Greener Journal of Biomedical and Health Sciences

Vol. 9(1), pp. 76-86, 2026

ISSN: 2672-4529

https://gjournals.org/GJBHS

DOI: https://doi.org/10.15580/gjbhs.2026.1.041126053

Genetic, Epigenetic, and Neurobiological Pathways in Bipolar and Major Depressive Disorders and the Case for Integrated Pharmaco-Psychotherapy

Theodaline Ndifon Feh[1]; Cynthia Ninyin[2]

[1] Erudite Scholar, Eagle Scholars Forge, Jos, Nigeria.
Email: fombohtheodoline@gmail.com

[2] Higher Institute of Professional Education and Practice (HIPEP), Bafousssam Cameroon.
Email: wiysenyuycyn@gmail.com

ARTICLE'S INFO

Article No.: *041126053*
Type**:** *Research*
Full Text: *PDF, PHP, HTML, EPUB, MP3*
DOI: ***10.15580/gjbhs.2026.1.041126053***

Accepted: *13/04/2026*
Published: *28/04/2026*

Keywords: *Bipolar disorder, Major depressive disorder, Epigenetics, Serotonin and norepinephrine, Integrated pharmaco-psychotherapy*

Corresponding Author

Theodaline Ndifon Feh

E-mail: *fombohtheodoline@gmail.com*

Article's QR code

ABSTRACT

Bipolar Disorder (BD) and Major Depressive Disorder (MDD) are complex mood disorders arising from dynamic interactions among environmental stressors, genetic vulnerability, and epigenetic modification. This paper synthesizes current evidence on negative life events—particularly childhood adversity, socioeconomic instability, and conflict exposure—as critical environmental predictors that shape vulnerability to mood pathology. While heritability estimates suggest substantial genetic contribution (approximately 30–50% for MDD and up to 80% for BD), gene–environment interaction models demonstrate that genetic predisposition alone is insufficient to explain disorder onset. Epigenetic mechanisms, including DNA methylation, histone modification, and microRNA regulation, provide a biological interface through which stress becomes embodied, altering gene expression without modifying DNA sequence. Central to this process are the serotonergic and noradrenergic systems, which mediate mood regulation, stress reactivity, and cognitive-emotional processing. Dysregulation within these neurotransmitter pathways—often in conjunction with hypothalamic–pituitary–adrenal (HPA) axis dysfunction, neuroinflammation, and oxidative stress—contributes to the clinical manifestation of depressive and bipolar episodes. The paper argues that understanding mood disorders requires tracing the pathway from environmental stress to synaptic transmission. Given this multifactorial etiology, treatment models must be equally integrative. Evidence supports the superiority of combined pharmacotherapy and psychotherapy in relapse prevention, mood stabilization, and functional recovery. By addressing both neurobiological imbalance and psychosocial stress, integrated pharmaco-psychotherapy offers a comprehensive framework particularly relevant in resource-constrained African contexts where trauma and socioeconomic adversity are prevalent.

ARTICLE'S INFO

INTRODUCTION

Bipolar disorder (BD) and major depressive disorders (MDD), are known worldwide as the most damaging psychiatric conditions. According to American Psychiatric Association, 2022 (DSM-5-TR), Bipolar and major depressive disorders comes from the nuance interconnection of neurobiology, epigenetics, genetics, and environmental factors. Mood disorders interfer with all aspects of the lives of affected individuals, including impaired cognitive functioning, increased risk of psychiatric hospitalization, substance use disorders, family dysfunction, deficits in educational performance, and more (Carlson and Kashani, 1988; Lewinsohn et al., 1998). Bipolar disorder (BD) and major depressive disorder (MDD) are two of the most common mood disorders. Bipolar Disorder is defined by mood instability and is diagnosed based on the recurrent occurrence of alternating manic or hypomanic and depressive episodes (Grande et al., 2016). Manic/hypomanic episodes are typified by elevated mood, increased energy and activity, and decreased need to sleep, and depression episodes are characterized by depressed mood, decreased interest, and anhedonia or lack of pleasure (Otte et al., 2016), while Major Depressive Disorder presents as depression episodes only and has the same diagnostic criteria as bipolar depression episodes

According to modern research, epigenetic induced by environmental stress factors, and negative life events, shapes vulnerability to mood disorder and not mainly by genetic makeup as was presumed by earlier researchers. Serotonin and norepinephrine is core to the understanding of mood disorders, and neurotransmitters are critical for stress response, attention, mood regulation, and motivation. When these systems are disrupted, it mediates the effect of environmental factors and genetic makeup and provides the groundwork for operative treatment interventions.

Statistics from (WHO, 2023) shows that depression globally affects more than 280 million people. Resent research studies in Africa suggest that one out of four persons are likely to encounter mental health conditions in their life time, with the most common being depression (WHO Africa).The less prevalent is bipolar disorder, which because of it episodic relapse, suicide risk, and chronic courses, is associated with greater disability attuned life years. In most African nations, the mental health systems is limited in terms of resource personnel, and in some cases with 100,000 individuals to be taken care of by one psychiatrist (WHO Mental Health Atlas, 2020 or 2023) in many regions despite the huge burdens that are associate with bipolar and major depressive disorders.

The characterization of poverty, infectious diseases, conflict exposure, rapid urbanization, and limitations in access to mental health services in the African continent, promotes patterns of occurrence of mood disorders (Petel et al., 1999). In Cameroon, mood disorders are enhanced by the on-going Anglophone crisis, sociocultural, economic, and political factors. All of these influence the community interpretations of manic episode through supernatural, spiritual, and or cultural lenses, limiting the way individuals seek help, clinical intervention timing, and adherence to both pharmacological and psychotherapy treatment. In Cameroon this is further exacerbated by gender base violence, family displacement, limited adequate nutrition, and lack of job opportunities, academic or occupational pressure which are prevalent stressors.

This paper seeks to explore Negative life events, epigenetics, and genetic makeup as predictive factors in the development of Bipolar and Major depressive disorder (MDD), with the focus on serotonin and nor-epinephrine and their application in integrated pharmaco-psychotherapy within the Africa and Cameroon contexts.

CONCEPTUAL FRAMEWORK

Predictors of Mood Disorders

1. Negative Life Events

Life events are defined as discrete experiences that disrupt an individual's usual activities, causing substantial change and readjustment, such as marriage, physical illness, or death in the family (Holmes &Rahe). Negative life events such as childhood adversity, physical trauma, death of a loved one, have been found to be one of the strongest predisposing factors for a mood disorder, especially depression (Brown et al.,1989). Studies of negative life events in adults with mood disorders have found that exposure to negative life events plays a significant role in the onset and maintenance of mood disorders.(Kendler et al.,1997; Jaffee et al.,2002). Specifically, for bipolar disorder, studies have found that bipolar adults experience increased severe negative life events prior to the onset and recurrences of depressive and manic episodes. (Alloy et al., 2000; Johnson et al., 2005)

The most predictive indicator of mood disorder is negative life events. These events are:

- **Childhood Adversity**- The brain emotional regulatory system is very susceptible during the developmental stage of childhood. Experiences of physical abuse, emotional neglect, and sexual assault can cause stress response pathways to be persistently altered leading to mood disorders. The likelihood of this alteration affecting stress responses in adulthood is very high. Though not every child who experiences adversities goes on to develop depression later in life (Brown et al.,2019). Instead, these adverse childhood experiences likely interact with existing vulnerabilities to account for the development of this disorder.

  Among the most widely studied vulnerabilities that may share a moderating relationship with early life adversities in predicting depression in adulthood are genetic diatheses. Genetic diathesis and adverse childhood experiences interactions have been implicated in the pathophysiology of depression. For example, the interaction between FKBP5 polymorphisms and childhood maltreatment in a diffusion tensor imaging study predicted structural differences in brain regions associated with emotional processing and regulation and implicated in depression (Tozzi et al., 2016).

  The African especially in Cameroon experience adding layers to childhood adversity that leads to mood disorders according to UNHCR reports:

  - Exposure to socio-political violence, where individuals are kill at increasing rate, and the destruction of properties leaving families stranded.
  - Displacement during conflicts e g North West and South West regions of Cameroon, DRC, South Sudan etc
  - Children orphaned by HIV/AIDS
  - Early child labour
  - Early child marriage

All these experiences lead to hyperactive stress response system and serotonergic motioning, hence shaping the neurodevelopmental processes in children

- **Adult Stress and Socioeconomic Difficulties-** These stress can come from;

  - Exposure to political instability like the case of Cameroon, DRC, Nigeria etc.
  - Unemployment
  - Migration stress
  - Marital crises in most families
  - Financial constrains

A recent systematic review of epidemiological research in LMICs found a very strong relationship between many indicators of poverty and common mental disorders (Lund et al., 2011). Rates for common mental disorders are about twice as frequent among the poor compared to the rich in Brazil, Chile, India and Zimbabwe (Patel et al., 1999). Studies, including those in low-income countries, show that people who lose their livelihood are more likely to develop mental health problems or commit suicide (Khan et al., 2008, van der Hoek and Konradsen, 2005).

Multiple studies covering different cultures and regions show that parental divorce exacerbates developmental challenges and can lead to mental health problems. A 14-year-longitudinal Australian cohort study found that adolescents with a history of parental divorce

showed 1.6 times more risk for depressive episodes than those from intact families (Patton et al., 2014). An American study confirmed that parental divorce in early childhood predicted depressive symptoms in adolescence (Ge et al., 2006).

- **War and Conflict (Collective Trauma in Africa)**

The world has experienced significant number of conflicts which increases the risks of mood disorder development. For example:

a. The displacement of hundreds of thousands of individuals because of the Anglophone crisis in Cameroon has increased depression, and bipolar relapse rates (OCHA).
b. Young people in conflict zones are at risk of developing mood disorders in relation to their exposure to continuous traumatic events. The more general literature on trauma indicates differential effects of war experiences on mental health with exposure to specific war experiences such as killing or wounding others associated with hostility and sexual abuse related to anxiety (Betancourt et al., 2010a). A study with formerly abducted youth in Northern Uganda found that deaths, sexual abuse, and witnessing violence were associated with reporting symptoms of depression and anxiety (Amone-P'Olak et al., 2014a).
c. The genocide that took place in Rwanda left great intergenerational trauma (Schaal & Elbert, 2006), influencing mood disorders among survivors children.

2. GENETIC MAKEUP PREDICTORS

Genetic background plays a crucial role in mental disorders. The onset of mood disorder is a manifestation of the interactions of genetics with chronic stress, childhood maltreatment or traumatic life events. Twin studies show about 37% heritability in major depressive disorder (Suillivan et al.,2000), and 80% in bipolar disorder. Other Studies suggest that depressive disorder has a heritability of only 30–50% (Kendler et al., 2006, 2018; Polderman et al., 2015), while the heritability of Bipolar Disorder is up to 60–80% (Johansson et al., 2019; Fabbri, 2021). Early pedigree studies suggested that Major Depressive Disorder demonstrated familial aggregation, with first-degree relatives having a 1.84-fold higher risk of developing depressive disorders compared to the general population (Sullivan et al., 2000).

Evidence for a genetic component to mood disorders has been documented consistently using family, twin, and adoption studies. The first genetic studies of mood disorders were conducted more than 70 years ago and included assessment of concordance rates for monozygotic and dizygotic twins with mood disorders (Lohoff et al.,2008).

Twin studies suggest a heritability of 40% to 50%, and family studies indicate a twofold to threefold increase in lifetime risk of developing Major Depressive Disorder among first-degree relatives. This degree of familial aggregation, coupled with the high heritability from twin studies, generated optimism that molecular genetic techniques would reveal genes of substantial influence on Major Depressive Disorder risk. Unfortunately, gene localization and identification has been a slow, labor-intensive process. Genetic investigators have encountered similar frustrations with other common complex traits like asthma, hypertension, and diabetes mellitus.

The major impediments to mood disorder gene localization and identification are as follows: 1) no single gene is necessary and sufficient for Major Depressive Disorder; 2) each susceptibility gene contributes a small fraction of the total genetic risk; and 3) complex genetic heterogeneity, meaning that multiple partially overlapping sets of susceptibility genes which interact with the environment can predispose individuals to similar syndromes that are indistinguishable on clinical grounds. This article provides an overview of the current efforts to identify genetic risk factors for MDD (Falk, 2010)

3. EPIGENETICS

Epigenetics occurs when the fundamental DNA sequence remains unchanged, but there is a change in the gene expression of the DNA. This can be seen in such mechanism as histone modification, DNA methylation, and microRNA regulation, which are all intermediary between biological vulnerability and environmental stressors. This deeply explains why two individuals can respond very differently to the same adverse conditions, but possesses the same genetic background.

- .DNA Methylation. The methylation of the receptor gene provokes extreme stress response. Individuals exposed to childhood trauma are mostly identified with DNA methylation. Meaningful examples of this is observe in the African context, with children exposed to war, pregnant woman experiencing extreme stress, neglect in orphan children, survivors of gender based violence, Famine and malnutrition survivors etc.
- Modification of Histone influences chromatin structure, gene accessibility, altering serotonin transporter expression
- MicroRNAs are altered during period of stress, influencing the sensitivity of serotonin receptor.

Some studies of epigenetics in relation to the effects of stress

There is growing evidence that the human epigenome is influenced by psychological stress. In particular, stressful life events have been shown to lead to long-lasting methylation at the glucocorticoid receptor gene and other methylation marks across the genome (Burns et al., 2018; McGowan,2015). Such epigenetic effects may mediate the embodiment of stressful life events and contribute to their physiological and behavioral outcomes, such as the persistent cognitive alterations, activation of the HPA axis and increased risk for psychopathology and chronic diseases (Brown et al., 2019; McEwen,2019).

In support of this, post-mortem brain tissues from suicide subjects and blood samples from mood disorder patients showed that childhood abuse increased DNA methylation at the *NR3C1* promoter corresponding with reduced GR expression (McGowan et al., 2009; Perroud et al., 2011).

4. MOOD REGULATION BY SEROTONIN AND NOREPINEPHRINE

Mood disorder neurobiology relies heavily on serotonin (5-HT) and norepinephrine (NE). Both classic and contemporary models for understanding mood disorders, such as Bipolar Disorder or Major Depression, rely on the idea that affective dysregulation results, in part, from dysregulation of monoaminergic systems (Thase, 2009; Otte et al., 2016). Early monoamine theories believed there was a deficiency of the neurotransmitter as the main reason for mood disorders; however, more recent conceptualizations of mood disorders include more complex dysfunction in receptors, transporters, intracellular signaling cascades and the modulation of gene expression (Haroon et al., 2017; Duman & Aghajanian, 2012).

The serotonin (5-HT) neurotransmitter is widely spread throughout the central nervous system, especially through its projections from the raphe nuclei to several areas of the brain: the prefrontal cortex (PFC), hippocampus, amygdala and limbic structures, all of which have important roles in the emotional regulation of moods, cognitive abilities, and stress response. The serotonin (5-HT) neurotransmitter compound regulates many different functions in the body including appetite, sleep/wake cycles, sexual function, pain, impulse control, and mood stability (Otte et al., 2016). In terms of impaired mood, research has shown that when there is a decrease in 5-HT neurons their transmission would lead to "low mood," "irritability," "rumination," and "thoughts of suicide" while studies have shown that a malfunctioning serotonin transporter (5-HTT) increases sensitivity to stress and susceptibility to developing depression (Klengel & Binder, 2015).

The neurotransmitter norepinephrine (NE), primarily produced in the locus coeruleus, is responsible for regulating arousal, attention, vigilance, energy mobilization, and the "fight-or-flight" response. Psychomotor retardation, fatigue and difficulties concentrating experienced during depressive episodes—along with increased arousal, disturbed sleep and irritability observed in mania—all relate to dysregulation of noradrenergic activity (Thase, 2009; Vieta et al., 2018). Most importantly, the systems for serotonin and norepinephrine have a dynamic interaction rather than a static separation. Changes that occur in one of the systems may also modify functioning within the other through overlapping intracellular signalling pathways.

Chronic stress, especially where there are high rates of poverty, displacement from homes, and sociopolitical instability, can destabilize serotonin and norepinephrine systems through chronically activated hypothalamic–pituitary–adrenal (HPA) axis activity and inflammatory processes (Miller & Raison, 2016). Increased glucocorticoid levels disrupt serotonergic receptor sensitivity and inhibit hippocampal neurogenesis. In addition, inflammatory cytokines influence monoamine metabolism by activating the kynurenine pathway (Haroon et al., 2017). Thus, biological embedding of environmental adversity occurs at the synaptic level.

The primary goal of pharmacological treatments for Major Depressive Disorder (MDD) is to enhance monoaminergic neurotransmission. Selective serotonin reuptake inhibitors (SSRIs) have the ability to raise the amount of serotonin available at the synapse, while serotonin–norepinephrine reuptake inhibitors (SNRIs) increase serotonin and norepinephrine levels. The use of these drugs enhances neurotransmitter levels. Additionally, these medications can lead to neuroplasticity-related processes such as increased expression of brain-derived neurotrophic factor (BDNF) and hippocampal neurogenesis (Duman & Aghajanian, 2012). The use of lithium continues to be the gold standard of mood stabilizers for the treatment of Bipolar Disorder.

Lithium acts not only through its neurochemical modulation of neurotransmitters, but by limiting excessive noradrenergic signaling, stabilizing intracellular second messenger systems, and providing neuroprotection to limit risk of relapse and suicidality (Vieta et al., 2018).Yet while there are neurobiological explanations for mood dysregulation, there are also cultural and relational contexts in which human beings experience imbalances in neurotransmitters. In African cultures, where grief, communal identity, spiritual interpretation of suffering, and ritualized life play critical roles in emotional processing, neurochemical dysregulation converges with culturally-constructed systems of meaning-making (Sele & Whittaker, 2025). For example, interpreting despair, mania or suicidal ideation may be construed through either spiritual or communal frameworks, which have a direct relationship with help-seeking behavior and commitment to treatment. Cultural resilience mechanisms, such as: sacred music; communal worship; and linguistic identity, can function to regulate stress pathways and promote a greater emotional stability (Sele, 2025; Sele, Davou &

Zongo, 2025) in addition to or in conjunction with neurobiological treatments. Therefore, although these cultural processes do not replace neurobiological treatments; rather, they add context for and may ultimately enhance the engagement of psychotherapy.

Thus, serotonin and norepinephrine function as mediators within a biopsychosocial ecology, as opposed to merely serving as chemical substrates of mood. Dysregulation of these neurotransmitters is the result of the complex interplay between genetics, epigenetics, chronic stress exposure and socio-cultural meaning systems;, therefore, effective interventions will require an integrated model of treatment in which monoaminergic systems are pharmacologically stabilized, and accompanied by psychotherapeutic and relational interventions.

Mechanisms that linked stress to Bipolar and Depression

I. **HPA Axis Dysregulation**- The hypothalamic–pituitary–adrenal (HPA) axis constitutes one of the major endocrine systems that maintain homeostasis when the organism is challenged or stressed (Dhabhar ,2014).. Stress is generally regarded as an essential evolutionary response to external stimuli, triggering “fight or flight” mechanisms that are crucial for survival. In mammals, this response is primarily mediated by the HPA axis, a negative feedback system that regulates the body’s physiological response to stress. Within seconds to minutes, Hypothalamus pituitary adrenal axis activation enables the body to prioritize critical functions like cognition and energy supply, while temporarily down regulating maintenance-related functions, such as digestion

II. **Neuroinflamation**- Recent evidence has indicated that bipolar and major depressive disorder arises from a state of neuroinflammation (Miller and Raison, 2016; Setiawan et al., 2015). Factors related to contemporary Western lifestyles, such as unhealthy diet and low physical activity, increase susceptibility to inflammatory dysregulation and chronic stress, both of which increase the amount of proinflammatory cytokines in peripheral blood, leading to low mood and sickness behavior (Rantala et al., 2018)

III. **Oxidative Stress**- Oxidative stress is commonly associated with the pathogenesis of diseases, such as cancer, cardiovascular disease, and diabetes. Additionally, it plays a key role in brain aging, increasing the risk factors for most neurodegenerative diseases, the pathophysiology of dementia, and many psychiatric disorders, such as depression, schizophrenia, bipolar mood, and anxiety disorders (Nicolai et al., 2015; Chen and Liu, 2017; Liguori et al., 2018; Singh et al., 2019). Neuronal membranes are particularly vulnerable to oxidation because of the large amount of unsaturated fatty acids associated with their elongated morphology

IV. **Neurotransmitter Imbalance**- All chemical messages transmitted between synapses involve both excitatory and inhibitory actions that keep systems in check and ensure that the response is neither too much nor too little, but "just right." It is a delicate balance and one that can lead to mental and physiological problems if the messaging is either excessive or deficient (Teleanu et al.,2022).

V. **Brain Region Changes**- Atrophy of the hippocampus and the prefrontal cortex can change it morphology as a result of stress. Neurogenesis in both areas can be stimulated with the right use of antidepressant (Duman & Aghajanian,2012).

The Role of Norepinephrine and Serotonin in Mood Disorders

Norepinephrine

Norepinephrine (also called noradrenaline) is a neurotransmitter (a type of chemical messenger between nerve cells) in the central nervous system and acts both as a neurotransmitter and as a hormone to help regulate stress responses. In terms of stress responses, norepinephrine, along with epinephrine, is responsible for creating what many people refer to as the "fight-or-flight" reaction (Dhabhar, 2014). When norepinephrine acts on adrenergic receptors, it causes an increase in heart rate, redistribution of blood flow to the skeletal muscles from other organs, improvement in alertness and the release of glucose—all of which are necessary to ensure survival in times of acute stress.

Norepinephrine has important regulatory roles in attention, executive functioning, arousal, motivation, and emotional reactivity within the central nervous system (Ressler & Nemeroff, 2000). Dysregulation of noradrenergic neurotransmission has been intimately connected with the development of mood disorders. Dysregulation of the noradrenergic system (hyperactivity and hypoactivity) is linked to the symptoms of bipolar disorder. Hyperactivity of the noradrenergic system can produce symptoms common to manic and hypomanic states such as irritability, insomnia, psychomotor agitation, increased goal-directed activity and arousal (Vieta et al., 2018). Conversely, hypoactivity of the noradrenergic system is associated with the core depressive symptoms of impaired concentration, psychomotor retardation, fatigue, decreased motivation and anhedonia (Thase, 2009).

Chronic stress can lead to sustained activation of the locus coeruleus-norepinephrine system which further increases mood instability and vulnerability to relapse (Miller & Raison, 2016). Excessively prolonged

dysregulation of the noradrenergic system may also result in decreased functioning of the prefrontal cortex.

Serotonin

Most of the body's serotonin (5-HT) is produced in the intestine from tryptophan, although it is also widely found throughout the central nervous system and is distributed throughout the digestive system (Otte et al., 2016). In the brain, serotonergic neurones are generally found in the raphe nuclei, which sends projections to the limbic system and the cortex that affect mood, impulse control, and how we integrate stress.

Although serotonin is generally regarded as a neurotransmitter that has an inhibitory effect on the target tissues, its function depends on the receptor to which it binds and the context of its release. It has an effect on many functions, including mood, sleep-wake cycles, appetite, sexual response, pain sensation, thermoregulation, bone density, and the healing of wounds (Haroon et al., 2017). A lack of serotonin transmission is one factor that can lead to mood disorder and/or major depressive disorder (Mann, 2003) associated with symptoms such as low mood, irritability, cognitive rigidity, rumination, and suicidal ideation. Reductions in expression of the serotonin transporter (5-HTT) and in serotonin receptor sensitivity can also occur, leading to increased vulnerability, especially in association with early life stress and epigenetic influences (Klengel & Binder, 2015).

Furthermore, serotonin has an important role in the modulation of excessive stress responses via the inhibition of the central nervous system. When there is low serotonin activity, the amygdala is more reactive, emotional regulation is more difficult, and there is increased impulsivity (Otte et al., 2016). This disruption may lead to depressive symptoms and/or suicidal behaviour, particularly when there are psychosocial stressors present.

Integrated Perspective

The monoaminergic system does not work independently; both norepinephrine and serotonin form a connected network together to create a stable affective experience. The interaction between these two neurotransmitters influences neuroplasticity, stress adaptation, and emotional processing in conjunction with cognitive processing. Disruption, i.e., genetic predisposition, chronic stress, or inflammatory response can lead to an imbalance of norepinephrine and serotonin (Vieta et al., 2018; Miller & Raison, 2016).

Therefore, mood disorders can be viewed as disturbances to highly developed neurochemistry related to both survival and quality of life. In this way, SSRIs and SNRIs, which focus on the restoring of the balance of serotonin and norepinephrine, and mood stabilizers and adjunctive treatments, which address the broader signaling pathways and intracellular cascades (Thase, 2009).

Psychotherapy as an Indispensable Adjunct in Bipolar Disorder Management

While medication remains a key component of treating bipolar disorder, research is increasingly showing that medication alone does not provide the entire solution to the ongoing issues of the more emotionally, psychologically, and cognitively vulnerable aspects of this disorder that feed cycles of relapse. Although mood stabilizers, antipsychotics, and antidepressants can assist in dealing with both mania and depression, they will not repair maladaptive cognitive schemas, poor emotional regulation, problems with interpersonal instability, or sensitivity to stress, which all put individuals at risk of recurring episodes (Geddes & Miklowitz, 2013). Clinical studies have shown that for most patients with BD medication alone did not reduce the frequency of relapses nor allow them to regain a functional quality of life (Chiang et al., 2023).

There is a consensus that BD is not only the result of an imbalance of neurochemicals, but is a form of mood dysregulation that is affected by one's social, cognitive, and existential circumstances. Therefore, if someone has BD and decides to use therapy to create change, it is not simply an option but must instead be viewed as a necessary component of addressing this debilitating disorder. There is a substantial body of research supporting several therapeutic interventions such as cognitive behavioural therapy (CBT), interpersonal social rhythm therapy (IPSRT), family focused therapy (FFT), and psychoeducation that, when used in combination with medication, can produce measurable decreases in the frequency of relapses, hospitalizations, and severity of symptoms (Miklowitz & Chung, 2016; Novick, 2019).

CBT works to target irrational beliefs such as grandiose beliefs during manic phases and hopelessness in depressive phases to interrupt the cognitive distortions that drive the changes in mood. IPSRT works at stabilizing biological circadian rhythms and regularising social routines where the two are closely associated. FFT improves communication patterns within families and decreases expressed emotions within families. In African collectivist societies, the relational patterns greatly shape mental health trajectories and make FFT particularly critical in this context.

In general, emotion-regulation capacity will affect long-term outcomes as well. There is research that shows how developing emotional intelligence through environments that foster emotional awareness and regulation leads to greater psychological resilience (Sele & Mukundi, 2023). When you think about how to apply that research clinically, psychotherapy helps develop emotional literacy by helping the patient identify prodromal symptoms, regulate escalating emotions and develop adaptive coping strategies.

Psychotherapy is more than reducing symptoms. Psychotherapy can also assess the existential and cultural components of mental health,

which are typically not considered in a biomedical model. The literature examining dignity, community identity, and spiritual meaning in African cultures illustrates how psychosocial stability and moral and community integration are inseparable (Sele & Whittaker, 2025). Similarly, sacred music and culturally based practices have been shown to promote reflective processing and coherence of emotion (Sele, 2025), and both linguistic and cultural resilience contribute to the continuity of identity and the ability to tolerate stress (Sele, Davou, & Zongo, 2025). These findings suggest that when engaging in psychotherapy, it is essential to be mindful of the cultural dimensions of an individual and the ways in which they derive spiritual meaning.

Recent meta-analyses provide evidence that integrated treatment is more effective than medication-only approaches for preventing relapse, stabilizing mood, promoting medication adherence, and enhancing overall well-being through the combination of medication and structured psychotherapy (Miklowitz & Chung, 2016; Novick, 2019).

Psychotherapy not only manages symptoms through targeting both the neurobiological and psychosocial factors of illness but also changes cognitive, emotional, and relational patterns of functioning that govern the long-term trajectory of the disorder.

Bipolar Disorder requires an integrative treatment approach to effectively manage it. Although medication can manage the neurochemical imbalance of the disorder, psychotherapy helps individuals build the cognitive structure, emotional discipline, and relational supports needed to achieve long-term recovery. Only when psychotherapy and medication work together to manage a person's bipolar disorder do the outcomes of that individual become not only less severe but drastically changed over time.

Bipolar Disorder is a complex and multifactorial medical condition, which requires a multifactorial approach to treatment. The addition of psychotherapy to pharmacological treatment has been shown to be extremely effective in managing Bipolar Disorder, especially with regard to relapse prevention and improving long-term outcomes.

These main specific psychotherapies are proven to support mood disorders:

- Cognitive Behavioral Therapy (CBT)- Based on robust evidence, Cognitive Behavioral Therapy is one of the most well-documented and validated psychotherapeutic methods available. Interventional strategies are based on modifying dysfunctional behaviors and cognitions(Lepping et al., 2017) However, the effectiveness of Cognitive Behavioral Therapy depends on patient's capacity to observe and change their own beliefs and behaviors. Some simple techniques were developed to overcome this issue, especially in primary care management.
- Interpersonal and Social Rhythm Therapy (IPSRT)- Interpersonal and Social Rhythm Therapy is based on the idea that stabilizing daily routines, especially sleep–wake cycles, can play a crucial role in managing mood episodes in Bipolar Disorder. Research has shown that disruptions in sleep and social rhythms can trigger mood swings in Bipolar Disorder patients, making this therapy particularly effective (Swartz et al.,2012). Moreover, IPSRT places a strong emphasis on addressing interpersonal stressors, which often contribute to mood disturbances. By improving communication skills and fostering stable relationships, patients can better manage social challenges that may exacerbate Bipolar Disorder symptoms.
- Family-Focused Therapy (FFT)- Family therapy involves working with the entire family to address issues that contribute to an individual's mental health. This type of therapy is particularly useful in treating mood disorders in adolescents and individuals living in close-knit family systems
- Trauma-focused therapy
- Psychoeducation- This type of intervention educates depressed patients and (with their permission) family members involved in the patient's life about depression symptoms and management.
- Mindfulness-based approaches- Mindfulness-based interventions have gained attention for their ability to help Bipolar Disorder patients develop greater awareness of their thoughts and emotions. By fostering a nonjudgmental awareness of internal experiences, mindfulness-based therapies help patients detach from ruminative thinking patterns that can lead to depressive episodes.

Each of these therapies has a unique and evidence-based role in treating Bipolar Disorder and addressing its varcious dimensions, including mood regulation, social functioning, and emotional regulation.

Integrative Treatment: Medication as Foundation, Psychotherapy as Structure

Medications are essential to treating Bipolar Disorder (BD) by helping fix the neurobiological disorder that causes BD. For example, medications such as lithium, anticonvulsants, and some atypical antipsychotics help control the pathways in our brain that signal the neurotransmitters and help stabilize the release of those neurotransmitters. These medications will also decrease the number and severity of episodes of mania and depression (Geddes & Miklowitz, 2013). If we can keep the fluctuations of mood from becoming too large from one extreme to another, then we will have a body that will be stable enough to assist people with getting involved in psychological therapy. If a person is experiencing

severe mania or depression, they often have little if any insight into their behavior or emotions due to lack of emotional regulation which will make therapy harder to conduct (Grande et al., 2016).

Neurochemical correction will not, however, correct the behavioral problems that have occurred for many years; the maladaptive cognitive patterns, and weakened relational systems. These areas are the focus of therapy. There are three empirically supported forms of therapy (CBT, IPSRT, FFT) that provide individuals with the necessary skills to help regulate their emotions, manage their stress, create stability in circadian timing, and to identify the precursors associated with the onset of the manic or depressive episode (Miklowitz & Chung, 2016). Through psychoeducation and structured approaches to address cognitive distortions, individuals will learn how to identify warning signs of an upcoming episode (i.e., prodromal symptoms), to modify their catastrophic or elevated thought processes, and to have a solid plan for preventing forward relapse based on consistent behavior.

This comprehensive approach is effective because it does not only treat the symptoms (dysfunction) of the person, but also the whole person; therefore, it does not limit one's view of an individual's dysfunction as an imbalance of neurotransmitters. Consistency in research (Novick, 2019; Geddes & Miklowitz, 2013) shows that adding therapy to medication creates significant benefit for patients through: improved psychosocial functioning, increased compliance with medications, fewer hospitalizations, and lower rates of relapse compared to medications only. Therapy builds executive functions and emotional awareness, both of which can only be developed through therapy; thus, using both methods together leads to much better results than just using medication.

Psychosocial resilience is also relational and cultural in nature, as evidenced by emotional intelligence research, which shows that providing a structured environment which promotes the development of emotional literacy increases adaptive function. In the African context, where community and spirituality are key components of overall health and well-being, implementing holistic approaches creates a wider definition of dignity and enables individuals to flourish as human beings (Sele & Whittaker, 2025). In addition, cultural continuity and linguistic identity build psychological stability and resilience (Sele, Davou, & Zongo, 2025).

As a result, medication creates the neurobiological underpinnings of stability by calming the "storm" caused by dysregulation of mood circuitry, while the use of psychotherapy develops the long-term structure of recovery, including cognitive restructuring, development of relational stability, creating/instilling self-discipline, and restoring peace and meaning to one's life. When these two modalities are combined, they provide not only symptom control but also create long term psychological stability and improve quality of life. Therefore, the long-term management of Bipolar Disorder requires a synergistic approach where biological correction and psychological development are purposefully intertwined.

Medication Treatment for Mood Disorders

The most common medications doctors prescribe for major depressive disorder are antidepressants, including:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants that don't fit into the other categories, such as bupropion and trazodone
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (less common)

Starting an antidepressant may trigger a manic episode if you have bipolar disorder. Although doctors may prescribe them in some cases, they typically only do this in combination with a mood stabilizer. Common medications for bipolar disorder (CANMAT Guidelines for Bipolar, 2018 or 2012) include:

Mood stabilizers. These can help control mania. Examples include:

- Carbamazepine (Equetro, Tegretol)
- Divalproex sodium (Depakote)
- Lamotrigine (Lamictal)
- Lithium
- Valproic acid (Depakene)

Antipsychotics. Doctors first used these to treat schizophrenia, but now they're used to treat bipolar. Although they're also primarily for mania, you may also see a difference in your depressive symptoms. Some can be taken alone or in combination with a mood stabilizer. Examples include:

- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Cariprazine (Vraylar)
- Lumateperone (Caplyta)
- Lurasidone (Latuda)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Geodon)

Antidepressant-antipsychotic. Although antidepressants alone have a risk of triggering a manic episode, the medication Symbyax combines the antidepressant fluoxetine and the antipsychotic olanzapine to treat depression and work as a mood stabilizer. The FDA approved it for the treatment of depressive episodes associated with bipolar I disorder.

The most common side effects these medications cause include:

- Dizziness or nausea
- Drowsiness or fatigue
- Frequent urination, dry mouth, or increased thirst
- Muscle twitching in your hands, face, or other muscles
- Weight gain
- Acne or skin rash
- Blurred vision

CONCLUSION

The risk of Major Depressive Disorder and Bipolar Disorders are shaped by the interactions of negative life events, epigenetic gene expression, and genetic predisposition. These interactions are linked by the serotonin and norepinephrine pathways that support in mediating the cognitive, emotional, and behavioral symptoms of mood disorder. These biological vulnerabilities are bigger in African systems in which socioeconomic stressors and trauma are common place.

The effective combinations of pharmacotherapy and psychotherapy offer model approaches to the treatment of mood disorders. The growing burden of mood disorder in Africa can be addressed by strengthening the mental health systems in improving access to evidence based approaches to treatment, and increasing research in genetic and epigenetic

REFERENCES

Agnew-Blais, J., & Danese, A. (2016). Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: A systematic review and meta-analysis. *The Lancet Psychiatry, 3*(4), 342–349. https://doi.org/10.1016/S2215-0366(16)00012-8

Bergink, V., Larsen, J. T., Hillegers, M. H. J., Dahl, S. K., Stevens, H., Mortensen, P. B., Petersen, L., & Munk-Olsen, T. (2016). Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder. *Translational Psychiatry, 6*(10), e929. https://doi.org/10.1038/tp.2016.201

Bruni, A., Carbone, E. A., Pugliese, V., et al. (2018). Childhood adversities are different in schizophrenic spectrum disorders, bipolar disorder and major depressive disorder. *BMC Psychiatry, 18*, 391. https://doi.org/10.1186/s12888-018-1972-8

Chiang, K. J., Tsai, J. C., Liu, D., Lin, C. H., & Chou, K. R. (2023). Effectiveness of pharmacotherapy alone versus combined psychosocial interventions in bipolar disorder: A systematic review. *Journal of Affective Disorders, 324*, 123–135.

Dhabhar, F. S. (2014). Effects of stress on immune function: The good, the bad, and the beautiful. *Immunologic Research, 58*(2–3), 193–210. https://doi.org/10.1007/s12026-014-8517-0

Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: Potential therapeutic targets. *Science, 338*(6103), 68–72. https://doi.org/10.1126/science.1222939

Eagle Scholars Forge (2026), *Feh Theodaline Ndifon.* https://www.selemedia.org/scholars/hall_of_fame/feh-theodaline-ndifon/

Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. *The Lancet, 381*(9878), 1672–1682. https://doi.org/10.1016/S0140-6736(13)60857-0

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. *The Lancet, 387*(10027), 1561–1572. https://doi.org/10.1016/S0140-6736(15)00241-X

Haroon, E., Miller, A. H., & Sanacora, G. (2017). Inflammation, glutamate, and glia: A trio of trouble in mood disorders. *Neuropsychopharmacology, 42*(1), 193–215. https://doi.org/10.1038/npp.2016.199

Klengel, T., & Binder, E. B. (2015). Epigenetics of stress-related psychiatric disorders and gene × environment interactions. *Neuron, 86*(6), 1343–1357. https://doi.org/10.1016/j.neuron.2015.05.036

Mann, J. J. (2003). Neurobiology of suicidal behaviour. *Nature Reviews Neuroscience, 4*(10), 819–828. https://doi.org/10.1038/nrn1220

Miklowitz, D. J., & Chung, B. (2016). Family-focused therapy for bipolar disorder: Reflections on 30 years of research. *Family Process, 55*(3), 483–499. https://doi.org/10.1111/famp.12237

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology, 16*(1), 22–34. https://doi.org/10.1038/nri.2015.5

Nemeroff, C. B., et al. (1984). Elevated concentrations of corticotropin-releasing factor–like immunoreactivity in the cerebrospinal fluid of depressed patients. *Science, 226*(4680), 1342–1344.

Novick, D. M. (2019). Psychotherapy for bipolar disorder: Efficacy and mechanisms of change. *Current Psychiatry Reports, 21*(7), 60. https://doi.org/10.1007/s11920-019-1040-6

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers, 2*, 16065. https://doi.org/10.1038/nrdp.2016.65

Peng, H., Palma-Gudiel, H., McKenney, J., Ceasar, S. A., Zhang, Y., Poe, G., … North, M. (2020). Childhood trauma, DNA methylation of stress-related genes, and depression: Findings from two monozygotic twin studies. *Psychoneuroendocrinology, 113*, 104580.]https://doi.org/10.1016/j.psyneuen.2020.104580

Perroud, N., Paoloni-Giacobino, A., Prada, P., Olié, E., Salzmann, A., Nicastro, R., … Malafosse, A.

(2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. *Translational Psychiatry, 1*, e59. https://doi.org/10.1038/tp.2011.60

Ressler, K. J., & Nemeroff, C. B. (2000). Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biological Psychiatry, 46*(9), 1219–1233.

Sele, J. P. (2025). Sacred music as a catalyst for theological reflection and social development: A critical review of African Christian liturgical traditions. *Journal of Fine and Creative Arts, Music, Media and Communication Studies, 1*(2). https://www.researchgate.net/publication/396717884

Sele, J. P., Davou, S. Y., & Zongo, P. K. (2025). The role of the Berom language in fostering cultural resilience and sustainable development in Jos, Nigeria. *International Journal of Social and Economic Development, 1*(3), 82–86. https://www.researchgate.net/publication/397997660

Sele, J. P., & Mukundi, M. B. (2023). The impact of emotional intelligence on pedagogy: Fostering a supportive classroom environment. *Greener Journal of Social Sciences, 13*(1), 172–183. https://doi.org/10.15580/gjss.2023.1.122024210

Sele, J. P., & Whittaker, T. J. (2025). Who buries the believer? Church authority, human dignity, and the question of salvation in African and Caribbean Christian death rituals. *African Journal of Stability & Development, 17*(2), 1542–1572. https://doi.org/10.53982/ajsd.2025.1702.39-j

Setiawan, E., et al. (2015). Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry, 72*(3), 268–275. https://doi.org/10.1001/jamapsychiatry.2014.2427

Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2019). Oxidative stress: A key modulator in neurodegenerative diseases—and increasingly recognized in mood disorders. *Molecules, 24*(8), 1583. https://doi.org/10.3390/molecules24081583

Thase, M. E. (2009). Neurobiological aspects of depression and its treatment. *Journal of Clinical Psychiatry, 70*(Suppl 5), 3–8.

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., … Grande, I. (2018). Bipolar disorders. *The New England Journal of Medicine, 378*(5), 455–466. https://doi.org/10.1056/NEJMra1710763

Wrobel, A. L., Köhler-Forsberg, O., Sylvia, L. G., et al. (2022). Childhood trauma and treatment outcomes during mood-stabilizing treatment with lithium or quetiapine among outpatients with bipolar disorder. *Acta Psychiatrica Scandinavica, 145*(6), 615–627. https://doi.org/10.1111/acps.13493

Cite this Article: Feh, TN; Ninyin, C (2026). Genetic, Epigenetic, and Neurobiological Pathways in Bipolar and Major Depressive Disorders and the Case for Integrated Pharmaco-Psychotherapy. *Greener Journal of Biomedical and Health Sciences*, 9(1): 76-86**, https://doi.org/10.15580/gjbhs.2026.1.041126053.**