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REVIEW ARTICLE
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VITAMIN B COMPLEX AND ITS ASSOCIATION WITH ANXIETY AND DEPRESSION

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Abstract:
Background: In the metabolic processes, the Vitamin B complex including B6 and B12 play a vital role like increasing the neural inhibition and decrease excitation.
Objective: The objective of this study is to analyze the effect of essential vitamin, vitamin B And its association it's like logical disorders like anxiety and depression.
Data source: The database of Google scholar and PubMed were searched for relevant articles.
Materials and Methods: This review article examines the impact of the high dose supplementation of vitamin B6 and B12 on various behavioral parameters like the balance between the inhibition and excitation of the neurons. In addition to this, it also showed inhibitory function that acted as various sensory measures. These included battery of tactile sensitivity, rate of binocular rivalry reversal, and detection of visual contrast.
Results: The results of the double-blind study suggest that high-dose supplementation of Vitamin B6 enhanced the neural influences i.e. inhibitory GABAergic. This inhibitory neural influence is known for its production of GABA.
Conclusion: The vitamin B6 supplementation started a trend towards decreasing depression and the reduction of self-reported anxiety. The supplementation also enhanced the visual contrast detection's suppression. But, on other outcome measures, this supplementation had no reliable impact. Also, the vitamin B12 supplementation, induced a pattern towards visual processing and changes in anxiety.

Keywords: Vitamin B6, Anxiety, Depression, Vitamin B12. Neural influences.

Introduction:

Mood can significantly impact the body both mentally and physically. Positive moods often lead to increased energy, improved focus, and lower stress levels, while negative moods can contribute to fatigue, tension, and impaired cognitive function. Hormonal and neurotransmitter changes play a role in these effects (Whiteford, 2015).

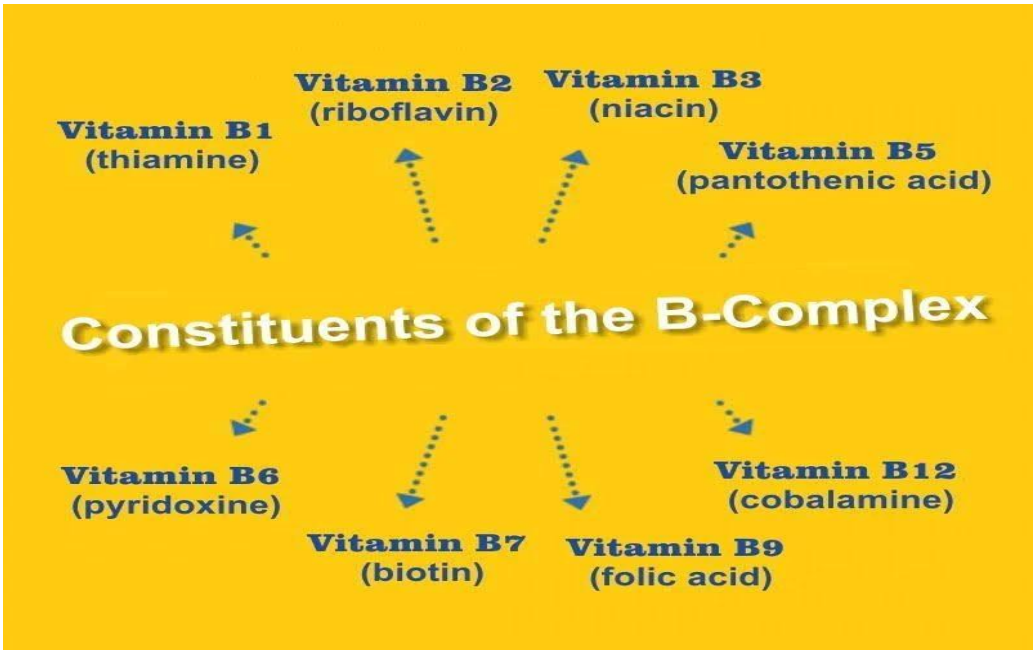
Depression is a mental health disorder characterized by persistent feelings of sadness, hopelessness, and a lack of interest or enjoyment in activities. It can affect daily functioning and lead to physical symptoms. Depressive illness is a complex condition characterized by various factors, including genetic, hormonal, immunological, biochemical, and neurodegenerative factors (Hariri, 2005). Diet plays a crucial role in modulating each of these factors, suggesting a plausible influence on both the development and progression of this mental health condition (Jacka, 2017). Understanding the interplay between these aspects highlights the potential significance of dietary choices in managing and mitigating depressive symptoms (Lai, 2014).

Depression and anxiety, recognized as highly prevalent chronic illnesses, share a complex relationship with diet and nutrition. The impact of diet on the biological processes underlying depressive illnesses (Kennedy, 2016) emphasizes the potential role of nutritional interventions in addressing not only physical but also mental well-being. Exploring this connection further could pave the way for comprehensive approaches to managing and alleviating the burden of these pervasive mental health conditions (Long, 2013).

Stress is when faced with challenging situations, our bodies often activate the "fight or flight" response, leading to the release of hormones such as cortisol (Scholey, 2018). While short-term stress can be a natural and potentially advantageous reaction, long-term or chronic stress can significantly impact both mental and physical well-being, contributing to conditions like anxiety and depression. Indeed, research suggests a link between diet and brain health, with nutritional interventions potentially playing a role in reducing depressive symptoms (Almeida, 2014). Exploring the improvement in diet quality over the last two decades as a modifiable risk factor for mood disorders reveals promising outcomes, regardless of individual levels of self-efficacy and physical activity (Rajkowska, 2000).

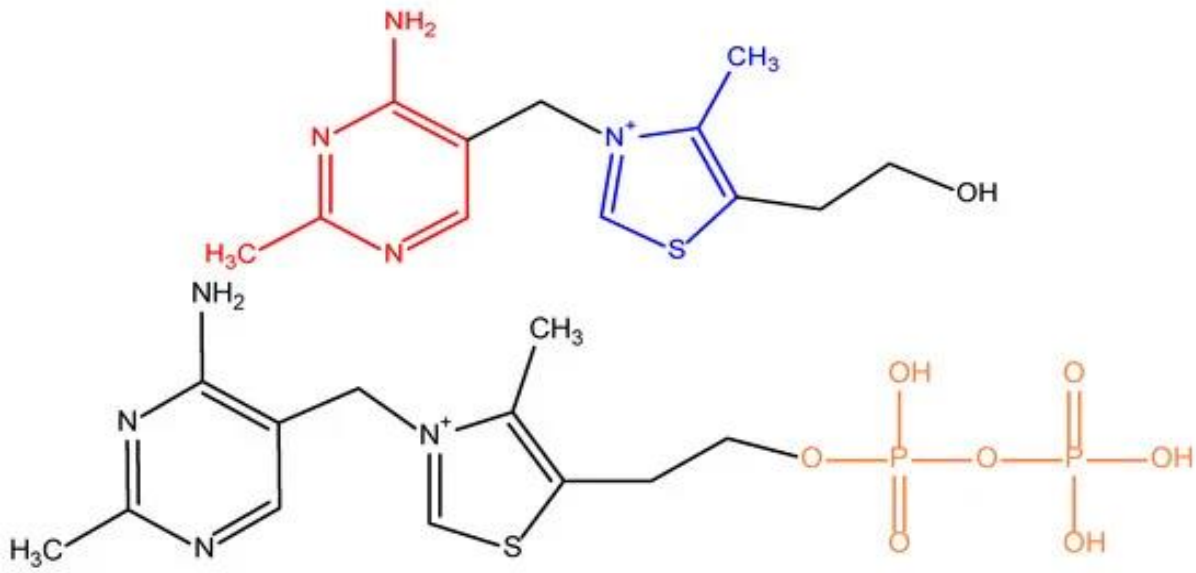
The observed link between a poor diet and worsened psychological health, as well as the potential positive impact of the Mediterranean Diet and B-group vitamins on mood, highlights the significance of nutritional factors in mental well-being. Deficiencies in vitamin B12 or folate are linked to a higher risk of depression, underscoring the significance of assessing nutritional status when examining mood disturbances and psychiatric disorders (Norman & Schmitz, 2007).

Vitamins play crucial roles in various bodily functions, supporting processes like energy metabolism, immune function, and tissue repair. Specifically, vitamin B complex, including B6, B9 (folate), and B12, is linked to mental health. Deficiencies in these vitamins may contribute to conditions like depression and stress (Laville & Segrestin, 2017) Vitamin B6 helps produce neurotransmitters like serotonin, which regulates mood. Folate is involved in the synthesis of dopamine and serotonin, impacting mood regulation. Vitamin B12 is essential for the production of myelin, a protective coating for nerves (Morris, 2011).



Research suggests that deficiencies in B vitamins may be linked to an increased risk of depression and stress. However, it's essential to approach mental health holistically, considering various factors such as lifestyle, diet, and individual differences. Certainly, B vitamins are vital cofactors in cellular processes such as the methionine and folate cycles, impacting DNA methylation and homocysteine clearance (Bowman, 2012). Deficiencies in B6, B12, and folate can disrupt these pathways, potentially resulting in elevated homocysteine levels. Some studies suggest a link between hyper-homocysteinemia and poor mood, with up to 30% of depressed patients showing elevated homocysteine. Consequently, supplementing with B group vitamins to lower homocysteine levels could potentially offer mood-related benefits (Arrazola, 2014).

Absolutely, B vitamins play a crucial role in one-carbon metabolism, influencing the synthesis and regulation of key neurotransmitters like dopamine and serotonin. Since these neurotransmitters are implicated in mood regulation, depression, and anxiety, B vitamin supplementation could provide an alternative or adjunctive treatment.



Structure of Vitamin B complex:

This approach may be promising for optimizing mood by modulating neurotransmitter function, potentially with a lower risk of adverse side effects compared to standard antidepressants (Sarris& Murphy, 2016). It's indeed challenging to isolate the specific mood effects of B vitamins in clinically depressed individuals due to interactions with antidepressants. The studies provide valuable insights into B vitamins as adjunctive therapy but may not fully address their standalone benefits. Additionally, variations in neural architecture among depressed participants make it harder to generalize mood benefits to non-clinical populations (Morris, 2011).

Certainly, the complexity of B vitamin research underscores the importance of considering baseline nutrient status, potential interactions with other vitamins and minerals, and individual variability in response to interventions. The emerging field of nutritional cognitive neuroscience adds another layer, emphasizing the need to connect nutrient biomarker patterns with neurocognitive health. Evaluating the effectiveness of individual B vitamins must be done in the broader context of dietary habits and the co-administration of other nutrients during interventions (Berti, 2015)

It appears that the interdependence of B group vitamins within the methylation cycle suggests that a combination of these vitamins might be more effective for mood regulation than individual supplementation, as argued by Kennedy. The existing research, including meta-analyses, indicates potential benefits, but further scrutiny is needed for broad-spectrum B group vitamins in both clinical and healthy populations (Long, 2013).

Certainly, focusing on individuals with suboptimal nutrient status as outlined by Monti, et al. can be a strategic approach to identify those at risk and potentially intervene with B vitamins for preventative measures against the progression towards clinical disorders. It aligns with the growing recognition of the link between nutrition and mental health. 8 The need for additional research, particularly in non-clinical or at-risk populations, is crucial to ascertain the suitability of B vitamin supplementation for improving mood and potentially reducing the risk of mood and cognitive disorders. The evolving comprehension of the influence of nutrient status on mental health calls for thorough investigation.

The focus of this review is on the impact of vitamin B complex, particularly those rich in B vitamins and broad-spectrum B vitamin combinations, emphasizing cognitive mechanisms and psychiatric symptoms based on relevant previous studies (Kennedy, 2011). The review aimed to (Whiteford, 2015) delve into various aspects of mood, including stress based (Long, 2001) also examine the influence of nutrient status on mood by analyzing blood biomarkers, and (Jacka, 2013) assess the potential benefits of B vitamin for at-risk populations compared to healthy ones.

Materials and Methods:

The research approach encompassed a thorough exploration of databases including Medline (PubMed, Web of Science) and Google Scholar for randomized controlled trials up to January 2025. Various keywords associated with interventions (such as B vitamins, vitamin B complex), mood outcomes (including mood, depression, anxiety, affect, stress, fatigue, mood disorder), and study designs (like randomized controlled trial, and clinical trial) were amalgamated. Filters were applied to include human studies, adult samples, and publications from 2000 onwards. Furthermore, supplementary findings were sought by examining reference lists from pertinent studies.

The review criteria encompassed randomized, double-blind, placebo-controlled trials that provided data on measurable mood outcomes like stress, well-being, and fatigue. Studies investigating the prevalence of clinical mood disorders were excluded to enhance uniformity. Adhering to PRISMA guidelines, the review-maintained consistency across the included studies.

The inclusion criteria for the reviewed studies specified a daily supplement with B group vitamins. This inclusion allowed for supplements containing additional vitamins or minerals, as well as those with B group vitamins only. The rationale, based on Kennedy's findings, emphasized the potential enhanced effectiveness of multiple B group vitamins compared to single nutrients. The minimum intervention period was set at four weeks.

The eligibility section appears to have been thorough, considering vulnerability factors while ensuring participants are healthy and without a diagnosis mood disorder diagnosis. Additionally, you've

mentioned an interest in blood biomarkers of B vitamin levels, and studies from 2000 onward were included.

Study Selection and Data Extraction:

It's a systematic approach which was followed in the article search and evaluation process, involving multiple reviews.

Using Rayyan's methods (Cochrane Collaboration, 2014), one reviewer (LY) carried out the article search, eliminated duplicates, and filtered publications based on titles and abstracts. Two experts evaluated the papers that were going through full text evaluation. Both researchers agreed on the following articles for this review.

After each study was evaluated in relation to the inclusion criteria, a pair of editors (LY and SG) finished the data extraction process. The length of the study, sample numbers, and sample characteristics (age, gender) were taken out. Only information on tablets containing vitamins from the B group and the group receiving a placebo were retrieved in the case of multiple armed trials. When there were several time scores, only values pertaining to the standard and end-point statistics were taken out. It was noted what kind, version, and kind of questionnaires were used. Each supplement's daily B vitamin dosage composition was also retrieved. Reviewers noted if there was a way to quantify the consumption of B vitamins objectively, such as biomarkers in the blood or dietary intake.

Mood outcomes were divided into three categories: stress, depression symptoms, and anxiety symptoms. Out of the eighteen studies, twelve were considered suitable for meta-analysis. The average shift in the intake of B vitamins group was subtracted from the average shift in the placebo group, and the resulting mean changes were divided by the pooled average difference at baseline to determine the effect sizes.

$ES = \underline{x}1 - \underline{x}/s$

The overall effect was tested in all studies using a random effects model with a standardized mean difference. The I^2 statistic was utilized to test for heterogeneity in all models, and the models were evaluated based on the parameters. I^2 levels between 0% and 40% might not matter.

Furthermore, moderate heterogeneity may be represented by 30%–60%, substantial heterogeneity by 50%–90%, and large heterogeneity by 75%–100%. When significant heterogeneity ($I2 \geq 75\%$) was detected, funnel plots were examined to find potential sources of heterogeneity, and it was decided whether or not to eliminate outliers in order to bring homogeneity up to a suitable level (Shamseer, 2015).

To avoid having participants represented twice in the same evaluations, just one measure was used in studies reporting comparable information from multiple measures. To help with homogeneity, where two or more of these variables were recorded, the chosen outcome utilized in a systematic review was only determined by the number of times it had been reported throughout trials.

Results:

For the initial search of this review article, there were 5358 records collected. In this search, 4600 abstracts and titles were assessed for related RCTs. 31 studies with their full text were screened to check their potential eligibility. A sum of eighteen articles were included in this systematic review as they were up to the mark as per the inclusion criteria.

It was identified that four articles were taken from the same cohort of participants but deriving different data from them (Haskell, 2010). So, after taking these into consideration, there was a sum of 2015 participants for this review study across sixteen trials. 8 of these studies used participants that were accounted as "at-risk" while the other 8 studies utilized healthy participants. The "at-risk" sample consisted of people with sedentary lifestyle or a sedentary occupation, increased psychological distress, chronic psychological stress, subjective fatigue, history of hypertension, nursing home residents, celiac patients, and highly stressed adult employees. Importantly, all of the participants were otherwise healthy and had no clinical diagnosis of the respective disease. The intervention period for these participants had a length ranging from 28 days to 2 years. For participants of fourteen trials, the

B vitamin was induced as a broad-spectrum multivitamin. For the rest of the two trials, the B group supplements were given individually which contained folate, B12, and B6. About the eighteen trials, three included females only, five included males only, and the rest of the trials included both female and male participants. Two of these studies examined the baseline dietary habits and reported them in the form of 3-day food record and questionnaires.

Two of the studies used the B vitamin which all of the trials include 8 B group vitamin. All of the trials utilized supplements that contained vitamin B12 and B6. One study among these also included folate. Sixteen of these studies also included vitamin B1, B2, B3, and B5. The least included vitamin was B7 which was a part of only ten studies (Carroll, 2000). As compared to the recommended doses of these vitamins set by the National Health and Medical Research council, Australia. The intake of B vitamins was double in the supplements given to the participants. Some supplements exceeded the intake up to 300 times. In one study, the intake of B vitamin was similar to the recommended daily intake (Macpherson, 2016).

Taking the other constituents into consideration, two studies utilized the B vitamin only, seven studies had other constituents and the number was there to four. The rest of the studies used supplements that had a higher number of botanical constituents and other micronutrients. The study led by MacPherson container supplements that had largest number of other constituents. The number was 37 other constituents. The impact of above explained supplementation on the broader spectrum of mood and specific spectrum of anxiety, stress, and Depression is summarizes in the following section. Importantly, it is to be considered that each specific result is either derived from a subscale of the problems or a direct measure of anxiety, depressive symptoms or stress. In 11 articles, it was reported that there is a positive outcome for overall mood over the placebo.

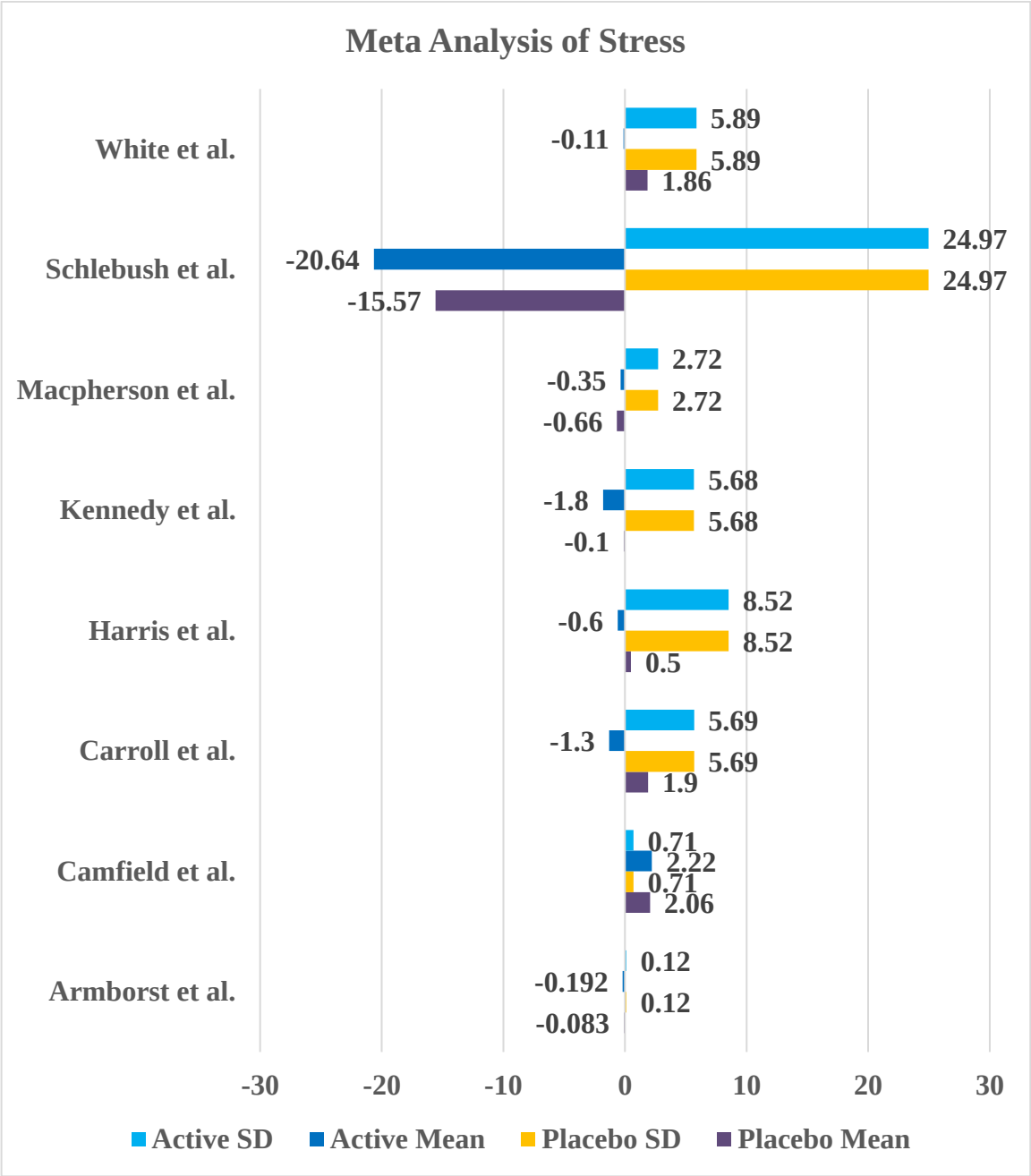
In the 11 studies, there was at least one measuring spectrum for overall mood like a measure of present psychological state or current mental health measure. Five of these used a general health questionnaire. Of these five studies, two found no impact on overall mood and three reported positive impacts of vitamin B supplementation on mental health (Harris&Kirk, 2011). The other five studies employed a profile of mood states (POMS). These studies reported no supplementation impact on mood disturbance.

In the study conducted by Harris, it was reported that the supplementation reduced the negative symptoms if mood like stress, anxiety, and Depression (Hallert et al., 2009).

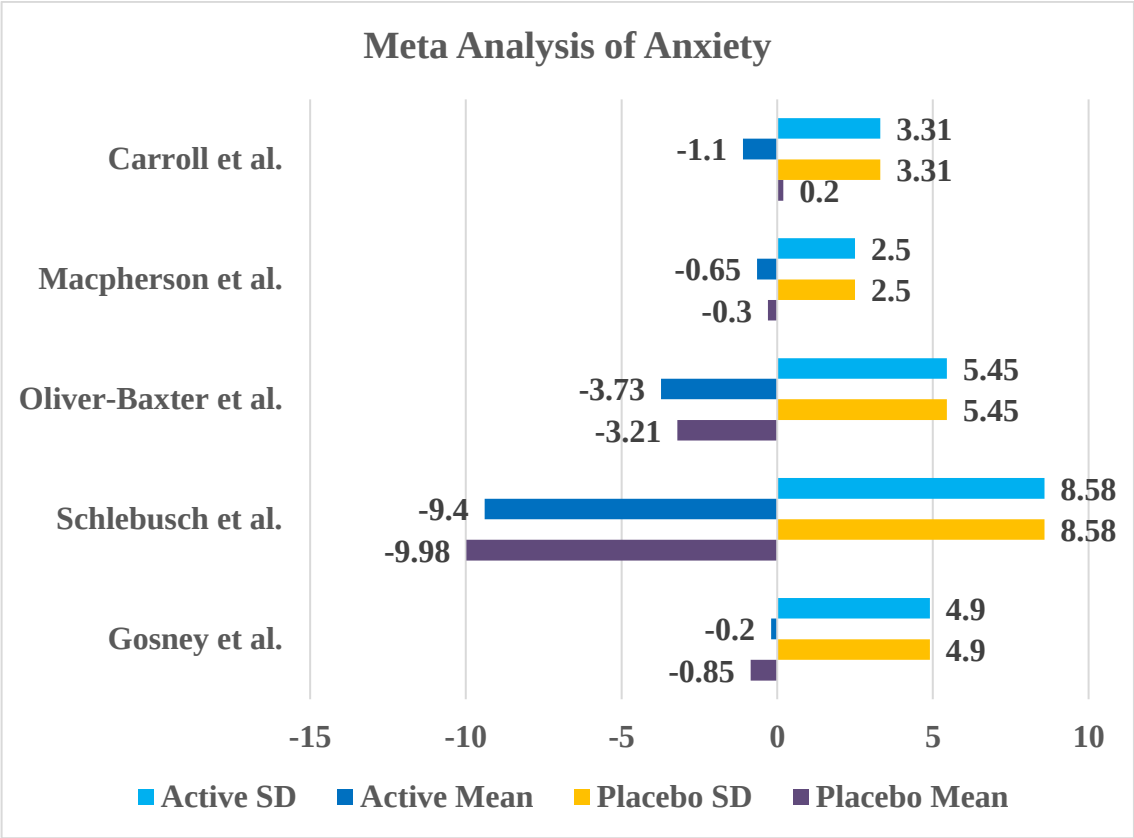
Among all of the mood dimensions, the most widely studied one was depression. Eleven articles included the measure of dimension. However, between the measures of depression, there was a large amount of heterogeneity, with a sum of 7 different measures. Out of the five studies utilizing the profile of mood states' depression-detection scale, only one study indicated a positive impact of supplementation within a short intervention period. Regarding depressive symptoms, two additional studies reported positive effects in a specific subgroup, where participants initially reported lower scores. Conversely, several other studies conducted relevant analyses and concluded that there were no discernible impacts on the entire cohort, including those participants with comparatively higher depressive symptoms at baseline.

Following a meta-analysis of nine studies, no evidence emerged suggesting that supplementation provided benefits for the depressive symptoms among participants. Examination of funnel plots uncovered two significant outliers, with one favoring the placebo and the other favoring supplementation. Upon removal of these outliers, the results demonstrated homogeneity. Consequently, the meta-analysis indicated an overall reduction in depression through supplementation. However, statistical significance was not attained following the test.

Ten studies included the measure of stress and out of these, 7 used the Perceived Stress Scale. 3 studies reported that the impact of supplementation was positive as they reduced the subjective stress. In addition to these, 3 other studies used PSQ and BSI and reported vitamin B supplementation to be beneficial. Accumulatively, 6 studies reported B supplementation to be beneficial. Meta analysis also showed a reduction in the symptoms of stress. However, across the measures, there was a moderate amount of heterogeneity as well (Stough, 2011).



The anxiety measure was included in ten studies. In a period of 28 to 30 days, two studies showed benefit to anxiety symptoms upon using supplementation. Additionally, another study reported benefits in one subgroup. This subgroup had poorer status at baseline. Lastly, some studies reported a significant positive impact of supplementation in male participants. The rest of the studies found no positive impacts. Meta analysis showed no positive impacts for the symptoms of stress (Ford, 2008).



Seven studies, out of sixteen trials, measured the status of vitamin B and its impact after supplementation through gathering information related to blood bio-markers. The most widely studied vitamin was folate. 4 of the studies measure virgin B12, 3 of the studies measured B6, and I've studied nested B2 and B1 status. Out of these z five studies measured homocysteine as a mechanism. At the baseline, if the biomarkers are assessed, it gives a chance to measure and record the nutritional status of all the members included in the studies. A mean level was not reported in any of the studies that could be consistent with the baseline recorded clinical deficiency. Three studies that were measuring homocysteine recorded a normal range that was less than 15umol/L. However, the rest of the two studies recorded higher levels. Participants showed mean's one standard deviation and it recorded to be high range.

As compared to the placebo, all studies recorded levels of B vitamins to be increased and homocysteine levels to be decreased. Since the results even appeared in shorter trials of 28 days, it can be concluded that vitamins of B group are readily absorbed in the blood. Measuring folate was an exception in this study as three studies recorded no positive change after supplementation.

Discussion

The review indicates some evidence supporting the positive impact of B vitamin supplementation on mood, particularly in reducing stress. However, the reduction in depressive symptoms is also noted. Notably, most supplements exceeded recommended daily intakes significantly, yet baseline B vitamin status across studies did not indicate clinical deficiency. This suggests a potential limitation in observing mood effects despite high supplementation levels.

The analysis highlights the nuanced effects of B vitamin supplementation on mood, emphasizing the importance of examining specific facets like stress and depressive symptoms. While broad mood measures show benefits in some studies, focusing on subscales unveils specific domains sensitive to B vitamin status. Notably, stress improvement was consistent across more than half of the studies, whereas depressive symptoms' benefits were less prevalent. The recommendation to use measures with both overall scores and subscales acknowledges the complexity of mood assessment in healthy samples (Long, 2013).

The challenges in comparing trials arise from varied supplement factors, participant diversity, and study designs. Only two of the 18 studies focused on B vitamins alone, while others used multi-vitamins. The caution in interpreting results is highlighted due to the potential influence of other constituents in multi-vitamin/mineral formulas on mood effects. The strict criterion for B group vitamins reflects a consideration of synergistic effects, although it may limit study selection. Despite high B vitamin supplementation, exceeding recommended daily intakes, benefits for mood were inconsistent across studies and facets (Kennedy, 2016). The observed pattern suggests that while micronutrient levels generally increased post-supplementation, the correlation with improved mood outcomes was poor in studies examining this association. Notably, participants in these trials generally had non-deficient B vitamin status, potentially limiting the detection of mood effects (Morris, 2011). The lack of mood improvement in a study on folic acid in healthy males suggests that supplementation benefits might be more pronounced in individuals with baseline deficiencies or mood disorders. Further rigorous investigation is needed to reconcile differences between observational studies in clinical groups and intervention studies in healthy populations (Williams, 2005).

The review suggests that studying B vitamins in at-risk populations, even without a clinical diagnosis of a mood disorder, provides a more comprehensive understanding. More than half of the studies with at-risk samples found a positive impact on mood outcomes. Subgroup analyses in some studies further support the potential benefits, emphasizing the importance of exploring at-risk groups for B vitamin research in mood disorders. Novel recruitment strategies, like nation-wide mail-out invitations, could help include individuals with sub-clinical mood symptoms who may have been overlooked in previous studies focused on 'healthy' population (Hallert, 2009).

It appears that the connection between diet and mood in supplementation research is lacking comprehensive consideration of baseline food intake and dietary habits, with limited focus on B vitamin biomarkers. Additionally, few studies explore the association between changes in vitamin status and mood outcomes (Armborst, 2018).

Certainly, measuring baseline dietary habits alongside biomarker status in future studies is crucial for unraveling the intricate relationship between individual nutrients and mood, especially considering the impact of overall diet quality on this association. Recognizing nutritional status across various markers at baseline is key to identifying areas in a participant's diet that may benefit from improvement. It's noteworthy that supplementing individuals with optimal nutrient status may not be efficacious, emphasizing the importance of targeting those with sub-optimal levels in intervention research (Walters, 2017).Absolutely, it's crucial to recognize that single-nutrient supplementation doesn't replicate the intricate interactions found in a complete diet. Dietary factors, medication use, and lifestyle choices like alcohol intake can significantly impact nutrient absorption and response to interventions. Monitoring biomarkers like methylmalonic acid and homocysteine adds depth to understanding the underlying mechanisms in supplementation research (Oulhaj & Jernerén, 2016).

The review suggests potential benefits of B vitamin supplementation in addressing stress but acknowledges inconclusive evidence for depressive symptoms and lack of benefit for anxiety. The water-soluble and well-tolerated nature of B vitamins offers promise for addressing nutritional deficiencies. However, the review emphasizes the need for further research with more rigorous methodologies before recommending B vitamins for mood benefits in healthy or at-risk populations. Suggestions include considering participants with poorer nutrient status or mood outcomes at baseline and utilizing methodologies that examine associations between changes in mood outcomes and biomarker status (Monti, 2015).

The strengths of this review lie in its adherence to the PRISMA method, thorough literature search, and nuanced consideration of 'at-risk' participants. Additionally, the extension of Long and Benton's work to explore mood facets enhances its value. However, limitations include methodological heterogeneity in trials, varying B vitamin dosages, and supplementation periods, contributing to detected meta-analysis heterogeneity. The use of multivitamin/mineral supplements complicates isolating specific effects of B vitamins (Long, 2013).

Conclusion:

It's interesting to see the growing consensus on the role of B group vitamins in neurological and psychiatric conditions. The potential benefits on mood for both healthy and at-risk individuals underscore the importance of further research, especially in groups with suboptimal nutritional status or subclinical mood disturbances. Understanding the interplay between baseline micronutrient status, dietary habits, and supplementation is crucial for evidence-based recommendations.

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