structural connectivity (Benedetti et al., 2016). This hypothesis is confirmed by Kamaeva et al. (2022), who discovered that the IgG isolated from the serum of BD patients was able to significantly induce hydrolyzation of myelin basic protein (MBP), functioning in myelin sheath integrity of brain oligodendrocytes. Interestingly, a novel finding by Kamintsky et al. (2019) showed that 27.8% (10/36) BD patients had a significant blood-brain barrier (BBB) leakage, related to the higher severity of depression and chronic course of illness. This subsequently gives rise to the possibility of BBB disruption as the cause of cytokines and antibodies presence in the brain, which makes BBB disruption a strong BD biomarker candidate (Patel & Frey, 2015).

Pro-inflammatory cytokines are also reported to be correlated with 5-HTT serotonin transporter protein and BDNF level. The accumulation of pro-inflammatory cytokines in the depressive phase enhances the 5-HTT gene expression, which is associated with the decreased extracellular serotonin levels and activation of presynaptic and postsynaptic serotonin receptors. Consequently, the BDNF protein production can be reduced, resulting in neuroplasticity disruption in BD patients (Sigitova et al., 2017). As a matter of fact, the 5-HTT gene-linked polymorphic region (5-HTTLPR) polymorphism was demonstrated to be correlated with impulsive behaviors in BD cyclothymic patients, especially in females, accompanied by the increase of serotonergic activity (Boscutti et al., 2022). These alterations support the notion that neuroinflammation plays a major role in the disruption of synaptic transmission and plasticity.

Imbalance in Calcium Homeostasis

Calcium homeostasis is implicated in various neuronal functions, including the maintenance of neuronal plasticity, neurotransmitter release from the presynaptic cells, energy production, and membrane excitability (Kawamoto, Vivar, Camandola, 2012). The dysregulation of calcium levels is therefore associated with the occurrence of neurotransmitter imbalance and neuronal excitability alterations (Kato, 2019). Reduction in calcium levels induces severe depression since the neural circuits involved in emotions are dysregulated (Chen et al., 2021). In contrast, an increase in intracellular calcium levels may happen upon the disruptions in OXPHOS levels due to hyperexcitability (Harrison, Hall, Mould, Al-Juffaly, & Tunbridge, 2021; Kato, 2017). Hyperexcitability is thought to arise from the excitatory neurotransmitter glutamate, demonstrated by a proteomic study which found that the glutamate levels were significantly higher in BD patients with manic phase (Nasru, Razak, Yaacob, & Azman, 2021). A metabolomic study also found an increase in glutamine:glutamate ratio, which are signs of activated glutamatergic neurotransmission (Kubo et al., 2017). This increase in glutamate levels, as well as the decreased ability of glutamate reuptake by the astrocytes (Figure 2), contribute to the chronic excitation of glutamate receptors (including N-methyl-D-aspartate/NMDA) and subsequently causing excitotoxicity (Frizzo, 2019; Kim et al., 2017). Consequently, it is hypothesized that increased glutamate levels may cause neuronal death and impulsivity (Kim et al., 2017 ; Smaragdi et al., 2019), although no conclusive studies have directly found their correlation. The chronic excitation of glutamate receptors might give rise to chronic elevations of intracellular calcium as a result of the high need for calcium-mediated neurotransmitter buffering, explaining the correlation between glutamate and calcium levels (Verma et al., 2022). Moreover, the release of calcium itself is regulated by inositol-3-phosphate (IP3) and its precursor, myoinositol (MI). In BD patients, the genes encoding for MI transporters (SLC5A3, SLC5A11) are highly expressed, determining behavioral phenotypes and symptomatic patterns as well as exacerbating the high levels of intracellular calcium levels (Vawter et al., 2019).

DIAGNOSIS THROUGH PROTEOMIC BIOMARKERS

One potential alternative to accurately detect and distinguish BD from MDD and schizophrenia is through the use of proteomic biomarkers such as BDNF. The BDNF levels in the serum of BD patients are lower than healthy controls (Chiou & Huang, 2019). In addition, the presence of mature BDNF (mBDNF) protein as well as the ratio between mBDNF plasma levels and its precursor proBDNF (M/P) differentiates the depressive phase of BD from MDD. BD and MDD can be indicated by a low and high mBDNF to M/P ratio in the plasma, respectively (Wang et al., 2019; Zhao et al., 2017).

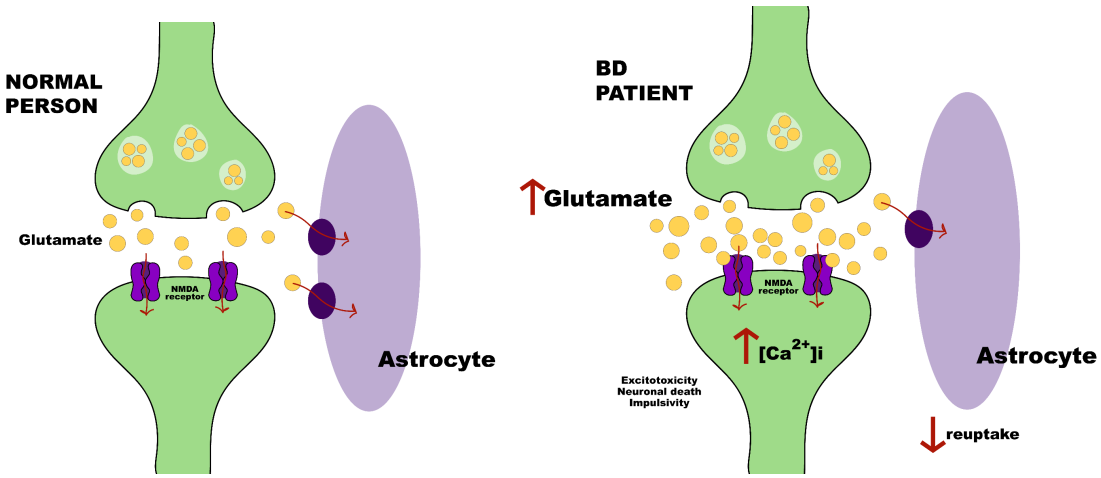

Figure 2. Schematic illustration of hyperexcitability leading to calcium imbalance (adapted from Lin et al., 2012).

The differential diagnosis through plasma BDNF levels performed by Shahyad et al. (2023) proved that BD could be properly distinguished from MDD with 73% sensitivity and 70% specificity, as well as from healthy controls with 83% sensitivity and 76% specificity. However, the usage of plasma BDNF levels to distinguish between BD and schizophrenia patients yielded inconclusive results. Dombi et al. (2022) argued that BD patients has only small reductions in the plasma BDNF level compared to healthy patients, whereas schizophrenia patients have moderately lower levels compared to healthy patients. In another study, the BDNF levels were significantly elevated in schizophrenia patients compared to healthy controls (Weickert et al., 2019). These inconclusive results further emphasize the need for differential diagnosis tool. The most possible differentiation between BD and schizophrenia diagnosis is by observing plasma BDNF levels in conjunction with oxidative stress marker changes. While BDNF levels demonstrates negative correlations with oxidative stress markers (e.g. superoxide dismutase) in schizophrenia patients (Wei et al., 2019), positive correlations between serum BDNF levels and oxidative stress markers (lipid hydroperoxides) were observed in BD patients (Newton et al., 2017). However, detecting multiple biomarkers simultaneously for the diagnosis of BD may not be cost- and time-efficient due to the involvement of multiple procedures and the requirement of more automated machines.

Other than serum BDNF, Coppens et al. (2020) found 66 proteins that were differentially expressed between the peripheral blood mononuclear cells of BD and MDD patients, namely HLA-DRB1, keratin, galectin-10, and mitogen-activated protein kinase 13. Smirnova et al. (2019) also proved that serum proteins with altered expression in BD and not MDD include apolipoprotein M, beta-casein, tetranectin, and cadherin-5. The complement protein C4 factor A and B involved in inflammation were significantly upregulated in BD patients compared to schizophrenic patients, while albumin upregulation can differentiate BD from other psychiatric disorder patients consuming lithium (De Jesus et al., 2017). Consequently, it can be argued that

proteomic approaches have the potential to detect distinctive biomarkers in BD patients for definitive diagnosis, rather than solely relying on its clinical manifestations.

GENOMIC AND TRANSCRIPTOMICS IN BIPOLAR DISORDER

Due to the strong association between BD and genetic factors, multiple large-scale genome-wide association studies (GWAS) have been conducted to identify the genetic risk factors of BD (Li et al., 2021a; Mullins et al., 2021; Stahl et al., 2019). Some of the major genes that have been found by GWAS to play a role in BD pathophysiology are summarized in Table 1. However, it is important to note that recent GWAS studies predominantly characterize BDI as the major BD cases, not BDII. The only distinctive gene that has been found in BDII is SLIT3, which functions during central nervous system maintenance (Huang et al., 2022). This further demonstrates that SLIT3 can be a fundamental genetic biomarker for BDII, highlighting the demand for BDII GWAS.

Table 1. GWAS profile of bipolar disorder.

BD subtype	Genes	Function	Expression Alteration	Effects	References
BDI	*CACNA1C* (rs1006737 mutant A allele)	Encodes for the alpha-1C subunits of the voltage-gated calcium channel, regulating influx of calcium	Increased	Increased hippocampal and prefrontal cortex activity, specific to BDI	Bigos et al. (2010); Huang et al. (2022)
				Impaired/delayed facial emotion recognition	Nieratschker et al. (2015)
				Disorganization of thought	Khalid et al. (2018)
	ANK3 (rs10994336 mutant T allele)	Encodes for ankyrin 3, associated with ion transporters coordination on nodes of Ranvier and axon initial segments; facilitating action potentials in myelinated neurons	Increased	Reduced integrity of anterior limb of the internal capsule (ALIC) white matter, impaired task switching, and increased risk decision making	Linke et al. (2012)
				Affects early visual perception stages and neural processes, disrupting facial emotion processing	Zhao et al. (2016)
				Fatigue	Khalid et al. (2018)
	TRANK1 (rs9834970)	Encodes for a large protein expressed mainly in brain and other tissues, contributing to the blood–brain barrier maintenance	Decreased	Altered gene expression related to neuronal development and differentiation	Jiang et al. (2019); Li et al. (2021b)

BD subtype	Genes	Function	Expression Alteration	Effects	References
	ODZ4/ TENM4	Encodes for teneurins involved in neuronal connectivity regulation during development, oligodendrocytes differentiation, and neuronal axon myelination	Decreased	Increased response of amygdala blood oxygen level-dependent (BOLD) during a reward task	Heinrich et al. (2013); Kohshour et al., (2022); Mühleisen et al. (2014)
	SCN2A	Encodes for the voltage-gated sodium channel alpha-2 subunit related to neurophysiology and cognitive functions (action potentials)	Not reported	Not reported yet, but some studies suggest impaired excitatory synaptic transmission and dendritic excitability, leading to visual processing impairment	Shin et al. (2019); Spratt et al. (2019)
	ITIH1/3/4	Encodes for inter-α-inhibitor (serine protease inhibitor) family with anti-inflammatory properties	Decreased	Not reported yet, but hypothesized to be associated with neuroinflammation	Sasayama et al. (2014); Qi et al. (2020)
	PACS1	Encodes for proteins associated with trans-Golgi network (TGN) membrane proteins localization	Increased	Significantly decreased the density of mice thin dendritic spines, which might affect their function	Chen et al. (2022)
	SHANK2	Encodes for large family of proteins functioning in the maintenance of scaffolds plasticity and development, specifically in the glutamatergic synapses	Decreased	Reduced post-synaptic scaffolds, inducing mania-like behavior (disrupted coordination and balance), cognitive impairments, and reward-seeking behaviors	Pappas et al. (2017); Unsicker et al. (2021)
	GRIN2A/B	Encodes for the NR2B subunit of NMDA receptor, located in the cortical/medial temporal brain regions	Not reported, but associated with risk T allele	Reduced white matter integrity in some brain regions, such as frontal lobe and cingulate gyrus	Kuswanto et al. (2013)
BDII	*FADS2*	Encodes for fatty acid desaturase enzymes	Increased	Impaired polyunsaturated fatty acids (PUFA) synthesis related to increased pro-inflammatory response in the prefrontal cortex	Liu and McNamara (2011)

BD subtype	Genes	Function	Expression Alteration	Effects	References
				Associated with lipid abnormality and hyperlipidemia, a pathophysiology of BD, especially BDII	Ikeda et al. (2018)

The presence of these genetic biomarkers in clinical settings to diagnose BD have not been well implemented. However, it is possible that genomic extraction and genotyping can be done to detect mutations in these genes, such as by following the methodology described by Khalid et al. (2018). Varying genes in CACNA1C may also be analyzed in conjunction with serum levels of BDNF. It was proven that patients with CACNA1C risk alleles demonstrated 46% higher M/P BDNF ratios than those without risk alleles, further strengthening the utilization of the widely researched CACNA1C gene as a diagnostic target (Smedler et al., 2021). Although the gain-of-function mutation of CACNA1C is also present in Timothy syndrome patients, the disruption of L-type calcium channels happens in an organ that is different from BD. The calcium channel in Timothy syndrome patients is mainly affected in the cardiovascular system, which in turn manifests as multiorgan system dysfunctions (Han et al., 2019a). This difference in location will not affect the misdiagnosis of BD using the detection of CACNA1C polymorphisms. Still, it is important to note that some of the genes in Table 1 may have no significant association with BD if examined individually. This is because some of the risk alleles may additively contribute to BD, and not individually, such as in the case of ANK3 and CACNA1C (Khalid et al. 2018).

Researchers have also recently utilized transcriptome-wide RNA editing modifications through RNA sequencing detection in the blood samples of patients with depression symptoms. This was performed to identify biomarkers or specific RNA editing sites located in specific sequences for the differentiation between BD and MDD (unipolar depression) patients. It was found that six genes (GAB2, IFNAR1, KCNJ15, LYN, MDM2 and PRKCB) allowed the separation between BD and MDD patients with 90.9% sensitivity and 84.6% specificity. These genes are generally involved in neuronal synaptic plasticity and/or inflammatory responses. However, the expression levels of these genes are still unknown (Salvetat et al., 2022).

CURRENT TREATMENTS

Pharmacotherapy is a critical component of effective BD treatment (Simonetti et al., 2020). Pharmacodynamic investigations using candidate genes have revealed the mechanistic routes of BD therapies, which include neurotransmission, intracellular messenger cascades, and other pathways (McElroy et al., 2020). Currently, various medications have been proven to be effective in treating BD, primarily mood stabilizers, anticonvulsant, and antipsychotics (Chiu et al., 2022; Holm et al., 2022).

Mood Stabilizers

The antimanic drug, widely known as a mood stabilizer, is one of the drugs that has been administered to treat BD, shown to significantly impact BD by attenuating the biphasic mood symptoms including depression (McIntyre et al., 2020). Lithium, the gold standard and first-line treatment for BD, has been classified as a mood stabilizer drug that exhibits extensive clinical evidence for maintenance treatment, acute mania, bipolar depression, and suicide prevention (Bauer & Gitlin, 2016; Song et al., 2017). Several theories have been established regarding the cellular target of lithium, and although it is highly relevant, the

mechanism of action for lithium is yet to be elucidated (Snitow, Bhansali, & Klein, 2021). The antimanic activity of lithium is also linked to its suppression of inositol monophosphates (IMPase), the enzyme responsible for the production of myo-inositol, potentially depleting intracellular inositol by reducing inositol *de novo* production, this inhibition might be indirect and not competitive (Berridge et al., 1989; Jadhav et al., 2017; Toker & Agam, 2014; Yu & Greenberg, 2016). Lithium has also been revealed to be an inhibitor of glycogen synthase kinase 3 (GSK-3) through binding directly to the magnesium-sensitive site and indirectly by increasing its phosphorylation, both of which hindering G6P metabolism for inositol *de novo* generation (Benedetti et al., 2013; Gould, Chen, & Manji, 2004; Muneer, 2017; Yu & Greenberg, 2016). While the ideas of inositol depletion and GSK-3 inhibition appear uncorrelated, it has been hypothesized that they are components of a single mechanism, in which inositol depletion might be caused by the GSK-3 inhibition.

Antipsychotics

Antipsychotic drugs are potent tranquilizers primarily used to control the manic phase of BD (Chiu et al., 2022). BD is typically treated with second generation drug, also known as atypical antipsychotics, which have both antimanic and antidepressant effects (Jauhar & Young, 2019; Kato, 2019; Ortega-Ruiz et al., 2022). Clinical trials have demonstrated quetiapine, a second-generation antipsychotic medication, to be effective in treating bipolar depression, resulting in low incidence of extrapyramidal side effects (Berk et al., 2017; Fornaro et al., 2016; Tournier et al., 2019). Quetiapine acts by binding itself to transmembrane neurotransmitter receptors and inhibiting them without causing an action potential, hence alleviating the symptoms of BD (Chernoloz et al., 2012). In the brain, quetiapine serves as a dopamine D2 receptor antagonist, the main targets for the antipsychotics drug, which is necessary for controlling mania and preventing manic switch while treating bipolar depression (Grunze et al., 2021; Serafini et al., 2022). Further advantages include reducing agitation or anxiety due to the low affinity of quetiapine for 5-HT1A receptors and moderate affinity for 5-HT2A receptors in the serotonergic system, resulting in the effect of partial agonist and antagonist actions towards the receptors, respectively (Han et al., 2019b; Jensen et al., 2007; Sanford & Keating, 2012; Srinivas et al., 2020).

Anticonvulsant

Anticonvulsants, often known as anti-seizure drugs, are also classified as mood stabilizers that function in various ways to reduce hyperactivity in the brain. It has been introduced as a novel treatment in BD patients, not only as a medication in cases of resistance, but also as a treatment standard with high efficacy and low incidence of side effects (Grunze et al., 2021). Although most anticonvulsant medications have been examined for their mood-stabilizing effects, only carbamazepine, valproate, and lamotrigine have established therapeutic efficacy in BD patients and have been approved by the Food and Drug Administration (FDA)/European Medicines Agency (EMA) (Bialer, 2012; Davico et al., 2018).

Carbamazepine and valproate have been approved for acute mania and mixed episodes, respectively. Carbamazepine is used off-label for BD maintenance therapy since it binds to the α-subunit of voltage-gated sodium channels (VGSC), keeping the sodium channels inactive and allowing fewer channels to open. This in turn inhibits the unnecessary generation of action potential (Gambeta et al., 2020; Peselow et al., 2016). Furthermore, valproate is a histone deacetylase inhibitor (HDACi) that has been shown to increase the activity of serotonergic (Wu & Shih, 2011), dopaminergic (Lai et al., 2019), and GABAergic systems (Tondelli et al., 2020), while inhibiting the glutamatergic transmission (Soeiro-de-Souza et al., 2018). It was also found that valproate can affect the intracellular signaling pathway by decreasing the levels of phosphoinositol (Yu, Daniel, Mehta, Maddipati, & Greenberg, 2017), inhibiting glycogen kinase-3β/Wnt

pathway (Xing et al., 2015), and down-regulating protein kinase C (Abrial et al., 2013), all of which are known to be disrupted in the brains of BD patients.

Lamotrigine, on the other hand, has been approved as a maintenance medication to delay the recurrence of depressive episodes (Besag et al., 2021). It was proven by Terao et al. (2021) that the time to relapse of manic and hypomanic episodes are more advantageous to BDII patients who are more susceptible to frequent phase switching. The specific mechanism of action of its preventive effect includes the persistent reduction of VGSC hyperexcitability by slowing down the binding of sodium to the VGSC fast inactivation state that develops when VGSC are overactivated (Nakatani, Masuko, Amano, 2013). Moreover, lamotrigine also has some antagonistic effects on γ-aminobutyric acid (GABA) and decreases the presynaptic release of excitatory amino acids, including glutamate and aspartate, since glutamate has been correlated with depressive phases and hyperexcitability (Abelara et al., 2012; Andreazza & Young, 2014; Bowden & Singh, 2012; Prabhavalkar et al., 2015). Interestingly, the administration of lamotrigine to rats has been found to elevate the low BDNF levels in amygdala (Abelaira et al., 2012), further strengthening the potential applications of this drug as one of the first-line BD treatment strategies.

Molecular Pathophysiology Regulation

The aforementioned medication options are limited by side effects, such as renal and thyroid dysfunction with long-term lithium therapy, weight gain, and metabolic abnormalities with atypical antipsychotics (Geddes & Miklowitz, 2013). Therefore, several drugs specifically targeting molecular pathophysiology, namely neuroinflammation and imbalance calcium homeostasis, are currently being developed (Kim et al., 2017). Proof-of-concept trials have shown that using anti-inflammatory drugs to target neuroinflammation may be a promising strategy for BD, where drugs such as celecoxib are proposed as adjunctive treatments for patients with BD (Gamble-George et al., 2016). In in-vivo studies, a cyclo-oxygenase-2 (COX-2) inhibitor, celecoxib, showed a promising therapeutic effect in improving depressive symptoms by altering serotonin production (Edberg et al., 2018; Nery et al., 2008). However, a 12-week double-blind placebo-controlled trial comparing adjunctive celecoxib and minocycline, another anti-inflammatory drug, with placebo in BD patients found no evidence that minocycline or celecoxib was superior to placebo as BD treatment (Husain et al., 2020). As a consequence, the trial results combined with existing evidence do not support the use of adjunctive anti-inflammatory drugs such as minocycline and celecoxib for the treatment of BD. Similarly, in regards to other molecular pathophysiology pathways, another report has found that long-term lithium treatment is associated with altered calcium metabolism, suggesting the similarity in the mechanism of action of calcium channel blocker and lithium (Cipriani et al., 2016). This outcome has prompted an investigation of calcium channel blocker to be an adjuvant therapy or even potential treatment for BD (Cipriani et al., 2016; D'Onofrio, Mahaffey, & Garcia-Rill, 2017). Despite that, a study by Yildiz et al. (2015) had shown that verapamil, an L-type Ca2+ channel (LTCC) blocker, did not show any significant result, and thus the involvement of LTCC antagonists toward BD remains inconclusive. It can therefore be said that molecular pathophysiology-targeting drugs are far away from creating a robust impact in BD treatment. The gap between in-vivo research and clinical applications is yet to be filled by more translational studies.

CURRENT STANDINGS AND RECOMMENDATIONS

The diagnosis of BD using SCID and MDQ is considered to be unreliable since both methods depend on clinical manifestations and can lead to misdiagnosis, thus only being performed for preliminary diagnosis. Instead, it is suggested for healthcare professionals to detect protein or genetic biomarkers elaborated in

this paper, both of which are specific to BD patients. This reduces the possibility of misdiagnosing BD with other neuropsychiatric disorders. However, the utilization of biomarker detection needs to be further studied to enable its application in point-of-care tests. The main concern regarding biomarker detection is accessibility due to the involvement of automated machines, which increases the cost needed. Other than that, there are little to no studies implementing molecular biomarkers as the main diagnostic method, and therefore their sensitivity and specificity in clinical settings remain unclear. This also relates to the fact that some of these biomarkers are closely associated with other neuropsychiatric diseases and need to be detected in conjunction with other markers for accurate diagnosis.

Moreover, even though a large body of evidence in this review has analyzed the molecular alterations specific to BD patients, the distinction between BDI and BDII can still be further investigated. The differentiation between the pathophysiology of these two types is paramount to facilitate accurate diagnosis and treatment. Consequently, it is advised to investigate their differences through omics-based approaches, such as through large scale transcriptomics analysis in BDII patients. The study should also be conducted in various populations with diverse backgrounds for more representative results that can adequately characterize the risk loci for each BDI and BDII patients. Southeast Asian countries may provide interesting demographics for further studies.

It is of utmost importance to find novel treatments targeting specific molecular pathways involved in BD pathophysiology to effectively treat BD phenotypes as an alternative to the current gold standard lithium. This is because lithium is widely used in other neuropsychiatric disorders and may not be suitable for specific treatment. On top of that, current treatments do not target the occurrence of neuroinflammation in BD patients, which can chronically damage the neuronal cells of BD patients. This further increases the demand to discover novel drugs to build upon the novel biomarkers identified in recent studies. Thus, it can be deduced that the conventional first-line lithium treatment strategies should be replaced with drugs targeting those biomarkers to reduce off-target effects. In addition, finding multiple drug strategies with synergistic effects, inducing both the reduction of pathophysiology and maintenance, should be considered for a long-term beneficial effect towards BD patients. Altogether, it is expected that the prevalence of BD can be decreased as more studies are conducted.

CONCLUSION

The gold standard diagnosis of BD, structured clinical interview for DSM-V, still remains unconvincing, demonstrated by the high percentage of misdiagnosis. This highlights the need for accurate diagnosis in clinical settings involving molecular biomarkers specific to BD patients, facilitating early detection and treatment. Consequently, sufficient amounts of studies analyzing the molecular mechanisms of bipolar disorder (BD) have recently been done, as evident by the detection of protein and genetic expression biomarkers specific to BD patients as well as their correlation with BD pathophysiology. However, these biomarkers have not been widely implemented as a main diagnostic tool in clinical settings, emphasizing the urgency for future studies to elucidate their specificity and sensitivity. Moreover, biomarkers to differentiate BDI and BDII are also expected to be found in a large-scale study with diverse backgrounds for more representative data. It is also imperative to find novel treatments targeting specific biomarkers and pathophysiology of BD as an alternative to the conventional lithium administration which yields off-target effects. On top of that, the outcome of the aforementioned drug targeting BD molecular pathophysiology has further pushed researchers to conduct more translational studies to provide convergent evidence regarding molecular pathophysiology roles in BD development and bridge drugs in in-vivo studies and their clinical applications.

ACKNOWLEDGEMENTS

We would like to acknowledge and thank Mrs. Gabriella Gita Febriana who made this work possible. Her insightful comments and recommendations carried us through the entire process of writing this project.

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