Bipolar Disorder: A Brief Literature Review of Diagnostic Issues, Epidemiology, and Potential Causes

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Abstract

Bipolar disorder (BD) is a complex mental disorder that has multiple modes of causality. In this brief review, we used PubMed and Google Scholar databases to conduct an analysis that focuses on the epidemiology, genetics, aberrant developmental processes, environmental influences, and diagnostic criteria of BD. Diagnosis of BD is often associated with several psychiatric disorders. SNPs located in genes, such as *CACNA1C* and *ODZ4* identified by several studies are potential contributors to the etiology of BD. Aberrant neurodevelopmental processes, such as the brain sulcation are shown to be different between the subtypes of BD. Environmental influences including life stressors, substance misuse, smoking, influenza, and the current COVID-19 pandemic have also played a substantial role in individuals developing BD. The goal of this manuscript is to educate the public on current research of possible etiologies and casual factors of BD. This study can be used by others in the science community as a guide for the signs, symptoms, causes, and therapeutic care of BD.

Introduction

BD is a mental disorder that leads to mood instability and changes energy, concentration, behavior, and sleep (1). Four types of BD exist: BD I, BD II, cyclothymic disorder (cyclothymia), and BD not otherwise specified (9). Each BD category is defined by a different manic episode or pattern. BD-I is a manic episode that lasts at least 7 days and can require hospitalization (7). BD-II is hypomanic with depressive episodes (7). If BD-II lasts for at least 2 years, it is then classified as a cyclothymic disorder (2). Unspecified BD does not meet criteria for major depression, BD-I, BD-II, or cyclothymia (i.e., less than one week of manic symptoms without psychosis or hospitalization) (1, 5, 8, 9).

BD has no significant preference for race or ethnicity (14, 16). However, BD does show an onset preference for age and is most common in patients younger than 25 years (14). The mean age for the onset of BD-I is 18 years, and 22 years in BD-II (14). The onset of BD tends to occur later in women than men, and women more often have a seasonal pattern of mood disturbance (14). Although the course and clinical features of BD differ between women and men, there is no evidence that gender affects treatment response to mood stabilizers (17). Existing comorbidities, such as migraines or anxiety, can prefer one sex over another (18–19). For example, the pathophysiologic intersection between migraine headaches and BD may be examined in women with a past medical history of migraine. Combined therapy can impact mood outcomes and treatment effectiveness (18, 20).

BD is a complex disorder that is inflicted heavily by trauma, climate, social support, infection/illness, genetics, epidemiology, and health (2). BD's clinical and etiological effects have both genetic and environmental factors that influence the subsequent prevalence and/or prevention of the disorder (4). A better understanding of the complex intersection between genomics, life events, and the disease is warranted (2, 15). Though the research in this field exhibits methodological challenges, the best genetic and environmental data has been obtained through diagnostic interviews based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) and International Classification of Diseases (ICD-10) standards (6–7).

In this literature review, we summarize and discuss research on the diagnostic criteria and impact of environmental factors, genetics, and neurobiological and epidemiological characteristics on the clinical course of BD.

Methods

A literature review was conducted using PubMed and Google Scholar databases utilizing the following key terms: bipolar disorder, bipolar depression, bipolar treatment, types of bipolar disorder, psychosis, mania, depression, mental health disorders, genetics and bipolar disorder, bipolar disorder comorbidities. These terms were included due to their relevance to bipolar disorder. No date range or journal exclusion was applied.

Discussion

Diagnosis of BD-I vs BD-II

It has been demonstrated that the creation of new self- and clinician-administered rating measures can improve the early identification of clinical characteristics in individuals with BD (22). Similar to this, a person's unique traits such as weight and lifestyle are extremely important in determining the underlying clinical diagnosis of BD (21). Medical comorbidities like obesity are just one of several external factors that contribute to the development of BD (23). According to the literature (25), there is a correlation between having BD and being overweight or obese. A significant number of patients in obese populations are affected by this metabolic condition, which ultimately lowers the quality of life. Endocrine abnormalities, dysregulation of the sympathetic nervous system, behavioral tendencies, and physical inactivity are shown to be shared risk factors between BD and metabolic syndrome (25). In addition to the above,

stress and related neuroendocrine alterations can be another set of factors linked to BD (26).

The use of medications by BD patients contributes to their disease pathology. For instance, certain drugs may have an impact on brain neurotransmitters as well as brain communication systems, which can result in manic-depressive disorder (26). This establishes a link as to why popular pharmaceutical therapies for BD may increase patients' medical burdens, resulting in weight gain and metabolic abnormalities (25). In BD patients, preventing and treating medical comorbidities lowers mortality and morbidity from the physical illness while also accelerating the course of the manic-depressive mental disorder (27).

BD-I

BD-I usually has at least one depressive episode which differentiates it from its subgroup (23). In perhaps 12–17% of cases, BD is not recognized until there is a mood "switch" into hypomania or mania, either spontaneously or with exposure to a mood-elevating substance (28). However, epidemiological findings from the Swedish national quality assurance register indicate that BD-I is the most stable sub-diagnostic group compared to BD-II and cyclothymic disorders (29). According to our research, BD-I requires medication that protects against mannerisms in which round-the-clock care is often necessary (29). Switch rates (also described as the transition from one mania to another) associated with antidepressant use is much higher in BD-I vs BD-II disorders relative to untreated individuals (30). When BD-I patients switch into excited states, they develop either full mania 45% of the time or hypomania 55% of the time (30). This study illustrates that the enhanced state of BD aids in the progression of psychosis in almost 95% of patients when antidepressants are administered. The mood-stabilizing treatment is determined by the dominant polarity behavior demonstrated by patients who display affective and emotional outbursts (29). Medical evidence has indicated that it is common for patients to change bipolar underdiagnoses (BD-I to BD-II and vice versa), which reveals uncertainty in the diagnosis.

BD-II

BD-II is diagnosed in individuals experiencing several protracted depressive episodes and at least one hypomanic episode, but no manic episodes (23). Until 27 years ago, BD-II was the outlier of psychiatric disorders — long recognized and referred to in the literature, but not a "real disorder" (24). Medical literature suggests that BD-II is especially difficult to diagnose accurately because of the lack of differentiation of this disorder from recurrent unipolar depression (recurrent depressive episodes; 24). In fact, unipolar depression is the most frequent misdiagnosis associated with BD-II patients who, by definition, never experience an episode of mania (31). Therefore, clinical depression is predominantly associated with BD-II far more than BD-I (32). BD-II patients who have a treatment-emergent affective switch (TEAS) develop hypomania 95% of the time (30). The TEAS phenomenon illustrates how antidepressants cause people to experience hypomania/mania. It is widely acknowledged as the first antidepressant for BD. This data suggests that there is a different clinical profile for BD-II and that it has a different susceptibility to the induction of mania (24). Furthermore, within the last few years, a debate has arisen on the validity and utility of BD-II as a diagnostic category. Some authors have suggested its elimination as a disorder category (now termed an existential crisis), while others support its continued inclusion in their diagnostic systems (33–39).

Misdiagnosing BD type I or II as unipolar depression results in many potential deleterious consequences. This includes the prescription of inappropriate drugs, such as antidepressants in the absence of a mood-stabilizing drug, which might lead to switching to mania, and ultimately, poor clinical and functional outcomes and high healthcare costs (40–41). Studies revealed that earlier-aged BD patients with an illness prior to BD are characterized by a lower rate of response to antidepressant medication. In contrast, multiple studies in the literature found that a higher rate of switching into mania or hypomania was found to be correlated with a higher switch risk (40). Now researchers question the treatment of bipolar depression with antidepressants due to insufficient data supporting their use.

Epidemiology of BD

The age of onset for BD-I and BD-II differs. For BD-I, the age of onset is between 17 and 25 years, while BD-II is slightly higher (46). Several epidemiological studies have reported the prevalence of BD-I to be around 1% (42–46, 49). In a large cross-sectional study involving 61,392 adults from 11 countries, the lifetime prevalence of BD-I was 0.6%, BD-II was 0.4%, and cyclothymia was 1.4%, providing a worldwide prevalence of 2.4% (45). Compared to international populations, the U.S. has the highest prevalence of BD (45, 47). Differences in international prevalence rates of BD have not been determined (48–49). Psychiatric comorbidities are common in patients with BD. In one study assessing 9,282 English-speaking respondents to a mental health survey, 97.7% of those diagnosed with BD reported comorbidities for other psychiatric disorders, such as anxiety disorders, impulsive control disorders, and substance misuse (14).

Disorders that affect the CNS, like BD, seem to have sex differences in prevalence and incidence rates (50). Incidence rates of BD are equal among males and females; however, males are more likely to have BD-I, whereas females are more likely to have BD-II (50–51). Some studies have reported these sex differences between BD-I and BD-II to be from steroidal hormonal dysregulation in some females (52–54). Knowledge of the epidemiology of BD can help with preventative care and enable clinicians to identify who may be more suspectable to this disorder (46). Understanding the risk and causal factors for BD can lead to early intervention of treatment for individuals and the population (46). Individually, BD patients can receive adequate follow-up care and proper medication dosing, which will enhance patient quality care (46). This will aid in implementing preventative care in suspectable populations leading to the improvement of overall mental health.

Genetics and BD

Although not included as diagnostic criteria in the DSM-5-TR, genetics can play a critical role in explaining the pathophysiology of many psychiatric disorders (55). Evidence for this comes

from twin studies, which have identified a causal genetic link with manifestation of BD disease. Several studies have illustrated concordance rates to be higher among monozygotic twins than in dizygotic twins, with heritability estimates of 60–85% (55–58). Although this evidence is promising, heritability alone cannot explain it all. Current research has focused on identifying specific genes involved in the pathophysiology of BD. Genome-wide association studies (GWAS), which assess the association between specific genetic loci variations with diseases, have identified multiple genes and single nucleotide polymorphisms (4, 11, 59) correlated to BD.

SNPs and BD

There are many common DNA variants whose effects are too small to detect individually but contribute to the risk of BD when analyzed together (3). The first study to use GWAS showed several genes involved in BD and researchers of this study were the first to believe BD may be polygenic (61). Years later, studies with larger sample sizes, with over 40,000 cases, have reported identifying over 35 different loci associated with BD (60, 62–64); providing supporting evidence of BD being polygenic. Each study found unique genetic loci but featured common SNPs in the genes CACNA1C and ODZ4 (61–65). CACNA1C is a gene that encodes calcium ion channels, which brings calcium into the cell (59). The SNPs for CACNA1C and ODZ4 are rs1006737 and rs12576775, respectively (3). Both variants for CACNA1C and ODZ4 are in the intronic region of the gene (3). Since the SNP is not located in the gene coding region, researchers theorized that the SNP for CACNA1C may be involved in gene expression (3). Research is still needed in this area to understand how rs1006737 influences the development of BD. In addition to BD, the ODZ4 gene is associated with other disorders, like autism spectrum and major depressive disorder (3). This gene has different functional roles in neuronal development and in the amygdala (1, 75). ODZ4 has a role in the proliferation and differentiation of oligodendrocytes, which are myelinating cells of neurons (3). In the amygdala, ODZ4 has a key role in reward processing (75). Future research is required to recognize how rs12576775 impacts the progression of BD.

Protein mutations impacting BD

Mutations in proteins associated with BD can also be a major causal factor of BD (66). Recent evidence reported de novo mutations found in genes in BD patients, EHD1, MACF1, and ANT1, were positively correlated with mood changes and serotonergic activity associated with BD (69–70). In one study, behavioral analyses on heterozygous conditional knockout mice (mouse models that have an inactivated gene of interest) of loss of function mutations in ANT1 showed diminished impulsivity (70). Researchers found serotonin turnover increased in the nucleus accumbens in this heterozygous loss of function ANT1 conditional knockout mice (70). Investigators suggested that heterozygous loss of function ANT1 causes dysfunction in serotonin activity and decreases impulsivity, resulting in a risk of developing BD (70). The mechanism for understanding how the loss of function ANT1 causes dysfunction in serotonin activity is an area for future research.

Signaling pathways and BD

Several investigations indicated signaling pathways are dysregulated in individuals with BD (63, 68–70). The Wnt signaling pathway plays a key role in the pathogenesis of BD (71, 74). In one study, researchers assessed whole genome microarrays on monozygotic twins with BD (72). Using ontology analyses, researchers found an upregulation in Wnt signaling pathways in BD patients (72). Investigations on why there is a difference in signaling pathways in BD patients is still needed. Moreover, in addition to identifying genes and mutations associated with BD, targeting signaling pathways can provide clinical and therapeutic advancements.

Aberrant brain structures and neurodevelopmental processes influencing BD

Brain magnetic resonance imaging (MRI) studies have shown conflicting evidence between the volume sizes of the hippocampus, amygdala, and thalamus between healthy controls and BD patients. Some studies reported patients with BD had small volume differences in the hippocampus, amygdala, and thalamus (77–78). These differences were not seen when comparing BD-I and BD-II patients (77). In an older study, researchers used positron emission tomography to measure blood flow and glucose metabolism of the prefrontal cortex (79). Investigators found the anterior cingulate cortex, which is the area of the brain important for attention and mood regulation, had reduced blood flow and glucose metabolism in patients with major depressive disorder and BD (79). Unlike the imaging results mentioned above, one study found through MRI that BD patients had larger amygdala volumes than healthy controls (80). Although there are conflicting results, these studies do show that there is a difference in the anatomical structure of the brain in individuals with BD compared to normal controls (76).

Aberrant neurodevelopmental processes can be a contributing risk factor for individuals with early onset of BD or with comorbidities of schizophrenia (81). Brain sulcation is a neurodevelopmental process, which reflects the folding of the cerebral surface. This process starts at the 10th gestational week and ends in the fetal brain during week 44 (82). The sulcal index refers to how buried the cortex is and is known as an indirect marker for early neurodevelopmental processes (82). To identify if there are changes in cortical folding between early-onset BD-I, BD-II with psychotic symptoms, and healthy controls, MRIs were performed, and sulcation indexes were determined (82). Researchers found that cortical folding was determined to be vastly different in patients with early-onset BD and psychotic BD (82). Specifically, patients with early-onset BD had an increased local sulcal index in the right prefrontal dorsolateral area and psychotic BD patients had a lower local sulcal index in the left superior parietal cortex (82). There is not enough current literature to appreciate why these differences occur in these two subtypes of BD. Future research in analyzing these neurodevelopmental processes in BD patients can aid in the development of better therapeutic care and improve patient outcomes.

Environmental influences of BD

Genetic transmission has been the primary component in BD etiology. However, the complexities of BD suggest other factors. BD exhibits variant penetrance effects, with clinical manifestations differing from one person to the next (83, 84). The diversity in clinical presentation and outcomes of BD suggest there are also environmental factors to be considered. There has been a wide variety of research (83–109) investigating the impact of environmental factors on BD onset. These factors include perinatal and prenatal exposures, alcohol, smoking, substance misuse, life stressors, physical environment, and COVID-19. Furthermore, research (83–109) suggests that these factors also play a role in how BD presents and progresses in individuals throughout their lives.

Prenatal exposures, perinatal exposures, and BD

There is limited literature on prenatal and perinatal exposures to alcohol and teratogenic chemicals in the etiology of BD onset in offspring. However, studies (85–91) suggest that some prenatal and perinatal factors including oxytocin, influenza, smoking, and fetal alcohol exposure, may play a role in BD onset.

Oxytocin

One study (85) explored exogenous oxytocin and BD. Their results showed an approximately two-fold increased risk of BD in offspring whose mothers received exogenous oxytocin to induce labor. Oxytocin is thought to disrupt GABA signaling leading to changes in nerve firing patterns like those with BD (85). With limited literature on the impact of oxytocin on BD onset, further research would help clarify the association.

Influenza

Studies (86–87) explored gestational influenza exposure as a possible risk factor for BD. Using a case-control study, one study (86) found a significant approximate four-fold increase ($p=0.003$) in BD onset following maternal influenza exposure during pregnancy. Additionally, another study (87) found a significant ($p<0.001$) five-fold increase in BD risk but only with psychotic additions, including hallucinations, delusions, and disturbing thoughts. On the contrary, the study (87) found no significant association between maternal influenza exposure and BD risk in offspring alone.

Alcohol

One of the most common disabling outcomes of prenatal alcohol exposure is fetal alcohol syndrome disorder (FASD). Studies show (88–91) that FASD typically co-occurs with mood disorders, including BD. In Canada, a study (89) tested 62 individuals with FASD. Amongst those, 92% were diagnosed with a mental health disorder, BD included. Surprisingly, a direct association between alcohol consumption in pregnant women and BD onset in offspring has not been investigated. Despite this, studies (88, 90–91) have concluded that prenatal alcohol exposure was associated with greater psychopathology and adverse physical health consequences in offspring.

Smoking

Smoking in pregnant women has been explored in the etiology of BD in their offspring. While there is limited research concerning perinatal substance exposure and BD, a study (92) discovered that mothers who smoked during pregnancy compared to those who did not have higher rates of psychopathology, with results showing a two-fold greater risk for BD in offspring prenatally exposed to smoking. Their results (92) were consistent and did not vary in smoking quantity, only revealing smoking during pregnancy as the one significant predictor for BD onset in offspring. Still, there is not substantial research out there regarding the potential risk of BD onset in offspring due to maternal smoking while pregnant.

Life stressors and BD

The role of early development environments has been widely explored in BD expression. Childhood trauma (CT) is more prevalent in those with BD than those without (83–84, 93). Along with more severe symptoms, CT can contribute to the early onset of BD. Studies reveal BD linkage to individuals with multiple childhood traumas (83, 93, 95–96). According to a study (93), more than half of their BD subjects recorded CTs. Consistent results (93–94) reported more frequent and more severe forms of CT in BD individuals than those without BD, with early exposure increases the risks of BD expression. CT concerning parenting psychopathy and maltreatment was reported as preexisting conditions for individuals experiencing BD episodes (94–95), with negative parenting styles contributing to BD and depressive disorder (94–95). In addition to CT, familial disruption, defined as any household structure outside of two parents, increases the risk of BD diagnosis and a higher prevalence of associated manifestations (83, 98). Familial disruption showed an increased risk of BD diagnosis with a 37% prevalence, showing significance (HR 1.69; 95% CI 1.51-1.89, HR 2.91; 95% CI 2.60-3.25) as a single exposure and under multiple exposures (98). Also, family relationships in individuals with BD pose the risk of minor improvement and shorter remission when under trauma and heightened chronic stress (83).

Substance misuse and BD

Studies (84, 99–101) show substance use as a risk factor for BD onset, heightened associated symptoms, more severe course of illness, higher rates of violence and suicide, and varying manifestations. Substance use disorder (SUD) can be a symptom of BD, which allows for misdiagnosis as SUD becomes the primary diagnosis rather than BD. BD co-occurs with SUD, further complicating the effects of BD (100–101). Consistent with the previous studies mentioned (84, 99, 101), literature (100) reported that patients in a BD onset group were more likely to have a SUD, and another reported an estimated 56% lifetime prevalence of SUD for individuals with BD (101). SUD, including alcoholism, cannabis use, opioid, and amphetamine use, has been observed in the daily lives of individuals before the development of BD, which suggests it may be a risk factor for BD (84, 99). The bidirectional mechanism of substance misuse increases manic symptoms and depression symptoms in individuals with BD (101).

Physical environment and BD

There is limited understanding of how the physical environment may play a role in the etiology of BD. However, research (102–103) suggests it may significantly impact the onset of BD. Literature (102) defined physical environment as the physical compartments of one's environment, including air quality, water supply, climate, and landscape. In addition to the physical environment, weather conditions, including the impact of sunlight and population, were also explored as risk factors in BD onset (102). According to a 2019 study (102), air quality, or the degree to which the air is pollutant-free measured by the environmental quality index (EQI), was the strongest predictor for BD, with the worst air quality associated with a 27% increase in BD rate ($p=<10\text{-}4$). Additionally, the study (102) discovered that the most populated counties had a BD rate increase of 16.4% ($p=0.0044$) than that of less populated counties. A study (103) also examined the impact of sunlight on the age of BD onset. Their results showed an inverse relationship between the maximum monthly increase in sunlight and onset, concluding that the higher the monthly increase in sunlight, the younger the age of onset (103).

COVID-19 and BD

While there is not much evidence that COVID-19 effects the onset of BD, people with primary BD are at a higher risk of the effects of COVID-19 than people without BD. Studies (104–105) found COVID-19 related stressors to play a role in heightening the symptoms manifested in individuals with BD. Isolation, restrictions, and lifestyle changes, including economic impacts at the hands of COVID-19, were observed. Compared to individuals without BD, BD patients were discovered to have augmented symptoms, including worsening cognitive symptoms, anxiety, and sleep disturbance (104, 106–107). Additional augmented symptoms included depressive episodes and an increase in the risk of relapse (104). A longitudinal study (108) found higher levels of mood and anxiety symptoms sustained through May 2020 of the COVID-19 pandemic, with individuals with BD having higher persisting levels of disruption than those without BD. On the contrary, other findings (108) showed no increase in symptom severity. Another finding was that utilization of mental health services significantly decreased during the pandemic as more restrictions and a world shutdown were in effect (108–109). BD patients' hospitalizations increased during a pandemic compared to BD hospitalizations pre-pandemic (104–105).

Conclusion

BD is a psychiatric disorder with multiple causalities and a lifetime prevalence of 1.5%. Key areas of research still lie in genetics, aberrant brain structural and developmental processes, and environmental components influencing BD. SNPs located in CACNA1C and ODZ4 genes, protein mutations, and signaling pathways were identified as potential contributors to the etiology of BD. Evidence suggests that individuals with early-onset BD and those with comorbidities of schizophrenia have different cortical folding patterns. Several environmental factors including life stressors, substance misuse, influenza, prenatal chemical exposure, patients' physical environment, and the current COVID-19 pandemic have also influenced BD. Future research is needed to use these modes of causalities for the development of more effective and more targeted therapeutic approaches and the promotion of preventative care.

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