Review

The Role of Inflammatory Cytokines in Adolescent Bipolar Disorder: A Systematic Review

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Abstract

Bipolar spectrum disorders (BSD) are neuropsychiatric conditions that involve manic symptoms and depression symptoms. The prevalence of Bipolar Disorder (BD) is 1% to 3% in youth, which is known to undermine their cognitive, emotional, and social functions. Among the many biological mechanisms underlying BD, pro-inflammatory cytokines are small proteins that are active in the immune system, which can affect neuronal activity by altering blood-brain permeability, neurotransmitter activeness, and causing damage to the neuronal cells. This systematic review examines different types of cytokines and how their level varies in adolescent BD. Specifically, the review examined pro-inflammatory cytokines IL-6, IL-8, TNF-α, and IL-1β and an anti-inflammatory cytokine IL-10. A total of 9 studies were included from screening two databases, PsycInfo and PubMed. Overall, the levels of IL-6, IL-8, TNF-α, and IL-1β positively correlated with BD symptoms. While these findings have implications for treatment, counseling, medication, and prevention strategies specific to adolescent patients, future research must address the inconsistency around IL-10 levels as well as other biomarkers such as Brain-Derived Neurotrophic Factors (BDNF).

Keywords: adolescent; bipolar disoder; bipolar spectrum disorder; cytokine; pro-inflammatory marker; neuro-inflammatory marker

I. Introduction

Bipolar spectrum disorders (BSD) are neuropsychiatric conditions which are characterized by shifting mood, alternating highs (manic or hypomanic) and lows (depression) [1]. Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is widely used to diagnose psychiatric symptoms, in which BSD are classified into three types: bipolar disorder (BD) I, II, and cyclothymia [1]. BD I is characterized by at least one manic episode, preceded or followed by hypomanic or major depressive episodes [2]. BD II is marked by at least one hypomanic and major depressive episode, yet lacking full manic episodes [2]. Lastly, cyclothymia is defined by a period of elevated mood symptoms and depressive symptoms for at least two years, yet is not included in major depressive, manic, or hypomanic criteria [2].

The prevalence of mood disorders worldwide is approximately 22%, with around 1% of BD and 7% of Major Depressive Disorder (MDD) [3]. BD occurs in 1% to 3% of youth, and 50 % of adolescents diagnosed with MDD convert to BSD [4,5]. Similar to other neuropsychiatric disorders like schizophrenia, researchers have indicated that 45% of first episodes of BD occur in an average age of 17 years [6]. Adolescence is a critical period, marked by the development of the nervous system, which is responsible for cognitive, emotional, and social functions [7]. One research highlighted that adolescents with the first episode of BD showed impaired cognitive function, as demonstrated by their memory, attention, and executive function [8].

Gene-environment interplays establish the epigenetic cause of BD, highlighting the complexity of its cause. Many mental disorders, including Schizophrenia (SCZ), BD, MDD, autism spectrum

disorder (ASD), and attention deficit hyperactivity disorder (ADHD), have high heritability [9]. Specifically, heritability for BD ranges is estimated to be 44%, according to a family-based study [10].

In addition, family history for BD increases the risk of developing BD [11]. Other environmental factors for psychiatric disorders exist. Childhood traumatic experiences, such as physical, sexual, or emotional abuse can contribute to psychiatric disorders [12]. These environmental factors can contribute to the development of stress, which is a risk factor for depression [13].

In diagnosing BD, symptom-focused strategy is widely used, yet it is limited to recognizing patients whose early onset is depression episodes. According to one study, assessing BD in youth primarily relies on interview and observation, lacking objective criteria [4]. This can lead to exacerbation of BD in adolescents, as misdiagnosis of BD in early onset results in insufficient medication and more severe episodes [14]. Therefore, identifying biomarkers that contribute to BD is needed to accurately assess BD in adolescent patients.

Among the many biomarkers, pro-inflammatory markers (PIM) are neurological markers that are involved in physiological processes of BD, such as glucocorticoid resistance, blood-brain barrier dysfunction, changes in neurotransmitter activity, and damage in neuronal cells [15]. Cytokines are small proteins that are responsible for immune responses, as they affect neuronal activity, including excitability and plasticity [16,17]. Specifically, cytokines activate the HPA axis, which in turn releases corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisols, while reducing the function of glucocorticoid receptors [18].

Cytokines that are directly correlated with neurological functions include tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-10 (IL-10), and interleukin-8 (IL-8).

Tumor necrosis factor alpha (TNF-α) is a type of cytokine secreted by macrophages, glial cells, and neurons [19]. As a pro-inflammatory cytokine, TNF-α affects the function of neurons, the amount of neurotransmitters, and the synthesis of myelin in the central nervous system by increasing blood-brain barrier permeability [19]. One longitudinal study reported that TNF-α is negatively associated with cortical thickness of the prefrontal lobe of individuals who are at risk of developing a psychotic disorder [20]. The cytokine's neurological role implies its correlation with Bipolar Disorder.

Another cytokine, Interleukin-6 (IL-6) has both beneficial and destructive potentials, contributing to the development, differentiation, regeneration, and degeneration of neurons [21]. IL-6 level was significantly correlated with mental disorders, as exemplified by a study that examined IL-6 gene expression in blood leukocytes, which was negatively correlated with hippocampal volume in schizophrenia patients [22].

Interleukin 1β (IL-1β) is a pro-inflammatory cytokine in the CNS, released by peripheral and brain macrophages [23]. One study demonstrated that administering lipopolysaccharide caused the expression of IL-1β, which in turn contributed to depression and anxiety in healthy participants [24]. Another finding highlighted that increased IL-1β mRNA levels in schizophrenia patients induced a decrease in Broca's area volume and verbal capability [25].

Interleukin 10 (IL-10) is an anti-inflammatory cytokine that maintains normal tissue homeostasis, thereby preventing autoimmune diseases [26]. According to one study, increased IL-10 levels effectively prevented neuronal degeneration, which is caused by neuroinflammation in diseases like Alzheimer's Disease and Parkinson's Disease [27].

Lastly, Interleukin 8 (IL-8) is a pro-inflammatory cytokine that is released by microglia, whose increased levels are found to be correlated with psychiatric diseases like BD, ASD, SCZ, and ASD [28].

For the adult group, an extensive amount of studies identified biomarkers that are associated with BD. One meta-analysis demonstrated that a pro-inflammatory marker, C-Reactive protein (CRP) was increased in adult BD patients compared to healthy controls (HC), especially highest during manic and depressive periods [29]. Another systematic review indicated that pro-inflammatory cytokines were elevated in the adult BD group compared to HC [30]. Yet, there are not enough studies that focus on cytokine levels within adolescent BD patients. Since cytokine levels in adults and adolescents differ significantly, findings from studies on adults cannot be fully generalized to youth patients [31].

This systematic review investigated the role of different inflammatory cytokines in bipolar disorder in adolescent patients.

II. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It conducted online searches of PubMed and PsycInfo, using keywords including "adolescent," "bipolar disorder," and "cytokines," for studies from 1990 until May 2025.

Initially, 132 papers were reviewed through skimming, leaving 52 research papers that are relevant to the topic. The inclusion criteria applied were the following: (a) study type: longitudinal, cross-sectional, and prospective repeated-measures study; (b) age: adolescents and young adults (mean age of 12 to 25 years old); (c) diagnosis of subjects: any bipolar disorder (BD-I, BD-II, BSD, and not otherwise specified BD (NOS-BD)); (d) symptoms: any symptoms of BD as defined by DSM-5 Diagnostic and Statistical Manual of Mental Disorders (DSM); (e) studies that examined any neuro-inflammatory cytokines; and (f) language: English only.

The exclusion criteria applied were the following: (a) study type: narrative reviews, systematic reviews, and meta-analysis; (b) age: adults and infants (outside of range 12 to 25); (c) diagnosis of subjects: other mood disorders than BD (e.g., MDD); and (d) studies that focused on other biological markers than cytokines or only focused on neurotrophic factors.

After a full-text review of 15 papers, 9 studies were included in the final analysis. Figure 1 illustrates the screening process used in this research.
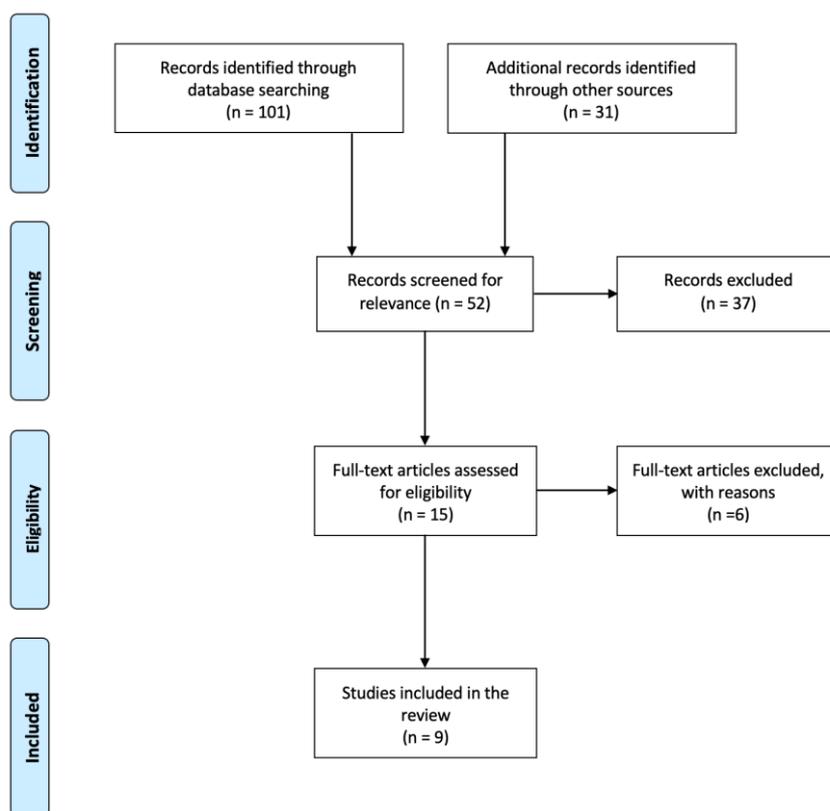

Figure 1. PRISMA Flow Diagram showing the process of literature review in this study.

III. Results

The following is the table summarizing the findings of each reviewed source. Detailed results in accordance with each type of cytokine are presented after.

Table 1. Detailed Findings of Reviewed Sources.

Reference	Year	Study Design	No. of participants	Age of participants (mean and SD)	No. of controls	Age of controls (mean and SD)	Cytokines	Research Focus	Confounding Factor controlled
Skibinska et al. [32]	2022	Longitudinal	25	18.28 (±2.82)	31	21.1 (±2.76)	IL-8, TNF-α	Examined defensive mechanisms and cytokines	Age, gender
Goldstein et al. [33]	2015	Longitudinal	123	20.4 (±3.8)	N/A	N/A	IL-6, TNF-α	Examined pro-inflammatory markers in lifetime characteristics, clinical characteristics, and metabolic syndrome variables	N/A
Goldstein et al. [34]	2011	Longitudinal	30	15.5 (±2.3)	N/A	N/A	IL-6	Examined bipolar subtypes and pro-inflammatory markers	N/A
Bai et al. [35]	2024	Longitudinal	21	12-17	69	12-17	TNF-α	Examined suicidal symptom severity and proinflammatory cytokines	Suicide severity, age, sex, BMI, education years, non-suicidal depressive symptoms
Karthikeyan et al. [36]	2022	Prospective repeated-measures study	43	17.27 (±1.51)	36	17.09 (±1.68)	IL-6, IL-10, TNF-α	Examined inflammatory markers as predictors of future mood symptoms and time for recovery	Age, sex, SES, BMI
Miklowitz et al. [37]	2016	Cross-sectional	18	16.0 (±2.1)	20	16.6 (±2.2)	IL-1β, IL-6, IL-8, IL-10, TNF-α	Examined systemic and cellular markers of inflammation in BD patients	N/A
Terczynska et al. [38]	2025	Longitudinal	24	18.95 (±3.52)	N/A	N/A	TNF-α, IL-8	Examined cytokines with temperament and character dimensions	N/A
Pearlstein et al. [39]	2020	Longitudinal	25	15.03 (±1.90)	N/A	N/A	IL-6, IL-12, IL-1β, TNF-α	Examined the changes in cytokine levels between pre- and post-cognitive behavioral therapy (CBT)	N/A
Hatch et al. [40]	2017	Cross-sectional	40	17.41 (±1.64)	20	16.06 (±1.67)	IL-6, TNF-α	Examined the link between cytokine levels in BD patients and cardiovascular disease (CVD) risk	Age, BMI

1) IL-6

IL-6 level increased for a longer duration of Bipolar Disorder (BD), maximum depressive severity, maximum hypo/manic severity, subthreshold mood symptom duration, and suicidal ideation [33]. Exposure to psychotic medication and obesity also led to higher IL-6 [33]. Family history of Attention Deficit Hyperactivity Disorder (ADHD) and substance use disorder (SUD) was negatively correlated with IL-6 level [33]. During euthymia, IL-6 level was lowered [33]. In addition, high levels of high-density lipoprotein (HDL) were associated with lower IL-6 [33]. There was no significant difference in IL-6 levels between BP-1 and BP-NOS patients, although obese subjects had higher IL-6 levels than nonobese subjects [34]. The ratio of IL-6/IL-10 was greater in the BD group compared to the HC [36]. There were no findings for IL-6 level as a predictor for future mood symptoms and time to recovery [36]. Controlling for age and BMI factors, IL-6 levels were increased in the BD group compared to the HC [40]. Adolescents with symptomatic BD resulted in the highest level of IL-6 [40]. There was a decreasing linear association of IL-6 between groups of symptomatic BD, asymptomatic BD, and HC [40].

2) IL-8

IL-8 level increased in the Bipolar Disorder (BD) group compared to the Major Depressive Disorder (MDD) group [32]. The study highlighted the negative correlations between IL-8 levels and immature defense mechanisms in the BD group [32].

IL-8 level did not show a significant correlation with temperament characteristics of individuals in the BD group [38].

3) TNF-α

Compared to the healthy control (HC) group, the BD group showed higher TNF-α levels [32]. The BD group also showed a higher level of TNF-α compared to the MDD group [32]. The study highlighted the negative correlations between TNF-α levels and immature defense mechanisms in the BD group [32]. Other variables, including low socioeconomic status, lifetime suicide attempts, lifetime self-injurious behavior, family history of SUD, psychosis duration, and high triglyceride, were correlated with higher levels of TNF-α [33]. Patients in the BD group had higher TNF-α levels compared to MDD and HC [35]. There were no findings for TNF-α level as a predictor for future mood symptoms and time to recovery [36]. TNF-α level did not show a significant correlation with temperament characteristics of individuals in the BD group [38]. Controlling for age and BMI factors, TNF-α levels were increased in the BD group compared to the HC [40]. There was a decreasing linear association of TNF-α between groups of symptomatic BD, asymptomatic BD, and HC [40].

4) IL-10

IL-10 was lower in patients' symptomatic periods [36]. There were no findings for IL-10 as a predictor of time to recovery [36]. IL-10 was positively associated with increased severity of mood symptoms in the future phase [36].

5) IL-1β

Plasma levels reported that IL-1β was higher in the BD youth group than in controls [37].

IV. Discussion

Studies of cytokine levels in adolescent BD patients are insufficient. This study aimed to investigate changes in inflammatory cytokine levels for adolescent BD patients, aged 18 or younger.

IL-6 levels positively correlated with the mood symptoms across adolescent BD groups, as confirmed by several studies [33,40]. These findings are congruent with the fact that the increased level of IL-6 is linked with other mental disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and brain cancer [41]. Goldstein et al. confirmed the positive correlation between IL-6 levels and symptomatic duration, which can be explained by the findings that overproduction of IL-6 leads to longer periods of neuroinflammatory multiple sclerosis (MS) (33,41). As exposure to

medication and obesity had implications on IL-6 levels [33,34], future studies must control such factors when examining IL-6 levels in BD.

Although IL-8 levels increased in the BD group compared to the MDD group [32], there were no studies that examined the difference in IL-8 levels between the BD and HC groups. IL-8 levels are positively correlated with body mass, waist circumference, and lean body mass, but not significantly affected by sex [42], and these factors must be considered in future research comparing BD and HC.

Confirmed by multiple studies, it is evident that TNF-α levels increase across adolescent HC, MDD, and BD groups [32,35,40]. These findings are also congruent in adult BD patients, as a myriad of studies have found increased TNF-α levels [43,44]. It is known that TNF-α dysfunctions the brain blood-brain barrier (BBB); that is, it allows more inflammatory mediator cells and peripheral immune cells to infiltrate into the CNS, which leads to mood disorders [45]. These findings indicate that TNF-α can be an objective biomarker that can distinguish between BD and MDD diagnosis.

Hatch et al. found that TNF-α is the highest in the adolescent symptomatic BD group, followed by asymptomatic and HC [40], which implies that if medications are applied effectively to patients, TNF-α levels can be decreased accordingly. In fact, in an experiment using mice, antipsychotic drugs demonstrated anti-inflammatory effects, thereby decreasing the synthesis of IL-6 and TNF-α by lipopolysaccharides [46]. Therefore, the future direction of research that focuses on treatment for bipolar and mood disorders needs to effectively regulate TNF-α levels.

There exists a notable inconsistency around IL-10 levels in adolescent BD patients. Karthikeyan et al. found the lowered level of IL-10 in symptomatic periods [36], yet some studies found the elevated level of IL-10 in the adult BD group [47–49]. These discrepancies can be attributed to the detectability of IL-10. One research indicated that more than IL-10 was not detectable within 90% of elderly subjects [50]. As IL-10 levels are detectable at low levels in humans, the sensitivity of the bioassay also affects the IL-10 [51], which could also be attributed to past studies' inconsistency. In addition, according to Wiener et al., IL-10 levels are found to be dynamic: in earlier stages of mood disorder, IL-10 levels increased, while during the course of the disorder, the levels decreased [52]. To address these discrepancies, future researchers can examine the pro- to anti-inflammatory marker ratio, rather than examining solely IL-10 levels, as one study reported that the ratios have higher sensitivity than individual markers in BD youth [36]. In addition, they may examine the level of IL-10 based on symptoms during the course of the BD, which may yield specific changes in IL-10 levels.

A single study examined the increased IL-1β level in adolescent BD patients [37]. Similarly, one study found that IL-1β level is proportional to the severity of illness, and the level also increased in elderly BD patients compared to HC [53]. These findings can be attributed to the fact that IL-1β is known to be a biological marker that is central to explaining different human behaviors. One experiment using rats confirmed the positive correlation between acute stress and the level of IL-1β [54].

This study examined cytokines as primary biomarkers for adolescent BD, yet did not examine brain-derived neurotrophic factor (BDNF). According to Karthikeyan et al., BDNF did not have statistical differences in adolescent BD compared to HC [36]. In addition, another research confirmed reduced levels of BDNF at ages 10-19 years compared to 0-9 years and 30-39 years, which implies the age-related difference in the BDNF level [55]. There also lie other variables, such as age, weight, and gender, that affect BDNF levels, as one study reported lower platelet BDNF levels in women than men [56]. Still, BDNF must not be eclipsed as an inconsequential factor for other mental disorders, as a study showed its association with autism [57].

Goldstein et al. reported higher levels of high-sensitivity C-Reactive protein (hsCRP) for adolescents' longer duration of BD [33]. Yet, this study did not examine CRP levels as a valuable biomarker for adolescent BD because CRP can increase non-specifically in various conditions. Factors including infections, autoimmune conditions, cardiovascular events, past trauma or injury, cancer, diet, obesity, smoking, and alcohol were found to affect CRP levels [58], making it difficult to control for confounding variables and to accurately attribute changes in CRP levels specifically to adolescent BD patients compared to HCs. This suggests that cytokine levels may be influenced by such

confounding variables; hence, blood tests to detect cytokine levels must not be conducted on BD patients with autoimmune diseases, a history of steroid use, or alcohol or drug consumption [59–61].

One study found that TNF-α and IL-6 levels did not show any statistical difference for adult BD patients, compared to HC [48,59]. This implies the uniqueness of such markers in adolescent BD patients, which will be crucial in future studies specifically investigating medications, treatments, and prevention plans for adolescent BD.

Exemplified by some articles, cytokine levels are influenced by treatment and symptom variations [33,40]. Therefore, a single blood test alone has limitations in sufficiently reflecting the diversity of symptoms and changes in cytokine levels following psychiatric drug treatment. This must be considered in future research as well as other reviews of cytokine levels in adolescent BD patients.

A limitation of this systematic review is the small number of studies included. Also, due to the inaccessibility of specific patient data, studies including both adults and adolescents without disaggregated individual information could not be considered. Although Table 1 indicates whether the confounding variables were controlled for each study, future studies must effectively account for factors such as sex, gender, obesity, history of abuse, and family history, among others.

V. Conclusion

This systematic review included studies that reported differences in levels of cytokines, including IL-6, IL-8, TNF-α, IL-10, and IL-1β, for adolescents with bipolar disorder (BD). The levels of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, and IL-1β) positively correlate with adolescents' symptoms of bipolar disorder, which corroborates the preliminary findings about the effect of neuro-inflammation on neuronal activities. Further research is needed to address the inconsistency of the anti-inflammatory cytokine IL-10. Overall, this examination of multiple biomarkers will be useful in future research to implement treatment, counseling, medication, and prevention strategies specific to adolescents with bipolar disorder.

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