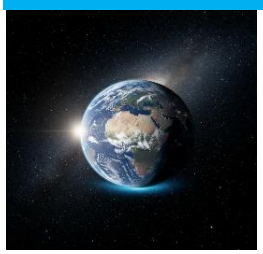
Journal of Education, Health and Sport. 2026;88:68648.
eISSN 2391-8306.

https://doi.org/10.12775/JEHS.2026.88.68648



Journal of Education, Health and Sport. eISSN 2450-3118

Journal Home Page
https://apcz.umk.pl/JEHS/index

STYCZYŃSKA, Małgorzata, WOJEWÓDZKI, Maciej, CYRZAN, Alicja, ZALEWSKI, Jakub, ZYSK, Adam, ZĄBEK, Mateusz, IWANOWSKA, Martyna, FLIS, Beata, GOSS, Adrian and FRONCZAK, Bartosz. Vitamin D, Vitamin B9 (Folic Acid) and Vitamin B12 Status in Bipolar Disorder: Associations with Symptom Severity and Course of Illness. Journal of Education, Health and Sport. 2026;88:68648. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2026.88.68648

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.01.2026. Revised: 15.02.2026. Accepted: 17.02.2026. Published: 19.02.2026.

Vitamin D, Vitamin B9 (Folic Acid) and Vitamin B12 Status in Bipolar Disorder: Associations with Symptom Severity and Course of Illness

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Abstract

Background: Bipolar disorder (BD) is a chronic mood disorder associated with substantial functional impairment and elevated suicide risk. Nutritional psychiatry has highlighted potential links between vitamin D, folate (vitamin B9), vitamin B12, and one-carbon metabolism (including homocysteine) and affective symptom burden, yet BD-specific evidence remains heterogeneous.

Aim: To organize and critically synthesize evidence on the relationship between vitamin D status (25[OH]D) and B-group vitamins-particularly folate (B9) and vitamin B12-and the clinical phenotype of BD, including symptom severity, illness phase, course features, cognition, suicidality-related outcomes, and the effects of supplementation where available.

Material and methods: All data were collected from publicly available sources. This article's databases were accessed via PubMed/MEDLINE and the Cochrane Library.

Summary: Current evidence supports frequent vitamin D insufficiency in BD but does not demonstrate an evidence-based therapeutic effect of vitamin D supplementation on bipolar depressive symptoms. Folate, vitamin B12, and homocysteine findings more consistently relate to bipolar depression and cardiometabolic comorbidity, while supplementation data remain preliminary and insufficient for routine adjunctive use beyond documented deficiency. In clinical practice, assessment and correction of vitamin D, folate, and especially vitamin B12 abnormalities should be considered as part of comprehensive medical care in BD, with vitamin B12 testing having particular value when presentations are atypical or medically suggestive.

Keywords: bipolar disorder; vitamin D; 25-hydroxyvitamin D; folate; folic acid; vitamin B12; cobalamin; homocysteine; one-carbon metabolism; supplementation.

Introduction

Bipolar affective disorder, commonly referred as bipolar disorder (BD), is a chronic psychiatric condition characterized by alternating periods of depressed mood depressive episodes) and elevated mood, that is, manic or hypomanic episodes. It is estimated that bipolar disorder affects up to approximately 2% of the population, making it a significant public health concern. The

diagnosis of BD may be challenging, particularly in cases where depressive episodes predominate over a prolonged period, which can lead to misclassification as unipolar depression. According to the criteria of the International Classification of Diseases, 10th Revision (ICD-10), the diagnosis of bipolar disorder requires the occurrence of at least two mood episodes, of which at least one must be manic or hypomanic episode; the duration of a manic episode should me at least 7 days, whereas a hypomanic episode should last at least 4 days. From a clinical perspective, bipolar disorder is usually divided into type I and type II. Bipolar I disorder is characterized by the occurrence of both depressive and manic episodes, each of which may reach considerable severity. In clinical practice, a predominance of the cumulative duration of depressive episodes over manic episodes is commonly observed. In bipolar II disorder, recurrent depressive episodes also occur; however, periods of mood elevation are milder, take the form of hypomania, and are typically shorter in duration than manic episodes in bipolar I disorder. Bipolar disorder is associated with a marked reduction in quality of life and significant impairment in social and occupational functioning. During manic episodes, psychotic symptoms, including grandiose delusions, may occur, whereas depression in the course of BD is characterized by frequent recurrences, rapid escalation of symptoms, and a high rate of treatment resistance, These factors contibute to an increased risk of suicide attempts (1).

Growing evidence indicates that the course of mood disorders, including bipolar disorder, is closely linked to metabolic factors, diet and lifestyle, forming the basis of the emerging concept of nutritional psychiatry (2,3). Narrative and systematic reviews emphasize that vitamin D and B-group vitamins, particularly vitamin B9 (folic acid) and vitamin B12, play a central role in one-carbon metabolism, homocysteine regulation, DNA methylation, neurotransmitter synthesis, hypothalamic-pituitary-adrenal axis function, inflammatory pathways and protection against oxidative stress (2,4,5). Deficiencies of these vitamins or low serum concentrations are associated with greater depressive symptom severity, more frequent depressive episodes and an increased risk of suicidal behaviour across different populations with psychiatric disorders (4,5,6). Meta-analyses of randomized controlled trials further indicate that vitamin D supplementation, especially in individuals with low baseline 25(OH)D levels, is associated with a modest but statistically significant reduction in depressive symptoms and a potential decrease in the risk of incident depression (7,8). At the same time, data on patients with severe mental illness, including bipolar disorder, suggest a high prevalence of unhealthy dietary patterns, vitamin D deficiency and disturbances in vitamin B9 (folic acid) and vitamin B12 metabolism,

while dietary and broader lifestyle interventions may influence depressive symptom burden and psychosocial functioning (9,10,11).

In the context of bipolar disorder, increasing attention has been directed towards the potential role of vitamin D, vitamin B9 (folic acid) and vitamin B12 as modulators of neurobiological processes relevant to mood regulation. These vitamins are involved in central nervous system functioning through their effects on monoaminergic neurotransmission, synaptic plasticity, inflammatory pathways and homocysteine metabolism, providing a biological basis for hypotheses linking their status to mood disorders (4,12,13). Vitamin D, via vitamin D receptors and activating enzymes expressed in brain regions implicated in emotion regulation, such as the prefrontal cortex and hippocampus, may influence neurotrophin expression, serotonergic and dopaminergic activity, and immune-inflammatory modulation, which has led to the proposal that it may be relevant to the pathophysiology of depression and bipolar disorder (12,15). Vitamin B9 (folic acid) and vitamin B12, in turn, play a central role in one-carbon metabolism, supporting appropriate DNA and protein methylation and the synthesis of key monoamine neurotransmitters; disturbances in these pathways have been associated with an increased risk of depressive disorders and suicidal behaviour (4,13).

Reviews including large cohorts of patients with major psychiatric disorders - among them bipolar disorder - indicate that deficiencies of vitamin D, vitamin B9 and vitamin B12 are relatively common and are considered potentially modifiable biological factors that may contribute to clinical severity and metabolic comorbidity, although the existing evidence is predominantly observational in nature (13,14). In bipolar disorder specifically, the role of these vitamins is only beginning to be systematically investigated; the available literature and review articles focus primarily on vitamin D, whereas conclusions regarding vitamin B9 and vitamin B12 are largely extrapolated from studies conducted in unipolar depression and other mood disorders (4,12-15). The background provides the rationale for a focused evaluation of the relationship between vitamin D, vitamin B9 and vitamin B12 status and symptom burden and illness course in bipolar disorder in the present review.

The aim of this review is to organise and critically synthesize the current evidence on the relationship between vitamin D status (25[OH]D) and B-group vitamins - particularly vitamin B9 (folic acid) and vitamin B12 - and the clinical phenotype of bipolar disorder (BD), including the occurrence and temporal dynamics of depressive, manic, and hypomanic episodes,

symptom severity measured with standardized rating scales, relapse patterns (including rapid cycling), psychosocial functioning, suicidality-related outcomes, and selected domains of cognitive performance (13-18). Based on the available reviews and clinical studies, the synthesis will address both observational evidence (associations between circulating levels/deficiency states and BD symptom patterns) and interventional evidence (whether correcting deficiencies has been examined as an adjunctive strategy in specific illness phases) (13-18). In the present review, we aim to answer whether, in adult patients with BD (type I/II), low levels of vitamin D, vitamin B9 (folic acid) or vitamin B12 (or elevated homocysteine as a proxy of disturbed one-carbon metabolism), compared with adequate levels, are associated with higher affective symptom burden and a less favorable course, and - where interventional evidence exists - whether supplementation of these vitamins influences symptom severity and selected prognostic indicators (13-19).

Research materials and methods

This work was prepared as a structured narrative review with a systematic search component. The literature search was conducted in PubMed/MEDLINE and the Cochrane Library and was complemented by hand-searching the reference lists of key eligible papers. The strategy combined MeSH terms and free-text keywords for bipolar disorder and the exposures of interest: vitamin D (including 25[OH]D and metabolism-related indices such as 24,25$[OH]_2$D and the vitamin D metabolite ratio, VMR), vitamin B9/folate ("folate/folic acid"), vitamin B12 ("vitamin B12/cobalamin"), and homocysteine, with additional terms capturing supplementation and dietary/lifestyle interventions; concepts were combined using AND/OR operators.

Eligible records included clinically relevant observational and interventional studies (e.g., trials of vitamin D supplementation and folate/L-methylfolate augmentation), meta-analyses and reviews, and selected case reports used to contextualize the differential-diagnostic relevance of extreme vitamin B12 disturbances (deficiency and iatrogenic excess). Outcomes of interest comprised circulating vitamin and/or homocysteine measures and their associations with bipolar disorder phenotype and burden, including symptom severity assessed with standardized scales (e.g., YMRS, HDRS, CGI-S, MADRS), illness phase (mania/mixed states, bipolar depression, euthymia), selected suicidality-related variables, cardiometabolic comorbidity, and specific cognitive domains (including executive functions and neuropsychological batteries; in some studies with concurrent biomarkers such as NfL). Screening was performed in two stages

(titles/abstracts followed by full-text review), and evidence was synthesized narratively and organized by exposure domain (vitamin D vs B9/B12 and homocysteine), study design, and clinical context (illness phase; inpatient vs outpatient sampling).

Vitamin D in Bipolar Disorder

Vitamin D has attracted increasing attention in bipolar disorder (BD) research due to its broad biological effects and the frequent occurrence of suboptimal vitamin D status in psychiatric populations. In clinical practice, vitamin D status is most commonly characterized by serum 25-hydroxyvitamin D (25[OH]D). More recent studies have also incorporated 24,25-dihydroxyvitamin D (24,25$[OH]_2$D) and the vitamin D metabolite ratio (VMR), allowing a more nuanced description of vitamin D metabolism within BD cohorts (15). Reviews focusing on vitamin D in BD emphasize substantial heterogeneity across studies, including differences in laboratory methods (e.g., liquid chromatography-tandem mass spectrometry, LC-MS/MS), interpretative thresholds, and clinical sampling frames (euthymic outpatients versus acute episodes, inpatient versus outpatient recruitment) (14). For evidence synthesis, this means that results should be interpreted in close relation to the study-specific definition of deficiency, clinical context, and analytical methodology (15,20-22). Clinically, the central question is whether vitamin D status relates to affective symptom severity in BD and whether such relationships differ across illness phases. In cohorts including acute mania or mixed episodes, lower vitamin D levels have been reported compared with control groups, alongside, associations between vitamin D concentrations and standardized symptom ratings, including the Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HDRS), and the Clinical Global Impression-Severity (CGI-S) (20). In within-subject comparisons across manic and euthymic states, vitamin D status has been described as less favorable during the acute phase, while euthymic measurements may approximate those observed in controls (22). Conversely, in a larger outpatient cohort dominated by euthymic patients, case-control differences in 25(OH)D and 24,25$(OH)_2$D were not consistently observed, yet small associations between manic symptom severity and metabolic markers (24,25$[OH]_2$D and VMR) were reported (15). Collectively, these findings suggest that any clinical relationships may be phase-dependent and may also vary according to whether analyses focus solely on 25(OH)D or additionally incorporate indices reflecting vitamin D metabolism (15,20,22). Interpretation of these observations requires careful consideration of confounding factors that influence 25(OH)D independently of BD, including seasonality and sunlight exposure, body mass index (BMI), physical activity, diet, metabolic comorbidity, and treatment context (including

hospitalization) (14). Euthymic cohorts have described a high prevalence of vitamin D deficiency alongside illness-course and lifestyle variables that may modify vitamin D status (23). In inpatient samples recruited during mood episodes, a large proportion of values have been reported below study-defined thresholds, while relationships with episode characteristics have not always been consistent (21). Accordingly, pooling outpatient euthymic cohorts with acute episode-based inpatient cohorts requires methodological caution, given that these populations differ in deficiency risk architecture and in clinical and environmental parameters (14,21,23). Beyond symptom ratings, cognitive functioning represents a clinically relevant domain, as cognitive deficits may persist in BD outside full mood episodes. Cross-sectional studies in euthymic patients have used standardized cognitive batteries (e.g., the Brief Assessment of Cognition in Affective Disorders, BAC-A) while concurrently assessing vitamin D status and markers of neuroaxonal integrity such as neurofilament light chain (NfL). One analysis reported a high prevalence of vitamin D deficiency and patterns suggesting that relationships between vitamin D status, NfL, and selected cognitive domains may be modified by age (23). In contrast, other studies incorporating multi-metabolite assessment (25[OH]D, 24,25$[OH]_2$D, VMR) did not identify significant associations with attention, memory, or executive functioning, nor clear interaction effects between diagnostic group and vitamin D status (24). From a clinical perspective, these findings indicate that potential vitamin D-cognition relationships in BD may be heterogeneous and dependent on sampling, measurement strategy, and co-occurring biological and clinical variables (23,24). For clinical interpretation, it is essential to distinguish observational evidence describing prevalence and correlates of low vitamin D from interventional evidence assessing supplementation effects in BD. Reviews note that observational studies are more numerous and enable characterization of the distribution of suboptimal vitamin D status in BD, whereas associations with symptom severity are less consistent and likely influenced by confounding (14). In a randomized placebo-controlled trial conducted in bipolar depression among participants with vitamin D deficiency (<30 ng/mL), cholecalciferol at 5,000 international units per day for 12 weeks increased 25(OH)D levels, yet did not demonstrate superiority over placebo in reducing depressive symptom severity (25). Based on the available evidence, there are no conclusive data supporting the use of vitamin D in the treatment of bipolar disorder.

Vitamin B9 (folic acid), vitamin B12 (cobalamin) and homocysteine in Bipolar Disorder

Vitamin B9 (folic acid) and vitamin B12 (cobalamin) are pivotal to one-carbon metabolism: 5-methyltetrahydrofolate donates a methyl group in the vitamin B12-dependent methionine

synthase reaction, enabling remethylation of homocysteine to methionine and supporting the generation of S-adenosylmethionine (SAM), the principal methyl donor within the central nervous system (26). The relevance to mood disorders stems from the fact that methylation capacity influences gene expression and the efficiency of neurotransmission-related pathways, while bioactive folate availability is mechanistically linked to monoaminergic synthesis and signalling-domains that remain central to both the pathophysiology and pharmacotherapy of depression and bipolar disorder (26). Consistent with this biological plausibility, observational meta-analyses have reported lower folate (vitamin B9) levels in individuals with depression and in patients with bipolar disorder compared with controls, albeit typically with small effect sizes (27,28). Interventional evidence adds a clinically meaningful layer: in double-blind randomised trials, adjunctive L-methylfolate (the bioactive form of vitamin B9) at 15 mg/day was associated with greater symptom improvement and higher response rates in subset of patients with selective serotonin reuptake inhibitor-resistant major depression (29). Importantly, impaired B9/B12 status may elevate homocysteine, which - beyond its value as a functional marker - can exert neurotoxic effects, including NMDA receptor-related mechanisms and amplification of oxidative stress, aligning with recognised contributions of glutamatergic dysregulation and oxidative processes in affective disorders (30,31). From a clinical perspective, severe vitamin B12 deficiency is particularly relevant because it can present with psychiatric phenotypes that mimic mood disorders (including mixed presentations with psychotic features) and may show marked improvement after replacement therapy even when haematologic abnormalities are minimal or absent (32,33,34).

Studies examining vitamin B9 (folic acid) and vitamin B12 concentrations in bipolar disorder (BD) are not fully consistent, yet several clinically relevant patterns can be outlined. A meta-analysis pooling six studies (481 individuals with BD and 760 controls) reported lower serum folate in BD, with a small but statistically significant effect (27). In some observational cohorts, however, a stable “deficiency signature” for folate or vitamin B12 compared with controls was not consistently observed, indicating that measured levels are strongly shaped by diet, body mass index, medical comorbidity, and pharmacotherapy (35). The most symptom-linked findings have been reported in bipolar depression: in an acute cohort, hyperhomocysteinemia >15 µmol/L affected approximately 45% of patients and was inversely associated with both folate and vitamin B12 concentrations (36). In a psychiatric inpatient analysis, a substantial proportion of patients within the bipolar spectrum had vitamin B12 levels below laboratory reference ranges while folate was most often within range; lower vitamin B12

also co-occurred with a family history of suicide (16). Functional correlates have been described as well, with lower vitamin B12 (and an adverse homocysteine profile) associated with poorer performance on selected executive-function tasks in bipolar depression (37). Regarding clinical phenotype and course, hyperhomocysteinemia during remission has been linked to a higher lifetime number of mixed episodes and lower vitamin B12 levels, whereas the association with folate has been weaker or absent (38). Evidence on treatment-response prediction remains mixed: one report suggested that higher baseline vitamin B12 may relate to greater short-term improvement after a single ketamine infusion in bipolar depression (39), while another analysis did not confirm baseline folate or vitamin B12 as reliable predictors of ketamine-related symptom change (40). Homocysteine can be viewed as a pragmatic marker of one-carbon pathway strain, with additional relevance to somatic risk in BD. A meta-analysis of nine cross-sectional studies (n=1547) found higher homocysteine levels in BD both during mania and euthymia, with a large effect size in mania (Hedges' g = 0.98; 95% CI: 0.80-1.17) and a smaller effect in euthymia (g = 0.30; 95% CI: 0.11-0.48) (30). In cohorts treated with second-generation antipsychotics, hyperhomocysteinemia has been reported to co-occur with metabolic syndrome, and one analysis linked hyperhomocysteinemia to markedly higher odds of meeting metabolic syndrome criteria (odds ratio ~8.4) (42). Clinically, these data matter because cardiometabolic comorbidity is a major driver of long-term outcomes in BD, and homocysteine may help identify patients who warrant a structured cardiometabolic risk assessment and targeted modification of risk factors (40-42). Interventional evidence for one-carbon supplementation in BD is limited but emerging. In a randomized clinical trial in BD type I during an acute manic episode (background treatment: valproate), folic acid 5 mg/day, folic acid 5 mg/day plus pyridoxine 80 mg/day, and placebo were compared over six weeks; the folic acid group showed a larger reduction in manic symptoms and a higher recovery rate at week 3 (approximately 79% vs 44% in placebo), whereas adding pyridoxine provided no additional benefit (18). In an open-label pilot study in BD type I depressive episodes, L-methylofolate 15 mg/day for six weeks was associated with a reduction in depressive severity (Montgomery-Åsberg Depression Rating Scale from ~23.4 to ~12.0) and clinical response in 6/10 participants (remission in 4/10) (44). Broader reviews across psychiatric disorders suggest potential benefit of folate-based augmentation in selected settings, although overall study quality and comparability remain limited (45). Indirect support comes from major depressive disorder, where L-methylfolate augmentation improved outcomes in SSRI-resistant depression (29), and from pharmacoepidemiologic data showing an association between folic acid prescription fills and fewer suicide attempts; this does not establish efficacy in BD, but it reinforces the clinical

relevance of folate-related biology across mood disorders (46). Case reports provide clinically tangible context, showing that extreme vitamin B12 disturbances may mimic bipolar affective syndromes and can meaningfully affect differential diagnosis. In a post-gastrectomy patient (84 years old, no prior psychiatric history), an acute manic syndrome with delusions was accompanied by a Young Mania Rating Scale score of 30, vitamin B12 <150 pg/mL, homocysteine 108.4 µmol/L, and markedly elevated methylmalonic acid; intramuscular vitamin B12 (1000 µg/day) with short-term antipsychotic treatment as followed by rapid improvement and no recurrence at six months (47). In a 16-year-old male with vitamin B12 deficiency, mixed affective symptoms with psychotic features and neurological signs were reported; after intramuscular vitamin B12 (500 µg/day) and low-dose risperidone, psychotic symptoms resolved by week 2 alongside neurological improvement (32). Acute psychotic depression has also been described as a predominant manifestation of vitamin B12 deficiency (48), and a recent report suggested mixed-state onset following excessive vitamin B12 supplementation (49). A newer post-gastrectomy case further indicates that severe vitamin B12 deficiency may present primarily with psychiatric symptoms even without classic macrocytosis, with rapid improvement after replacement (50).

Discussion

Key limitations of the evidence on folate, vitamin B12, and homocysteine in BD include the predominance of cross-sectional designs and substantial methodological heterogeneity (illness phase, control selection, varying cut-offs for deficiency and hyperhomocysteinemia, laboratory methods, and population nutritional context, including folate fortification). Confounding is often incompletely addressed (obesity, smoking, alcohol use, renal function, inflammation, and medications), limiting causal inference. Finally, interventional studies are few, typically small, and short-term, which precludes definitive clinical recommendations for routine supplementation in BD at this stage (18,44,45).

Based on the evidence summarized above, a major gap remains the scarcity of studies that can move beyond observed associations toward causal inference and clinically actionable recommendations. For vitamin D, most data are observational, and findings vary across illness phases and sampling frames (inpatients recruited during acute episodes versus euthymic outpatients), with additional heterogeneity in laboratory methods and interpretative thresholds. The impact of important confounders - seasonality and sunlight exposure, body mass index, physical activity, metabolic comorbidity, and treatment context - further limits clear

conclusions regarding symptom-related associations. The available placebo-controlled trial in bipolar depression demonstrated effective correction of 25(OH)D levels but no clinical superiority over placebo, highlighting the lack of adequately powered interventional studies across different BD phases and the absence of long-term outcomes addressing relapse patterns, cycling characteristics, psychosocial functioning, and cognition. Similarly, evidence on vitamin B9 (folic acid), vitamin B12, and homocysteine is dominated by cross-sectional studies with substantial methodological heterogeneity, including variable cut-offs for deficiency and hyperhomocysteinemia, differences in nutritional background (including folate fortification), and analytic approaches, which constrains comparability. Although clinical signals suggest that hyperhomocysteinemia and lower B-vitamin levels may co-occur with more severe bipolar depression and selected course features, prospective studies evaluating predictive value for relapse and sustained symptom burden are lacking. Interventional data on folate-based approaches in BD remain limited, typically involve small samples, short follow-up, and minimal replication, and do not yet support routine supplementation strategies or identification of patient subgroups most likely to benefit.

Conclusions

The available evidence indicated that suboptimal vitamin D status is common in bipolar disorder, yet associations between serum 25-hydroxyvitamin D (25[OH]D) and affective symptom severity are inconsistent and appear to depend on illness phase and clinical context. Studies focusing on acute episodes (mania or mixed states) have reported lower vitamin D levels and associations with standardized symptom ratings in some cohorts, whereas outpatient euthymic samples have shown less consistent case-control differences and weaker clinical links. Importantly, the placebo-controlled trial in bipolar depression demonstrated a clear rise in 25(OH)D after supplementation but no clinical advantage over placebo, supporting the conclusion that vitamin D supplementation cannot currently be recommended as an evidence-based treatment for bipolar depressive symptoms. For vitamin B9 (folic acid), vitamin B12, and homocysteine, the pattern is more coherent in the context of bipolar depression and cardiometabolic risk. A meta-analysis suggests a small reduction in folate levels in BD compared with controls, while the most consistent symptom-linked findings involve frequent hyperhomocysteinemia in acute bipolar depression accompanied by lower folate and vitamin B12 levels. Homocysteine has also been reported to be elevated in BD during both mania and euthymia, with larger effects in mania. Clinically homocysteine may serve as a pragmatic indicator of one-carbon pathway strain, and its reported links with metabolic syndrome in

populations receiving antipsychotic treatment underscore its relevance to somatic risk in BD. Interventional evidence for folate-based strategies remains preliminary: adjunctive folic acid showed benefit during acute mania in one trial, and an open-label pilot suggested improvement in bipolar I depression with L-methylfolate, but these findings are constrained by limited sample sizes, short follow-up, and the need for replication. From a clinician's perspective, the most defensible implication is to view assessment and correction of vitamin D, vitamin B12, and folate abnormalities primarily as part of comprehensive medical care in BD, particularly in patients with metabolic comorbidity, dietary risk, or atypical presentations. Vitamin B12 testing has additional diagnostic value because severe deficiency can present with affective syndromes that mimic BD and may require prompt replacement. At the same time, current evidence does not support using vitamin supplementation as a substitute for mood-stabilizing treatment; supplementation may be considered only as an adjunct in the presence of documented deficiency or one-carbon pathway abnormalities, within standard monitoring and BD management frameworks.

Disclosures

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All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict Of Interest:

The authors declare no conflict of interest.

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