HTA Austria
Austrian Institute for
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GmbH

Combination Therapy with Antidepressants and Vitamin B Complex Compared to Antidepressant Monotherapy

A Systematic Review

Final report

AIHTA Project Report No.: 182 | ISSN: 1993-0488 | ISSN-online: 1993-0496

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Vienna, April 2026

Project leader & author: Susanne Fasching, BScN

Project Support

Systematic literature search & hand search: Susanne Fasching, BScN

External review: Priv.-Doz. Dr. phil. Claudia Wild

Correspondence: susanne.fasching@outlook.com

Cover photo: © he 2R Artificiality – stock.adobe.com

This Study was conducted as a Master-Thesis at Paracelsus Medical University, Master Programme Public Health, Center for Public Health and Healthcare, Research, Strubergasse 21, 5020 Salzburg, Austria

This report should be referenced as follows:

Fasching S. Combination Therapy with Antidepressants and Vitamin B Complex Compared to Antidepressant Monotherapy. A Systematic Review. AIHTA Project Report No.:182; 2026. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Josefstädter Straße 39 | 1080 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Dr. rer. soc. oec. Ingrid Zechmeister-Koss, MA, managing director

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AIHTA Project Reports are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Project Report No.:182

ISSN 1993-0488

ISSN online 1993-0496

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List of abbreviations

AI ..... Adequate Intake
APA ..... American Psychiatric Association
ATC ..... Anatomical Therapeutic Chemical
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BÄK ..... Bundesärztekammer
BDI ..... Beck Depression Inventory
CBT ..... Cognitive Behavioural Therapy
CI ..... Confidence Interval
DFE ..... Dietary Folate Equivalents
DGBS ..... Deutsche Gesellschaft für Bipolare Störungen
DGE ..... Deutsche Gesellschaft für Ernährung
DGPPN ..... Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde
DSM-III-R ..... Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM 5 ..... Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-5-TR ..... Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
DSM-III-R ..... Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DALYs ..... Disability Adjusted Life-Years
GAD ..... Generalised Anxiety Disorder
GAD ..... 7 Generalized Anxiety Disorder Scale 7
GBD ..... Global Burden of Disease
HAMA ..... Hamilton Anxiety Rating Scale
HAM-D ..... Hamilton Depression Scale
Hcy ..... Homocysteine
HDRS ..... Hamilton Depression Rating Scale
HIC ..... High-income Country
ICD ..... 10 International Classification of Diseases, 10th Revision
ICD ..... 11 International Classification of Diseases, 11th Revision
ICTRP ..... International Clinical Trials Registry Platform
INAHTA ..... International Network of Agencies for Health Technology Assessment
IQR ..... Interquartile Range
ITT ..... Intention-To-Treat
LIC ..... Low-Income Country
LMIC ..... Low- and Middle-Income Countries
KBV ..... Kassenärztliche Bundesvereinigung
MADRS ..... Montgomery Åsberg Depression Rating Scale
MAOI ..... Monoamine Oxidase Inhibitor
MeSH ..... Medical Subject Headings
MDD ..... Major Depressive Disorder
Mg ..... Milligram
MCID ..... Minimal Clinically Important Difference

MINI ..... Mini-International Neuropsychiatric Interview
MMSE ..... Mini Mental State Exam
MADRS ..... Montgomery–Åsberg Depression Rating Scale
µg ..... Microgram
N ..... Number of Participants
NA ..... Not Applicable
NaSSA ..... Noradrenergic and Specific Serotonergic Antidepressant
NARI ..... Noradrenaline Reuptake Inhibitor
n.d. ..... No Date
NDRI ..... Norepinephrine Dopamine Reuptake Inhibitor
NICE ..... National Institute for Health and Care Excellence
NR ..... Not Reported
NRCT ..... Non-Randomised Controlled Trial
NTP ..... Nortriptyline
NVL ..... Nationale Versorgungsleitlinie
OSF ..... Open Science Framework
OR ..... Odds Ratio
PDD ..... Persistent Depressive Disorder
PHQ-9 ..... Patient Health Questionnaire-9
PICO(S) ..... Population, Intervention, Comparator, Outcome, (Study design)
PLP ..... Pyridoxal 5 Phosphate
PPDGJ-III ..... Pedoman Penggolongan dan Diagnosis Gangguan Jiwa – III
PRI ..... Population Reference Intakes
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta Analyses
PRESS ..... Peer Review of Electronic Search Strategies
Pts. ..... Patients
RCT ..... Randomised Controlled Trial
RoB 2 ..... Cochrane Risk of Bias 2 tool
RR ..... Risk Ratio
ROBINS-I ..... Risk Of Bias In Non-randomized Studies – of Interventions
SARI ..... Serotonin Antagonist and Reuptake Inhibitor
SDI ..... Sustainable Development Index
SEM ..... Standard Error of the Mean
SF 36 ..... Short Form Health Survey (36 Items)
SNRI ..... Serotonin Norepinephrine Reuptake Inhibitor
SD ..... Standard Deviation
SSRI ..... Selective Serotonin Reuptake Inhibitor
SWiM ..... Synthesis Without Meta-analysis
tHcy ..... Total Homocysteine
TCA ..... Tricyclic Antidepressant
UL ..... Tolerable Upper Intake Level
USD ..... United States Dollar
WHO ..... World Health Organization
WHOQOL BREF .... World Health Organization Quality of Life Abbreviated Version

Executive Summary

Background: Anxiety and depressive disorders account for a significant proportion of the global mental health burden. Treatment challenges in antidepressant therapy have stimulated interest in adjunctive nutritional interventions, such as B vitamins, due to their role in neurobiological processes relevant to mood regulation. However, existing systematic reviews have not focused specifically on adjunctive regimens combining multiple B vitamins with antidepressants. Consequently, this systematic review aimed to evaluate the efficacy and safety of combining a vitamin B complex (≥2 B vitamins) with antidepressant medication to improve symptom severity in depression and anxiety.

Method: A systematic literature search targeting clinical trials involving patients (≥18 years) with clinical diagnosis of depression or anxiety was performed. Eligible studies compared vitamin B complex supplementation plus antidepressant treatment with antidepressant monotherapy. The primary outcome was change in symptom severity on validated scales; secondary outcomes included response rate, remission rate, cognitive outcomes, quality of life and safety outcomes. Study selection, data extraction, and risk-of-bias assessment were performed by one reviewer. Evidence was summarised narratively, and the certainty of evidence was not formally graded.

Results: The review included two double-blind randomised controlled trials (RCTs), two open-label RCTs, and one non-randomised controlled trial (NRCT), totalling 320 study participants. All included studies assessed depressive outcomes; no studies evaluating anxiety were identified. One open-label RCT and one NRCT reported significant improvements in depressive symptom severity with folic acid (vitamin B9) plus vitamin B12; however, the evidence is limited by small sample sizes and a high risk of bias. The remaining three trials assessing ≥3 B vitamins showed no significant benefits. The largest, lowest-risk-of-bias trial with the longest follow-up found no significant difference in depressive symptom severity but an improved response over 12 months. Cognitive outcomes and adverse events showed no significant differences, but evidence was scarce due to a small number of events. Trial comparability was limited by clinical and methodological heterogeneity.

Conclusions: Overall, evidence for adjunctive vitamin B complex supplementation with antidepressants remains very limited, warranting high-quality RCTs.

anxiety and depressive disorders - significant global burden

systematic review to evaluate the efficacy and safety of combining vitamin B complex with antidepressant medication

systematic literature search, study selection, data extraction, and RoB assessment

outcomes:
symptom severity, response rate, remission rate, quality of life, safety

results: 320 participants in 5 studies: 2 blinded RCTs, 2 open-label RCTs, 1 NRCT for depression

heterogeneous studies, limited evidence, high RoB: no significant difference to monotherapy

vitamin B complex supplementation with antidepressants remains unclear

Zusammenfassung

Hintergrund: Angst- und depressive Störungen tragen erheblich zur globalen Krankheitslast bei. Herausforderungen in der Therapie mit Antidepressiva haben das Interesse an adjunktiven ernährungsbezogenen Interventionen, wie der Supplementierung mit B-Vitaminen geweckt, da diese an neurobiologischen Prozessen beteiligt sind, die für die Stimmungsregulation relevant sind. Allerdings haben sich bisherige systematische Reviews nicht spezifisch auf additive Behandlungsregime konzentriert, die mehrere B-Vitamine in Kombination mit Antidepressiva einsetzen. Ziel dieser systematischen Übersichtsarbeit war es daher, die Wirksamkeit und Sicherheit der Kombination eines Vitamin-B-Komplexes (≥ 2 B-Vitamine) mit einer antidepressiven Medikation zur Verbesserung der Symptomschwere bei Depressionen und Angststörungen zu evaluieren.

Angst- und depressive Störungen: erhebliche globale Krankheitslast

Systematisches Review zur Wirksamkeit und Sicherheit der Kombination eines Vitamin-B-Komplexes mit Antidepressiva

Methode: Es wurde eine systematische Literatursuche nach klinischen Studien mit Patient*innen (≥18 Jahre) mit klinisch diagnostizierter Depression oder Angststörung durchgeführt. Eingeschlossen wurden Studien, die die Gabe eines Vitamin-B-Komplexes zusätzlich zu einem Antidepressivum mit einer Monotherapie verglichen. Primärer Endpunkt war die Veränderung der Symptomschwere anhand validierter Skalen; sekundäre Endpunkte umfassten Ansprech- und Remissionsrate, kognitive Endpunkte, Lebensqualität und Sicherheit. Studienauswahl, Datenextraktion und Bewertung des Verzerrungsrisikos wurden von einer Person durchgeführt. Die Evidenz wurde narrativ zusammengefasst; eine formale Bewertung der Evidenzsicherheit erfolgte nicht.

systematische Literatursuche, Studienauswahl, Datenextraktion und Bewertung des Verzerrungsrisikos

Endpunkte: Veränderung der Symptomschwere, Ansprech-/ Remissionsrate, Lebensqualität, Sicherheit

Ergebnisse: Fünf Studien mit insgesamt 320 Teilnehmer*innen wurden eingeschlossen: zwei doppelblinde randomisierte kontrollierte Studien (RCTs), zwei open-label RCTs und eine nicht-randomisierte kontrollierte Studie (NRCT). Alle Studien untersuchten depressive Endpunkte; Studien zu Angststörung wurden nicht identifiziert. Ein open-label RCT und ein NRCT berichteten signifikante Verbesserungen der depressiven Symptomschwere unter Folsäure (Vitamin B9) plus Vitamin B12, waren jedoch durch kleine Stichproben und ein hohes Verzerrungsrisiko limitiert. Drei Studien mit ≥3 B-Vitaminen zeigten keine signifikanten Effekte. Die größte, methodisch robusteste Studie zeigte keinen Unterschied in der Symptomschwere, aber ein verbessertes Ansprechen über einen Zeitraum von 12 Monaten. Für kognitive Endpunkte und unerwünschte Ereignisse zeigten sich keine signifikanten Unterschiede; die Evidenz war jedoch aufgrund der geringen Anzahl von Ereignissen begrenzt. Die Vergleichbarkeit der Studien war durch Heterogenität eingeschränkt.

Ergebnisse: 320 Teilnehmer*innen in 5 Studien: 2 verblindete RCTs, 2 open-label RCTs, 1 NRCT

heterogene Studien, kleine Stichproben und ein hohes Verzerrungsrisiko:

keine signifikanten Unterscheide zur Monotherapie

Schlussfolgerungen: Die Evidenz für eine adjunktive Supplementierung mit Vitamin-B-Komplex zusätzlich zu Antidepressiva ist sehr begrenzt. Weitere hochqualitative RCTs sind erforderlich.

Antidepressiva Supplementierung mit Vitamin-B-Komplex bleibt unklar

1 Introduction

1.1 Background

Anxiety and depressive disorders account for a significant proportion of the global mental health burden [1] and contribute substantially to societal and economic burdens due to their high prevalence, associated disability, and considerable direct and indirect costs [2], World Health Organisation (WHO) [3]. While depressive disorders are known to be associated with pronounced functional impairments and reduced quality of life [4, 5], similar patterns are observed in anxiety disorders [6], highlighting the need for effective and well-tolerated treatments to prevent chronicity and loss of participation. Treatment challenges in the use of antidepressants have stimulated interest in safe and accessible augmentation and adjunctive strategies [7, 8]. Aside from established approaches, nutritional interventions, such as B vitamin supplementation, have received scientific attention [9, 10]. B vitamin supplements are widely available and often marketed for improving energy and mood. Their biological plausibility derives from the role of B vitamins in neurobiological processes relevant to mood regulation, including one-carbon metabolism and neurotransmitter synthesis [11]. Against this background, the present review focuses on evidence for vitamin B combinations as adjuncts to antidepressant therapy in depression and anxiety.

Angst- und depressive Störungen sind eine erhebliche globale Belastung für die psychische Gesundheit

Bedarf an wirksamen und gut verträglichen Behandlungen, um Chronifizierung und Teilhabeverlust zu verhindern

die Supplementierung mit B-Vitaminen bekommen wissenschaftliche Aufmerksamkeit

Depression and anxiety disorders are complex conditions with multifactorial causes and a wide range of therapeutic approaches. A comprehensive discussion of all relevant biological, psychological, therapeutic and social factors would exceed the scope of this thesis. Therefore, the following section focuses solely on aspects essential to understanding the background and context of the present systematic review from a public health perspective.

Review fokussiert auf Vitamin-B-Kombinationstherapie mit Antidepressiva

Public Health Perspektive

1.2 Global Burden of Depression and Anxiety

According to estimates based on Global Burden of Disease Study 2021 data, Zhang et al. [1] reported a global prevalence of 359.2 million cases of anxiety disorders and 332.4 million cases of depressive disorders in 2021. Together, anxiety and depressive disorders constituted approximately 9.1% of the total global disease burden and 63.1% of all mental health disorders. Middle and low- Socio-Demographic Index (SDI) regions account for most global cases of depression and anxiety, largely because of their substantial population sizes [1]. SDI is a composite measure of development that is closely associated with health outcomes (Global Burden of Disease Collaborative Network (GBD), [12]. Between 1990 and 2021, population growth and population ageing contributed to a 71% increase in anxiety-related disability-adjusted life years (DALYs) and a 79% increase in de-pression-related DALYs [1]. One DALY represents the loss of one year of healthy life, helping to quantify the population-level impact of health conditions [13].

weltweite Prävalenz von 359,2 Millionen (Angststörungen) und 332,4 Millionen (depressive Störungen) im Jahr 2021

9,1 % der globalen Krankheitslast und 63,1 % aller psychischen Störungen

geschätzte 12 Milliarden verlorene produktive Arbeitstage

öffentliche Ausgaben für psychische Gesundheit: 2 % der nationalen Gesundheitsbudgets

Every year, depression and anxiety generate an estimated 12 billion lost productive workdays. The global economic burden is estimated at one trillion USD [3]. Spending levels differ sharply by income group: high-income countries (HICs) invest up to 65 USD per capita in mental health, whereas low-income countries (LICs) allocate 0.04 USD per person [14]. Government expenditure on mental health accounts for only about two percent of national health budgets [15]. HICs generally benefit from stronger health systems, broad insurance coverage and better access to diagnosis and treatment, whereas low- and middle-income countries (LMIC) have limited healthcare infrastructure, workforce shortages and greater social and environmental challenges. In addition, poverty and lower education levels often delay care-seeking, while ageing populations and lifestyle-related conditions are more prominent in HICs [14, 15].

Global Burden of Depression

Prävalenz von Depressionen in Ländern mit hohem Einkommen bei Menschen im Alter von 30 bis 39 Jahren am höchsten

Depressive disorders affected an estimated 332.4 million individuals worldwide in 2021 and were responsible for 56.3 million DALYs [1]. Across countries with high to medium-low SDI levels, the prevalence of depression is highest among people aged 30-39. In contrast, countries with low, medium-low SDI levels show peak rates in the 20-29 age group [16]. DALY rates reached their maximum among men aged 55-59 and among women aged 60-64, with women exhibiting higher levels overall [17].

selbst in einkommensstarken Verhältnissen oft unbehandelt

Despite this substantial and age-spanning burden, global treatment coverage for depression remains limited. Worldwide, only about a third of individuals living with depression obtain any form of treatment [14]. In low- and middle-income settings, the proportion of individuals receiving treatment for depression is markedly reduced [18]. By contrast, coverage is higher in high-income settings, although still incomplete: in 2021, approximately 61.0% of U.S. adults aged 18 years and older who experienced a major depressive episode received treatment within the previous year, increasing to 74.8% among those with severe functional impairment [19]. Looking ahead, projections suggest that the global burden of depressive disorders will remain above 2019 levels through 2040 [1].

Global Burden of Anxiety

Jugendliche im Alter von 10 bis 14 Jahren stellen die Altersgruppe mit der weltweit höchsten Prävalenz von Angststörungen dar

In 2021, anxiety disorders affected an estimated 359.2 million people worldwide. The global burden attributed to anxiety disorders amounted to approximately 42.5 million DALYs. As in depression, females exhibited higher prevalence and DALY rates than males across most age groups [1]. GBD data indicate that anxiety disorders are more prevalent in countries with high and medium SDI levels [16].

nur ein kleiner Prozentsatz erhält eine Behandlung

Adolescents aged 10-14 represent the age group with the highest global prevalence of anxiety disorders. Moreover, age patterns differ by development level: in low- and low-moderate SDI countries, prevalence peaks between ages 15 and 25, whereas in high, high-moderate, and medium SDI regions, the highest rates occur later, around ages 30-35 [16]. Globally, only 27.6% of people with a 12-month anxiety disorder receive treatment and fewer than 1 in 10 receive possibly adequate care [20]. Looking forward, projections also suggest for anxiety that from 2022 to 2040, the global burden of anxiety disorders will remain above 2019 levels [1].

1.3 Causes and Risk Factors for Depression and Anxiety

komplexe Störungen mit multiplen Einflussfaktoren

Overall, the causes of depression and anxiety are complex, with no single factor fully explaining their development. A review of the evidence identified multiple influencing factors, including biological factors such as physical health-related factors, genetic influences, gut microbiome alterations, inflammatory processes, stress-related mechanisms, and cognition, as well as psychological and social determinants [21].

Biologische Aspekte (genetische Einflüsse, Veränderungen des Darmmikrobioms, Entzündungsprozesse) sowie psychologische und soziale Aspekte (Armut, Arbeitslosigkeit, belastende Ereignisse, Erkrankungen, Alkohol- oder Drogenmissbrauch)

Among the contributing risk factors for depression are poverty, joblessness, stressful life events, medical illness, and difficulties related to alcohol or drug misuse [22]. Maltreatment during childhood is the leading determinant of disease burden, with violence by an intimate partner representing a stronger contributor among females, whereas childhood sexual abuse accounted for a larger share of the burden among males [17]. While multiple psychosocial, demographic and clinical factors are associated with anxiety disorders, bullying victimisation is the only risk factor for which sufficient evidence of a causal relationship has been established within the GBD framework [23]. The risk of developing anxiety is higher among people who have experienced abuse, major losses or other adverse events [24].

1.4 Management of Depression and Anxiety

Folge ist beeinträchtigte soziale und berufliche Funktionsfähigkeit

Both depression and anxiety disorders have substantial consequences, including impaired social and occupational functioning, increased risk of cardiovascular and metabolic diseases, higher utilisation of healthcare and increased risk of suicide [25, 26]. People living with mental disorders are also more affected by homelessness and inappropriate incarceration [27].

hohe Komorbidität zwischen Angst- und depressiven Störungen

By Calkins et al. [28], high rates of comorbidity between anxiety and depressive disorders have been addressed, with evidence suggesting that approximately 60% of individuals meet diagnostic criteria for both conditions within a one-year period. When compared to those with only one disorder, individuals with comorbid presentations experience higher functional impairment, diminished quality of life, and treatment outcomes that are not as favourable. Although comorbidity is clinically and epidemiologically relevant, it will not be examined in detail within the scope of this review.

Auszug aus 2 klinischen Leitlinien (LL): NICE, AWMF

The management of depressive and anxiety disorders is presented based on two well-established clinical care guidelines. As both guidelines are extensive, only a limited number of aspects are outlined; completeness cannot be achieved. Content and recommendations of other treatment guidelines may differ.

Clinical Characteristics and Management of Depression

Klassifizierung von Depression nach Diagnostic and Statistical Manual of Mental Disorders (DSM)

Depressive disorders present themself by a depressed, hollow, or irritable mood along with associated changes that have a substantial impact on the person's ability to function (American Psychiatric Association (APA) [29]). Specific diagnostic criteria are outlined in the International Classification of Diseases, 11th Revision (ICD-11; [30]) and in the Diagnostic and Statistical Manual of Mental Disorders 5th ed. ([DSM-5]; [31]) and vary depending on the classification system.

Terminologie für depressive Störungen variiert je nach Diagnosewerkzeug

Several diagnostic categories, including major depressive disorder (MDD) and persistent depressive disorder (PDD, dysthymia), which vary in symptom duration, severity, and recurrence pattern exist [31]. PDD, for example, is characterised by a depressed mood lasting at least two years in adults and can be preceded by major depressive episodes (MDE) or present simultaneously with them [32]. ICD-10 uses the term “depressive episode” and differentiates between mild, moderate, and severe forms, while also defining recurrent depressive episode as a separate diagnosis [30]. In older studies, the term bipolar depression was used to refer to a depressive episode occurring within bipolar disorder, although no independent diagnostic category in DSM-5-TR [29], or in the older version DSM-III-R [33], could be identified. Accordingly, in this review, cases labelled as “bipolar depression” were interpreted as depressive episodes within bipolar disorder. Other depressive disorder categories, such as disruptive mood dysregulation disorder, premenstrual dysphoric disorder, as well as substance/medication-induced, mixed depressive and anxiety disorder, and unspecified depressive disorders, are also part of the depressive disorders classification [31].

The terminology for depressive disorders varies across diagnostic tools. To enhance readability, the terms will therefore be used synonymously throughout this text unless otherwise specified.

Management of Depression

NICE-LL 2022 zu “Depression in adults”, AWMF-Nationale VersorgungsLeitlinie [NVL] 2022 zu Unipolarer Depression

The United Kingdom NICE (National Institute for Health and Care Excellence) guideline *Depression in adults: treatment and management* 2022 [34] outlines a stepped-care model called “matched care model” in which treatment intensity is matched to symptom severity, ranging from low-intensity psychosocial interventions for less severe depression to high-intensity and combined pharmacological and psychological therapy for more severe cases. The severity of depression is determined by three key factors: the intensity of symptoms, the duration of the episode, and the degree of functional impairment in personal and social life [34]. The German National Care Guideline for Unipolar Depression (Nationale VersorgungsLeitlinie (NVL) Unipolare Depression; Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), & Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [35]) follows a comparable severity-based treatment approach.

Betreuungsmodell angepasst an Intensität der Symptome, Dauer der Episode, Grad der funktionellen Beeinträchtigung

Clinical Characteristics and Management of Anxiety

Klassifizierung von Angststörung nach Diagnostic and Statistical Manual of Mental Disorders (DSM)

Anxiety or fear-related disorders are defined by excessive and persistent fear, anxiety and associated behavioural disturbances, with symptoms severe enough to hinder functioning or result in distress [24]. Diagnostic criteria are also outlined in the DSM-5 [31]. The ICD-11 includes several diagnostic entities under this group, such as generalised anxiety disorder (GAD), panic disorder and social anxiety disorder [30].

Management of Anxiety

NICE LL 2021 "Generalised Anxiety disorder and Panic disorder in Adults"

angepasstes Betreuungsmodel

According to the NICE guideline *Generalised Anxiety disorder and Panic disorder in Adults: Management* and the *S3 Guideline for the Treatment of Anxiety Disorders* [36, 37], anxiety and panic disorders are likewise managed using a stepped-care approach, in which treatment intensity is matched to symptom severity ranging from low-intensity psychological interventions such as guided self-help and cognitive behavioural therapy (CBT) for mild cases, to pharmacotherapy, including antidepressants, and combined treatments for more severe or persistent conditions [36, 37].

1.5 Treatment of Depressive Disorders with Antidepressants

Antidepressiva bei Depression als eine Therapieoption

ev. auch bei Angststörungen

Although the introduction outlines the global burden and etiological context of both depression and anxiety, the present review focuses on depressive disorders. The treatment of anxiety with antidepressants is therefore not addressed. Also, the treatment of a depressive episode in context of bipolar disorders is not discussed, as only one study participant presented with this diagnosis, the subsequent discussion of antidepressant therapy is limited to depressive disorders reflecting the available evidence base. A separate guideline *S3 Guideline on the Diagnosis and Treatment of Bipolar Disorders* exists (Deutsche Gesellschaft für Bipolare Störungen (DGBS) & Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), [38]). The pharmacological management of suicidal patients with depression is likewise not discussed, as such patients did not constitute a defined or systematically examined part of the study population. A small number of participants in the study population were diagnosed with comorbid dementia, for which a separate guideline exists - the NICE guideline on dementia: *Assessment, management and support for people living with dementia and their carers* [39]. This guideline is not discussed in detail in the present review.

empfohlen von NICE und NVL

The NICE guideline provides general recommendations on the use of antidepressants in depression, but does not outline specific drug choices or detailed pharmacological protocols to the same extent as the *NVL Unipolare Depression*. The following description of antidepressant therapy is based on recommendations of the NVL *Unipolare Depression* [35], which represents the established standard of care in the German-speaking context. Recommendations in other guidelines may differ.

1.5.1 Principles of Antidepressant Therapy

NICE: Antidepressiva nicht als Erstlinientherapie und nur in Absprache mit Präferenzen des/der Patienten/in

The treatment of depressive disorders does not rely solely on pharmacological therapy. The NICE guideline states that antidepressant medication should not generally be used as an initial course of treatment for less severe depression and to be considered when it aligns with the patient's informed preference [34].

Antidepressants consist of a range of compounds that can help reduce the symptoms of depression. Depending on the specific medication, their ability to lift mood, ease depressive symptoms, and either stimulate or calm psychomotor activity can vary [40]. When selecting an antidepressant, the NVL *Unipolare Depression* recommends considering factors such as patient preferences, safety considerations, comorbidities and concurrent medications, treatment response, practical handling and monitoring requirements, availability and regulatory status, and biological parameters. Monitoring should be carried out, and both treatment effects and adverse effects should be systematically assessed. After reaching the standard dose, a minimum of 3-4 weeks (6 weeks in elderly patients) should be allowed for the therapeutic effect to emerge [35]. Improvements in psychomotor drive may occur earlier than the onset of mood-lifting antidepressant effects, which can temporarily increase the risk of suicidal behaviour during the initial phase of treatment [40].

große Anzahl unterschiedlicher Medikamente

NVL: Auswahl von Patientenpräferenzen, Nebenwirkungen, Begleiterkrankungen und Begleitmedikation, Ansprechen auf die Behandlung, etc. abhängig

1.5.2 Antidepressant Substance Classes

The NVL *Unipolare Depression* lists a broad range of antidepressant substance classes, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAO inhibitors), and several other agents [35]. For the purposes of this review, only SSRIs and TCAs are described in more detail, as these were the classes represented in the studies included in the review.

unterschiedliche Substanzklassen: SSRIs, SNRIs, NaSSAs, TCA, etc.

The dosage information and the overview of potential adverse effects are intended to provide only a general orientation and were taken from a standard pharmacology textbook [40]. Actual dosing requirements may vary across different patient groups depending on individual characteristics, comorbidities, and clinical circumstances.

Dosierung vom Patientengruppen und deren individuellen Merkmalen, Begleiterkrankungen und klinischen Umständen abhängig

Selective Serotonin Reuptake Inhibitors

SSRIs are part of the broader group of selective monoamine reuptake inhibitors [40] and are frequently chosen as an initial pharmacological treatment for depression and various other psychiatric conditions because of their favourable safety profile, proven efficacy, and good tolerability [41, 42]. This class of agents includes, among others, citalopram, escitalopram and fluoxetine [40].

Selektive Serotonin-Wiederaufnahmehemmer (SSRI)

Their primary mechanism involves blocking the reuptake of serotonin, which generally produces an activating effect. Typical daily doses are around 20-40 mg for citalopram, 10-20 mg for escitalopram [40] and 20 mg for fluoxetine [43]. Although the inhibition of serotonin reuptake occurs rapidly, the clinical antidepressant response usually develops only after one to three weeks. This delay is thought to be related to longer-term neuroadaptive processes, such as changes in receptor density within the central nervous system. These medications are used in the treatment of acute depressive episodes, obsessive-compulsive disorder, and post-traumatic stress disorder, in preventing relapse and in managing anxiety disorders. Common adverse effects may include headaches, dizziness, tremor, sedation, sleep disturbances, dry mouth, increased sweating and gastrointestinal complaints [40].

günstiges Sicherheitsprofil, nachgewiesene Wirksamkeit und gute Verträglichkeit

bei akuten depressiven Episoden, Zwangsstörungen, PTBS, Behandlung von Angststörungen

Tricyclic Antidepressants

Trizyklische Antidepressiva (TCA)

Tricyclic antidepressants (TCAs) are classified as non-selective reuptake inhibitors and receptor antagonists [40]. These medications act by blocking the reuptake of neurotransmitters, particularly serotonin and norepinephrine, thereby influencing neural processes involved in mood, attention and pain regulation [44]. TCAs are used in the treatment of depressive disorders as well as anxiety, sleep and obsessive-compulsive disorders, and they may also be employed in certain other psychiatric conditions, such as alcohol dependence. Typical adverse effects include constipation, urinary difficulties, increased sweating, sedation, dizziness, confusion, tremor, dry mouth, visual accommodation disturbances, hypotension, tachycardia, arrhythmias, weight gain and increased appetite. Due to their narrow therapeutic index, overdoses can be dangerous. Nortriptyline is a representative of this class and is usually administered at daily doses ranging from 50 to 200 mg [40]. Desipramine is also part of the TCA antidepressants. The initial dose is typically 25-50 mg per day, which can be gradually increased to a therapeutic range of 100-200 mg daily. The upper limit of dosing is 300 mg per day [45].

bei bei depressiven Störungen sowie Angst-, Schlaf- und Zwangsstörungen

Nebenwirkungen: Verstopfung, Harnwegsbeschwerden, vermehrtes Schwitzen, Sedierung, Schwindel, Verwirrtheit, Zittern und Mundtrockenheit

1.5.3 Established Augmentation Strategies

Strategien, um bei unzureichendem Ansprechen die therapeutische Wirkung zu steigern

The NVL *Unipolare Depression* considers patients treatment-resistant when they have failed to respond to at least two adequately dosed antidepressants from different pharmacological classes. The guideline states, however, that it remains unclear how non-response to psychotherapeutic interventions fits into the definition of treatment-resistant depression, particularly when psychotherapy is delivered alongside medication. In the guideline, treatment resistance is therefore defined as a lack of response to an initial intervention followed by nonresponse to at least one additional treatment strategy [35].

Medikationswechsel nach Re-Evaluierung: Lithium, atypische Antipsychotika, etc.

After reevaluating the diagnosis, adherence and plasma drug levels, treatment may be extended by switching to psychotherapy or include group-based interventions [35]. Additionally, guidelines advise thinking about switching to a different antidepressant drug or combining antidepressants [35, 46]. Medication-based augmentation techniques like lithium, atypical antipsychotics, intranasal esketamine, and intravenous ketamine are advised as a next step [35]. The NICE guidelines indicate that if no improvement is observed after 4-6 weeks and once other potential causes of non-response and steps have been addressed, medication-focused augmentation options also include adding a second-generation antipsychotic or lithium, or augmenting treatment with lamotrigine (an antiepileptic/mood stabiliser) or the thyroid hormone triiodothyronine [46].

B-Vitamins and Mental Health

B-Vitamine: zentrale Rolle in neurobiologischen Prozessen

Literature suggests that dietary patterns aligned with food-based guidelines and adequate nutrient intake are associated with the prevention and management of depression and anxiety [47] [48], and that pro-inflammatory diets increase the risk of depression [49], whereas healthier dietary patterns or specific nutrients may serve preventive and therapeutic roles [50, 51]. Research indicates that treating micronutrient deficiencies is essential for depressed patients [50]. Within this broader nutritional context, the B vitamins warrant attention due to their central role in neurobiological processes that are fundamental to normal brain function [11].

ausreichende Nährstoffzufuhr zur Prävention und Behandlung von Depressionen und Angstzuständen

1.5.4 B-Vitamins

insgesamt 8 anerkannte B-Vitamine

In total, eight B vitamins are recognised, all of which are water-soluble [52] and cannot all be stored within the body [20]. Only a small number of the 30 to 40 compounds that make up the B vitamin complex have significant clinical significance. Most of them participate in biochemical group-transfer processes in their active form as coenzymes [20]. The following section summarises all eight B vitamins, focusing on their dietary sources, the consequences of deficiency or excessive intake, as well as recommended daily intakes and upper safety limits. The information presented here is based on two textbooks [20, 52]; and recommendations provided by the German Nutrition Society (Deutsche Gesellschaft für Ernährung (DGE)), as well as the European Food Safety Authority (EFSA) publications "Scientific opinion on the tolerable upper intake levels for vitamins and minerals – Summary Report" [53, 54], "Dietary Reference Values for Nutrients - Summary report" [54] and the WHO's "Vitamin and Mineral Requirements in Human Nutrition 2nd Edition" [55]. All recommended nutrient intake values refer to adults aged 19 and older, excluding those who are pregnant or breastfeeding.

als Coenzyme an biochemischen Stofftransportprozessen beteiligt

DGE: Mangel oder übermäßige Zufuhr haben Konsequenzen empfohlene Tagesdosen und Grenzwerte sollten nicht überschritten werden

Definition of Terms

Referenzwerte von European Food Safety Authority (EFSA) definiert

When available, Population Reference Intakes (PRI) are reported, which represent the amount of a nutrient expected to meet the requirements of nearly every individual within a population group. Adequate Intake (AI) reflects the mean daily intake observed in healthy population groups and is presumed to meet nutritional needs [54]. The Tolerable Upper Intake Level (UL) refers to the highest long-term daily nutrient intake from all sources that is unlikely to lead to harmful health effects in humans [53].

Vitamin B1 (thiamine)

Vit B1 (Thiamin) in magerem Schweinefleisch, Innereien wie Nieren, Leber, Hirn und in ganzen unverarbeiteten Getreidekörnern

Almost all foods derived from plants and animals contain thiamine. Lean pork, organ meats like kidney, heart, liver, brain and whole unprocessed grains are the richest natural sources [52]. Severe vitamin B1 deficiency causes beriberi, which is still seen in regions where polished rice is a dietary staple. Loss of appetite, neuropathy, cognitive decline, nausea, exhaustion, and muscle atrophy are among the symptoms [52]. A healthy diet provides sufficient thiamine [56]. The PRI amounts 0.072 for females to 1.1mg/Megajoule/day for males [54], the DGE states 1.0mg/day for females [56]. The EFSA reports insufficient data to establish a tolerable upper intake level (UL) for vitamin B1 [57], no harmful side effects have been reported from high intakes of thiamine [56].

Vitamin B2 (riboflavin)

Vit B2 (Riboflavin) in Milch, Leber, Nieren und verschiedene Gemüsesorten

Riboflavin is broadly distributed across plant- and animal-based foods and rich sources include milk, liver, heart tissue, kidney and a range of vegetables [52]. Toxicity from riboflavin is unlikely, as only small amounts can be absorbed [55]. Deficiency manifests as ariboflavinosis, a condition characterised by mucosal lesions and seborrheic dermatitis [20]. A healthy diet generally ensures adequate riboflavin intake [58]. The PRI amounts 1.6mg/day [54]. EFSA reports that no UL can be defined for vitamin B1 due to insufficient data [57].

Vitamin B3 (niacin, nicotinic acid)

Vit B3 (Niacin) in magerem Rind-, Kalb-, Schweinefleisch, Innereien und Geflügel, Fisch (Sardellen, Thunfisch, Lachs und Makrele), Mungobohnen, Erdnüssen und Pilzen

Rich sources include meats (lean beef, veal, pork, organ meats, and poultry) and fish (anchovies, tuna, salmon, and mackerel). Mung beans, peanuts, and mushrooms are examples of plant-based foods that offer significant amounts of vitamin B3 [59]. Prolonged intake of high oral doses of nicotinic acid may cause liver toxicity and various skin-related adverse effects [55]. Pellagra, a condition marked by dermatitis, diarrhoea, and dementia, is caused by a deficiency [20]. Niacin deficiency is rare in industrialised countries and typically occurs only in the context of disease, such as among other alcoholism, chronic diarrhoea or liver cirrhosis [59]. The recommended intake is 1.6 mg niacin equivalents per megajoule of energy consumed [54]. ULs are reported separately for niacin forms and should not be exceeded in the long term; they are set at 10 mg/day for nicotinic acid and 900 mg/day for nicotinamide [57].

Vitamin B5 (pantothenic acid)

Vit B5 (Pantothensäure) in Innereien, Fisch, Eier, Muskelfleisch und Weichkäse, Vollkornmehl, Erd- und andere Nüsse

Particularly high levels of pantothenic acid can be found in animal products like organ meats, fish, eggs, muscle meat and soft cheeses. Good sources of plant foods include whole-grain flour, peanuts and other nuts [60]. No clinically relevant toxicity has been identified [55]. Increased hair and nail fragility could be a sign of a vitamin B5 deficiency [20]. However, since pantothenic acid is readily available in a wide variety of foods, deficiency through diet is considered rare [55]. The AI amounts to 5mg/day [54]. EFSA reports that no UL can be defined due to insufficient data [57].

Vitamin B6 (pyridoxin)

Vit B6 (Pyridoxin) in Vollkornprodukten, Wal- und Haselnüssen, rote Paprika, Sardinen, Makrelen

Whole grains, walnuts and hazelnuts, red bell peppers, sardines, mackerel, and pork are all good food sources of vitamin B6 [61]. Vitamin B6 deficiency can lead to anaemia and neurological problems. Prolonged high vitamin B6 intake (≥500 mg daily or 8 mg/kg body weight) can provoke nerve damage, alongside skin problems and reduced muscle strength while lower doses, above 100 mg per day, have been linked to minor neurological side effects [61]. Diet-related deficiency is uncommon and often occurs alongside shortages of other B vitamins and other factors such as alcohol misuse and the use of oral contraceptives [61]. The recommended daily PRI amounts 1.6mg for females and 1.7mg for males [54]. UL is set at 12mg/day [57].

Vitamin B7 (biotin, vitamin H)

Vit B7 (Biotin) in Leber, Niere, Eigelb und Hefe

Liver, kidney, egg yolk and yeast are among the richest sources of biotin [52]. As the intestinal absorption capacity for biotin is restricted, toxicity is not a problem [55]. Although intestinal bacteria produce notable amounts of biotin, this synthesis does not fully meet the body's needs. Usually, a deficiency only develops when gut microbiota suppression is coupled with a low-biotin diet

[62]. A lack of biotin resulting from inadequate dietary intake is rarely seen [63]. The AI of 40μg of is reported [54]. EFSA reports that no tolerable upper intake level can be defined due to insufficient data [57].

Vitamin B9 (folate, folic acid)

Vit B9 (Folsäure) in Vollkornprodukten, Weizenkeimen, Hülsenfrüchten, Nüssen, Sprossen, grünem Gemüse, Tomaten und Orangen

Folate is provided by a wide variety of foods, including whole-grain products, wheat germ, legumes, nuts, sprouts, green vegetables, tomatoes and oranges. Additional notable sources include potatoes, eggs and liver. The industrially produced, synthetic form of the vitamin is referred to as folic acid [64]. A long-term excess of folic acid may lower the seizure threshold and can also contribute to the development of gastritis and dermatitis. Folate deficiency hampers blood cell formation, causing megaloblastic anaemia and lowered white blood cell and platelet counts. It can also damage mucosal tissues in the mouth and gut and diarrhoea. Folate deficiency ranks among the most common vitamin shortages [20]. A PRI of about 330μg of dietary folate equivalents (DFE), is reported which can be met through a diet that includes folate-rich foods [64]. DFEs are used to express total folate intake by combining natural food folate with folic acid from fortified foods or supplements, calculated as: μg DFE = μg food folate + (1.7 × μg folic acid). UL are reported at 1000μg/d [57].

Vitamin B12 (cobalamin)

Vit B12 (Cobalamin) in Lebensmitteln tierischer Herkunft

The primary dietary sources of vitamin B12 for humans are animal-derived foods. The vitamin is synthesised exclusively by microorganisms, including certain species of intestinal bacteria [52]. A deficit rarely develops in healthy individuals because the body can store vitamin B12 for several years [20]. Prolonged vitamin B12 deficiency leads to pernicious or megaloblastic anaemia. It is rarely caused by diet alone, though vegans are more susceptible, but is most often due to impaired absorption, especially when the intrinsic factors is lacking (e.g. gastric disease, gastrectomy, autoimmune causes) or when the small intestinal mucosa is damaged. Genetic defects as well as long-term proton-pump inhibitor use, may also contribute. Neurological dysfunction often precedes hematological signs, resulting in ataxic-spastic symptoms and peripheral polyneuropathy [52]. The AI amounts 4.0μg per day [54]. No adverse effects by vitamin B12 intake have been reported by EFSA [57].

1.5.5 B-Vitamins and the Homocysteine Pathway

mögliche Erklärung für Rolle der B-Vitamine bei Depressionen: Homocystein-Stoffwechsel hängt Folsäure und Vit B12 ab

One possible explanation for the role of B vitamins in depression is their involvement in homocysteine metabolism, which mainly depends on folic acid and vitamin B12 [11]. Deficiencies in vitamin B12 and folate impair one-carbon metabolism, leading to elevated homocysteine levels and reduced S-adenosylmethionine levels [50]. One-carbon metabolism, which encompasses the folate and methionine cycles, is a central biochemical pathway [65]. As S-adenosylmethionine serves as a methyl donor in the rate-limiting steps of neurotransmitter synthesis, including serotonin, dopamine, and norepinephrine, lower concentrations of this compound have frequently been observed in individuals with depression. Elevated homocysteine levels, in contrast, promote the formation of neurotoxic metabolites [50]. Increased homocysteine levels have been linked to depression in the general population [50, 66].

erhöhte Homocysteinspiegel werden mit Depressionen in Verbindung gebracht

1.6 Current State of Research

Meta-Analyse mit 522 RCTs zu Antidepressiva: im Vergleich zu Placebo überlegen, wenn auch mit weitgehend moderaten Effektstärken

Antidepressants represent a cornerstone of treatment for depression and anxiety [67], and patients derive meaningful benefit. An extensive meta-analysis of 522 double-blind trials demonstrated that all the investigated antidepressants were superior to placebo, albeit with largely modest effect sizes [68]. However, therapy adherence can be problematic, as the antidepressant effect typically emerges after one to three weeks, whereas side effects often occur at the very beginning of treatment [40]. In a cohort of 39,800 patients with depressive disorders, adherence to antidepressant therapy was observed in only 31.02% of cases [69]. Also, non-response to antidepressants has been identified as a challenge. A review concluded that, depending on the context, an estimated 30-55% of patients are considered treatment resistant. Notably, there is no universally accepted definition of treatment-resistant depression [70]. Consequently, in many cases, second-step treatment strategies are necessary [71]. Clinical practice guidelines outline further treatment steps, including augmentation therapy with pharmacological agents such as lithium and atypical antipsychotics [35] [46]. However, pharmacotherapy with these substance classes is frequently associated with adverse side effects [72] [73], as Schefft et al. [74] also argued in their review and therefore requires careful indication, close monitoring and ongoing clinical supervision [35, 46].

Adhärenz der Patient:innen nur bei 31%,

30-35% Therapieresistenz

bei vielen Patient:innen Augmentation (Therapiewechsel oder zusätzliche Maßnahmen) notwendig

Ernährungsinterventionen, u.a. Supplementierung mit B-Vitaminen zunehmendes wissenschaftliches Interesse

Beyond those established treatment approaches, nutritional interventions, including B vitamin supplementation, have attracted increasing scientific interest [9, 10]. Consistent with their biological relevance, low levels of certain B vitamins are associated with an increased risk of depressive disorder [75, 76] and accumulating evidence further suggests that B vitamin supplementation may be associated with a protective effect against the onset of depression and anxiety. In a longitudinal study of 3,849 older adults, individuals with low or deficient vitamin B12 status showed a 51% higher risk of developing depressive symptoms over a four-year follow-up period. No significant association was found between the incidence of depression and folate status [77]. According to a recent systematic review, reduced neurotransmitter synthesis, elevated homocysteine levels and worsened depressive symptoms are associated with folate and vitamin B12 deficiencies [78] and a cross-sectional study of 3,362 adults found an association between a higher risk of both depression and anxiety and lower dietary intake of vitamin B6 [79].

am häufigsten untersuchte B-Vitamin Supplementierungen:

B6, B12, Folsäure

marginale oder keine Effekte

Considering B vitamin supplementation, a longitudinal study comprising 3,503 older adult participants demonstrated that an increase of 10mg in vitamin B6 and 10μg in vitamin B12 intake from food and supplements was associated with a 2% reduction in the annual likelihood of depressive symptoms, whereas no significant relationship was observed for folate [80] and in a randomised trial of stroke survivors receiving vitamin B6, B12 and folic acid, participants in the intervention group showed a significantly lower risk of developing major depression over approximately seven years compared with placebo [81]. However, considering anxiety and depressive symptoms, a meta-analysis showed no statistically significant improvement of supplementation with ≥3 B vitamins in an “at risk” population [82] and in the Women’s Antioxidant and Folic Acid Cardiovascular Study (n=4, 331) older women without history of depression were randomised to receive vitamin B6, folic acid and vitamin B12 or placebo for an average of 7 years and no between-group difference in incident depression was detected, although homocysteine levels showed a significant decline [83].

B-Vitamine als Ergänzung zur Behandlung mit Antidepressiva

When considering B vitamins as an add-on to antidepressant treatment, their potential adjunctive effects have been examined in clinical trials. In a meta-analysis of five RCTs (n= 584 patients) evaluating folate as an adjunct to SSRI/SNRI treatment, folate supplementation was associated with significantly higher response and remission rates, as well as significant reductions in depressive symptom severity across treatment durations of 4, 6, and ≥ 8 weeks, without evidence of an increased risk of adverse events [84]. An open-label RCT in a sample of 73 participants with low vitamin B12 levels found statistically significant evidence that vitamin B12 injections as add-on therapy lowered depressive symptom severity in patients who had not initially responded to antidepressant treatment [85]. In a small (n= 51) younger inpatient sample with MDD receiving SSRI treatment, additional vitamin B1 supplementation (300 mg/day) was related to an improvement in depressive symptoms after six weeks relative to placebo. However, by week 12, the mean differences no longer reached statistical significance [86].

Untersuchungen zu Effekten mit einzelnen B-Vitaminen (z.B. B12) zeigen gemischte Ergebnisse

Untersuchungen zur Kombination von Antidepressiva mit multiple B-Vitaminen (Vit B complex)

Evidence for the efficacy of combining antidepressants with multiple B vitamins, however, remains limited. As another review concluded, most studies have focused only on vitamins B6, B9 and B12, and the author argued that multivitamin interventions may better capture the combined biological actions of B vitamins as a group [11]. The limited response to antidepressant therapy and the underlying rationale for micronutrient assessment have formed the basis of multiple systematic reviews. However, each of the systematic reviews identified in the preliminary literature search for this review included only one RCT [87] that examined a combination of B vitamins as an adjunct to antidepressants [88, 89][9, 74], while some covered a broad range of nutraceuticals [90][9, 91][74] or addressed a healthy or 'at risk' population [82].

Forschungslücke soll hier geschlossen werden

This reveals a gap in the scientific literature on the adjunctive use of a B vitamin complex (≥2 B vitamins) with antidepressants, and the heterogeneity of existing findings on B vitamin supplementation further highlights the need for a systematic analysis of this question.

1.7 Objective

Ziel des systematischen Reviews: Erkenntnisgewinn, ob die Kombination einer Antidepressiva-Therapie mit einem Vitamin-B-Komplex zur Verbesserung der Behandlung von Depressionen und Angstzuständen beiträgt

This systematic review aims to synthesise evidence from clinical trials to evaluate whether the combination of antidepressant therapy with a vitamin B complex may represent a simple and accessible strategy to enhance antidepressant treatment and potentially reduce the public health burden of depression and anxiety. Specifically, it will evaluate the efficacy and safety of adjunctive vitamin B complex supplementation (≥2 B vitamins) in adults (≥18 years) with a clinical diagnosis of depression or anxiety who are receiving antidepressant therapy, compared with antidepressant monotherapy. Outcomes of interest include changes in symptom severity, response and remission rates, quality of life and cognitive outcomes, and safety outcomes, including adverse events and tolerability, dropout rates due to adverse effects, and all-cause discontinuation rates.

2 Methods

2.1 Study Design

systematischer Review: transparente Synthese der verfügbaren Evidenz

A systematic review design was chosen to address the research question, as this approach enables a comprehensive and transparent synthesis of available evidence. This structured method ensures reproducibility and objectivity by following predefined procedures [92] and offers a robust assessment of the current state of knowledge. Systematic reviews synthesise extensive evidence to evaluate the effectiveness of interventions, treatments, and diagnostic methods, playing a key role in guiding best practice and improving patient outcomes [93]. Accordingly, this review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to include all essential information on the review's justification, procedures, and outcomes. Application of this guideline aims to enhance research quality and supports reproducibility [94].

2.2 Protocol

Protocol in OSF

For this systematic review, a protocol was developed according to the PRISMA-P 2015 Statement and Checklist [95]and preregistered on OSF.org (https://osf.io/2c8zv/overview) on September 8, 2025.

Amendments to the Protocol

Veränderungen am Protokoll

Zugang zu Cochrane Library via Ovid

Kontakt zu Studienautor:innen

etc.

Several amendments to the protocol were undertaken. Inclusion criteria (population, intervention, comparator) elements were added during the literature search; however, these elements had already been specified in an internal protocol version predating the OSF registration, allowing the decision process to be followed. The research question was subsequently refined (see Section 2.3). The Cochrane Library was accessed via Ovid due to a lack of access through the Wiley Library. The database search was repeated once to ensure completeness, using the same search strategy without modifications. During supplementary hand-searching in Google Scholar, no predefined limit was initially applied; screening was subsequently restricted to the first 200 results. Authors were contacted only once during the data extraction phase to request missing or unclear information; no follow-up contact was undertaken. A standardised email template was not used. During study selection, no distinction was made between participants who were already receiving antidepressant treatment prior to trial initiation and those who initiated antidepressants as part of the study intervention; this was not prespecified. Data extraction was conducted using structured tables in Microsoft Word rather than Microsoft Excel. Risk-of-bias assessment was performed as a separate step and not as part of the data extraction process. Screening decisions were not shared but will be made available upon request. In the synthesis, outcomes assessed at the final follow-up were prioritised over intermediate time points; this decision was not prespecified in the protocol. An author's note disclosing the use of artificial intelligence tools for translation, language editing, and paraphrasing was added to the protocol after registration to improve transparency. All protocol

amendments and their respective dates will also be documented in the registered protocol and can be accessed there.

2.3 Research Question

grobe Forschungsfrage

The research question was developed using the PICO scheme (see Table 2-1), a structured approach to formulating clinical research questions [96].

In patients with depression and anxiety treated with antidepressant medication, does combination therapy with antidepressants and vitamin B complex lead to a greater improvement in symptoms compared to antidepressant monotherapy?

Table 2-1: PICO Elements

Pico element	Description of the PICO element
Population (P)	Patients with depression and anxiety treated with antidepressant medication
Intervention (I)	Combination therapy with antidepressants and vitamin B complex
Comparator (C)	Antidepressant monotherapy
Outcome (O)	Improvement in symptoms

Verfeinerung der Forschungsfrage

The initial formulation of the question was broad, and refinement was necessary to ensure methodological clarity. The research question was further specified without altering the underlying PICO framework, and this refinement is fully traceable within the preregistered protocol. In accordance with Cochrane guidance, minor refinements of the review question are permissible as long as they do not introduce bias and remain consistent with the pre-specified eligibility criteria [92]. The refined research question according to the eligibility criteria (Table 2-2) is as follows:

zur Präzisierung der Ein-und Auschlusskriterien

In adults (≥18 years) with a clinical diagnosis of depression or anxiety who receive antidepressant medication, how effective and safe is the combination with a vitamin B complex (≥2 B vitamins) compared with antidepressant monotherapy in improvement of symptom severity as measured by validated scales?

2.4 Eligibility Criteria

The inclusion and exclusion criteria for eligible primary studies were predefined and documented in the review protocol prior to conducting the review. The review selection criteria were based on the PICOS framework. The components of the research question relating to population, intervention, and comparison, along with the explicit definition of eligible study designs, underpin the review's pre-established eligibility criteria [97].

Table 2-2: Eligibility Criteria according to the PICOS Framework

Pico element	Description of the PICO element	
Population	▪ Adults (≥18 years) with a clinical diagnosis of depression or anxiety disorder. ▪ Treatment with antidepressive medication.	
Intervention	▪ Combination therapy of antidepressant and vitamin B complex (≥3 B vitamins of interest). If scarce, ≥2 B vitamins considered.	
Comparison	▪ Antidepressant monotherapy. ▪ Antidepressant plus placebo.	
Outcomes	**Primary outcomes** ▪ Change in depression or anxiety disorder symptom severity, assessed with validated clinician-rated or self-report scales.	**Secondary outcomes** ▪ Response rate. ▪ Remission rate. ▪ Quality of life. ▪ Cognitive outcomes. ▪ Adverse events and tolerability, including dropout rates due to adverse effects. ▪ All-cause discontinuation rates.
Study design	▪ Primarily randomised controlled trials (RCTs). If <5 eligible RCTs, non-randomised controlled trials (NRCTs) are also considered.	

Population

erwachsene Menschen mit Depression oder Angststörung

Eligible participants were adults (≥18 years) with a clinical diagnosis of depression or an anxiety disorder according to DSM-5, ICD-10 or other validated clinical assessment tools. Studies focusing exclusively on other psychiatric or neurological conditions without comorbid depression or anxiety, as well as studies on healthy participants, were excluded. Trials including both adults and children were only considered if adult data were reported separately. Participants must be treated with antidepressants. Importantly, during literature selection, no distinction was made between participants who were already receiving antidepressant treatment before trial initiation and those who started antidepressants as part of the study intervention. All standard antidepressant classes were eligible. Combination therapy with mood stabilisers or antipsychotics was excluded unless it was administered equally in both study arms, with the only difference being the addition of vitamin B supplementation.

Interventions

Antidepressiva Kombinationstherapie mit

Vitamin B complex

(≥2 B Vitamine)

Interventions of interest were combinations of antidepressant treatment with a vitamin B complex containing at least three B vitamins (e.g. B6, B9, B12). If insufficient studies were available, combinations with two vitamins were also accepted. Oral supplementation was prioritised, but other routes of administration were eligible if evidence was scarce. The focus was on add-on interventions, where vitamin B complexes are administered in combination with standard antidepressant therapy. Trials that are designed to evaluate both augmentation of antidepressant efficacy and acceleration of treatment response were included.

Comparator

Antidepressiva Monotherapie

Comparators included antidepressant monotherapy without vitamin B supplementation or antidepressant plus placebo.

Outcomes

primäre Endpunkte

The primary outcome was change in depressive or anxiety symptom severity, assessed using validated clinician-rated or self-report instruments (e.g. Hamilton Depression Rating Scale [HDRS], Montgomery–Åsberg Depression Rating Scale [MADRS], Beck Depression Inventory [BDI], Hamilton Anxiety Rating Scale [HAMA], Generalized Anxiety Disorder Scale [GAD-7]). Symptom severity was selected as the primary endpoint because it is widely used in antidepressant trials and represents a patient-relevant measure of treatment benefit.

sekundäre Endpunkte

Secondary outcomes, prioritised from high to low importance, included: (i) response, defined as a ≥50% reduction from baseline symptom scores, as it is a commonly used endpoint in clinical trials and easily interpretable; (ii) remission, defined using validated cut-offs of the respective instruments (e.g., HDRS ≤7, MADRS ≤6), as it provides information apart from response; (iii) quality of life, assessed with validated generic instruments (e.g., SF-36, WHOQOL-BREF), to capture patient-relevant outcomes beyond symptom reduction; and (iv) cognitive outcomes, where reported using validated measures, given the relevance of cognitive functioning to depression and anxiety. Safety and tolerability were assessed by extracting adverse events, including the frequency and type of event reported adverse events and dropouts due to side effects, and all-cause discontinuation rates, defined as withdrawals for any reason, as they are a widely used indicator of treatment acceptability.

Messinstrumente

Where multiple symptom instruments were reported, clinician-rated scales (e.g. HDRS, MADRS) were prioritised over self-report measures. All outcomes were extracted as reported in the original studies, irrespective of whether they were presented as dichotomous or continuous variables. If composite outcomes were provided, both the overall measure and its individual components were extracted. Studies were not excluded based on unreported outcome data; they were excluded only if the outcomes of interest were not measured.

Study Design

prospektive randomisierte und nicht-randomisierte klinische Studien

RCTs were eligible, as they are considered the gold standard for examining causal relationships, as randomisation minimises confounding and reduces bias inherent in non-randomised study designs [98]. If fewer than five RCTs were available, the decision was made to also consider NRCTs to make use of the best available evidence. Observational studies were excluded because they cannot rule out other factors that may influence outcomes. Case reports and case series were excluded due to their small sample sizes and lack of control groups. Qualitative studies were excluded because they focus on experiences rather than treatment effects. Reviews and meta-analyses were excluded because they do not provide original data; however, their reference lists were checked for additional eligible studies. To support the selection of appropriate study designs, the review draws on the Johanna Briggs Institute (JBI) recommendations for selecting quantitative study designs, which provide a structured approach for selecting experimental or observational designs [99].

Timing of Follow-up

Nachbeobachtungszeiten

Follow-up was categorised as early response (1–4 weeks), acute phase (6–12 weeks), longer-term response (≥4 months), and maintenance/relapse prevention (≥6 months) given the clinical course of depressive and anxiety disorders and the typical design of pharmacological trials.

Further Restrictions

keine weiteren Einschränkungen außer Sprachen: Deutsch, Englisch

No restrictions were applied regarding study setting, publication status (published, in press, or ongoing) or publication date. Database searches were conducted without language or date filters. Studies published in languages other than English or German were identified but excluded from the analysis.

Ethical Considerations

Verwendung von publizierten Daten

This systematic review is based exclusively on data from previously published studies. No primary data was collected, and no direct involvement of human participants occurred. Therefore, formal ethical approval was not required.

2.5 Information Sources

Database Search

Suche in Datenbanken im Sept/Okt 2025

Medline
Web of Science
Cochrane Library

A systematic literature search in the databases PubMed via MEDLINE, Web of Science Core Collection, Cochrane Library via Ovid (including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Cochrane Clinical Answers) was conducted in September 2025 and updated in October 2025 without adaptation of search strings. No filter functions were applied. The search strategies for each database are provided in the Appendix A1.

Additional Sources

INAHTA Db
Studienregister
PROPERO
Google Scholar

To identify additional literature the International Network of Agencies for Health Technology Assessment (INAHTA) database, the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov were searched to identify ongoing or recently completed trials, while PROSPERO was examined for ongoing or recently completed systematic reviews. To maximise completeness, the reference lists of all included studies and relevant systematic reviews were screened to identify additional eligible records. Additionally, a hand search in Google Scholar (https://scholar.google.at/) was performed, screening the first 200 hits.

Expert Contact

Kontaktaufnahme mit klinischen Expert*innen

Two subject-matter experts with research expertise in the field of B vitamins and depression were contacted via email to inquire about additional eligible studies and relevant background information. No response was received, and no additional unpublished studies or supplementary materials were identified.

2.6 Search Strategy

Search Concepts and Use of Terms

Suchbegriffe an jeweilige Datenbank-Anforderungen angepasst

Kombinationen von Suchbegriffen

The search strategy consisted of four conceptual blocks: (1) depressive and anxiety disorders, (2) antidepressive agents, (3) vitamin B complex and (4) combination therapy. The complete PubMed strategy was adapted for other databases (Web of Science, Cochrane Library, INAHTA, ClinicalTrials.gov, and WHO ICTRP) by adjusting syntax and field tags to match database requirements supported by the Polyglot Search Translator (https://polyglot.sr-accelerator.com/). The search strategy was constructed using Medical Subject Headings (MeSH) and free-text terms when possible, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions [100]. Since comparators and outcomes are often poorly reported [101], they were not included in the search strategy; comparators were captured via control groups and outcomes were assessed during screening. To ensure comprehensive coverage, a broad range of free-text terms, including truncation, was used. Search strategy development was performed iteratively, with terms refined according to retrieval results [100]. As the initial search retrieved many irrelevant records, combination terms were added to the search strategy to enhance specificity. The inclusion of broader terms, such as nutritional supplements or micronutrients, may have reduced specificity, as these descriptors also captured studies unrelated to B vitamins. However, this decision was made to minimise the risk of missing relevant trials that do not explicitly list individual B vitamins in titles, abstracts, or indexing terms.

The search terms are listed in Table 2-3, along with the rationale for their selection.

Validation of the Search Strategy

Validierung = Überprüfung der Vollständigkeit und Konsistenz

All steps of the literature search, including the development of search strategies, database searching, and documentation, were conducted by one reviewer (SF). The search strategy was assessed against the PRESS 2015 Checklist [102] to ensure completeness and consistency. The adequacy was confirmed by the retrieval of key studies identified in preliminary scoping searches and relevant reviews, as recommended by Cooper et al. [103]. In addition, citation searching and reference list checking helped evaluate the quality of the search strategy by identifying studies already captured by the original search, suggesting that the search is performing adequately [100]. Although peer review (according to PRESS-guidelines) was considered, the final strategy was not externally reviewed.

Table 2-3: Search Terms and Rationale for their Selection

PICOS element	Search terms	Rationale
Population: Patients with depression or anxiety disorder treated with antidepressants	Depression and anxiety: depression, major depressive disorder (MDD), depressive episode, recurrent depressive disorder, chronic depression, persistent depressive disorder (PDD), dysthymia, anxiety, generalised anxiety disorder (GAD), panic disorder, social anxiety, mixed anxiety and depressive disorder Antidepressants: antidepressant, antidepressive agent, selective serotonin reuptake inhibitor (SSRI, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine), serotonin norepinephrine reuptake inhibitor (NSRI, tricyclic antidepressants [TCA]: imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin), non-selective monoamine reuptake inhibitors (SNRI: venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran), monoamine oxidase inhibitors non-selective (non-selective MAOI: phenelzine, tranylcypromine), monoamine oxidase A inhibitors (MAOI: moclobemide), noradrenergic and specific serotonergic antidepressant (naSSA: mirtazapine), serotonin antagonist and reuptake inhibitor (SARI: trazodone, nefazodone), noradrenaline reuptake inhibitor (NARI: reboxetine), norepinephrine–dopamine reuptake inhibitor (NDRI: buproprion), levomilnacepran, vilazodone, agomelatine	The terms correspond to diagnostic categories defined in DSM-5 (APA, 2013b) as well as ICD-10 and ICD-11 (WHO, 1992; WHO, 2022b), aiming to capture the primary relevant depressive and anxiety disorders. The term chronic depression was added, as it was frequently encountered in the literature. Search terms were derived from the WHO Anatomical Therapeutic Chemical Classification (ATC) to ensure coverage of drug classes (2024), supplemented by the NVL *Unipolare Depression* (BÄK, 2022) and Cipriani et al. (2018) to include clinically relevant antidepressants. Some substances listed in the ATC classification were excluded because they are obsolete, regionally restricted or clinically not relevant (e.g. Johanniskraut).
Intervention: Combination therapy of antidepressant and vitamin B complex	Vitamin B complex: vitamin B complex, micronutrient, nutritional supplement, vitamin supplement, dietary supplements, nutritional interventions, dietary intervention, vitamin B1 (thiamine, thiamin, vitamin B1, aneurin), vitamin B2 (riboflavin, vitamin B2, lactoflavin), vitamin B3 (niacin, vitamin B3, nicotinamide, nicotinic acid, niacinamide), vitamin B5 (pantothenic acid, dexpanthenol), vitamin B6 (pyridoxine, pyridoxal, pyridoxamine, pyridoxal-5-phosphate [PLP]), vitamin B7 (biotin, vitamin B7, vitamin H, coenzyme R), vitamin B9 (folic acid, folate, vitamin B9, l-methylfolate, 5-MTHF [5-Methyltetrahydrofolate], levomefolate calcium, folinic acid, leucovorin), vitamin B12 (cobalamin, cyanocobalamin, methylcobalamin, hydroxocobalamin, adenosylcobalamin [coenzyme B12]) Combination terms: drug therapy combination, drug synergism, combined modality therapy, add-on, additive, adjuvant, augmentation, augmentative, combination therapy, supplementation, co-treatment, co-therapy, combined treatment, combination regimen, co-treatment, co-administration, co-intervention, concomitant, booster, concurrent therapy	The selection of synonyms for the B vitamins includes all eight vitamins (B1–B12) with scientific names, active forms commonly used in clinical studies and supplements, and relevant collective terms. A large number of synonyms is listed in international drug and supplement databases (DrugBank, n.d.; WHO, 2024), therefore the decision was made to deliberately restrict the list of B vitamin synonyms to primary relevant synonyms to keep the search string manageable. Covers standard terminology in trials of adjunctive/augmentation therapy to increase the specificity of the search.
Comparison		Considered at screening stage.
Outcomes		Considered at screening stage.
Study Design		Considered at screening stage.

2.7 Study Selection

Study selection was conducted in two stages: (1) title and abstract screening and (2) full-text assessment. Screening was performed by a single reviewer (SF). A predefined, self-developed screening sheet with eligibility criteria was used, and the form was pilot tested with one key study [87] to ensure clarity and consistency. Title and abstract screening were conducted manually by the software Rayyan [104] where the inclusion and exclusion criteria from the review protocol were implemented to guide decisions. Each excluded record was assigned at least one documented reason for exclusion to ensure transparency and traceability. Full-text screening was performed using the predefined screening sheet, with all inclusion and exclusion decisions systematically documented. A list of all excluded studies assessed at full text, including detailed reasons for exclusion, is provided in the Appendix A2; the full-text screening sheet template is also included there (Appendix A6). Completed full-text screening forms are available upon request.

Studienauswahl zweistufig:

Titel- und Abstractauswahl
Volltextauswahl

durch 1 Reviewerin

2.8 Data Collection Process

The data extraction tool was developed based on the "Collecting data – form for RCTs and non-RCTs" template [92]. The form was piloted using one eligible key study [87] and subsequently refined to ensure that all variables relevant to this systematic review's objectives were captured appropriately. Data extraction was performed by one reviewer (SF) following the prespecified protocol, including, but not limited to, study design, sample characteristics, intervention and comparator details, outcome measures, and results. An attempt was made to contact study authors for methodological clarification. An overview of author correspondence and response is provided in the Appendix A3. The extraction sheets, which can be found in the Appendix A5, were shortened due to their length. Page numbers indicating where specific information can be found, as well as additional extracted data (start and end point, clusters, resource requirements, economic information, integrity of delivery, number of participants moved from other group and reasons - no relevant details were reported in the full texts) are available upon request.

Datenextraktion in Vorlage

durch 1 Reviewerin

2.9 Data Items

Extracted data included design characteristics (first author, publication year, country, study design, sample size, duration of intervention and follow-up and withdrawals/exclusions). The extracted participant-level information comprised diagnostic criteria, disorder type, mean age, sex distribution, baseline symptom severity, inclusion and exclusion criteria, and comorbidities, where reported. Intervention and comparator details included the type and dose of the antidepressant (drug class and specific agent), the composition, dose, formulation, frequency and duration of B vitamin supplementation, co-interventions, compliance and the nature of the control condition (placebo or antidepressant monotherapy). Outcomes extracted included the primary outcome

extrahierte Datenelemente zu

Studien- und Patient:innen-Charakteristika

Endpunkte

(change in depressive symptom severity) and secondary outcomes (response, remission, adverse events, dropouts, quality of life, and cognitive outcomes), along with measurement instruments and information on statistical procedures. Additional study information captured included funding sources, conflict-of-interest declarations and ethical approval. All outcomes relevant to the predefined outcome domains were extracted for all available time points, instruments, and analysis sets as reported in each study.

2.10 Outcome Measures

Endpunkt
Messinstrumente

Since this review includes multiple validated outcome measures that differ in their conceptual focus and operationalisation, the relevant outcomes are shortly described below. Corresponding estimates of minimal clinically important differences (MCIDs) are presented subsequently.

Montgomery–Åsberg Depression Rating Scale

MADRS:
Schweregrad der depressiven Symptome und Veränderungen im Zeitverlauf

The Montgomery–Åsberg Depression Rating Scale (MADRS) is a clinician-rated instrument used to assess the severity of depressive symptoms and to detect changes over time, particularly in treatment studies. It consists of 10 items evaluating core depressive symptoms ("apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts"), each rated on a 0–6 scale, with higher total scores indicating greater symptom severity [105, 106]. MADRS scores are categorised as no depressive syndrome or remission (0-6), mild depressive syndrome (7-19), moderate depressive syndrome (20-34), and severe depressive syndrome (≥35) [35, 105].

Hamilton Depression Rating Scale

HDRS, HAM-D
Schweregrad der depressiven Symptome und Veränderungen im Zeitverlauf

The Hamilton Depression Rating Scale (HDRS, HAM-D) is a clinician-rated tool for measuring the severity of depressive symptoms. It was developed to quantify symptom severity and monitor treatment response over time. The most used version HDRS-17 contains 17 items covering mood, guilt, suicidality, anxiety, and somatic symptoms; with higher scores indicating more severe depression [107]. Additional versions exist, including the 21-item (HDRS-21) and 24-item (HDRS-24) forms; cut-off scores used for severity classification vary depending on the scale applied [35].

Patient Health Questionnaire-9

PHQ-9
Selbstauskunft zur Depressionen und zur Schwere der Symptome

The Patient Health Questionnaire-9 (PHQ-9) is a self-report instrument used to screen for depression and assess symptom severity. The PHQ-9 is also described as a dual-purpose instrument to also support the diagnosis of depressive disorders [108]. It consists of nine items reflecting the DSM criteria for MDD, each rated from 0 (not at all) to 3 (nearly every day), with higher total scores indicating greater depression severity. Items assessed include depressed mood, sleep disturbances, concentration problems, appetite changes, feelings of guilt, and suicidal ideation [109]. PHQ-9 scores are categorised as no depression or remission (<5), subthreshold to mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19), and severe depression (20-27) [35, 108].

Mini-Mental State Examination

MMSE
kognitive Funktionen, Orientierung etc.

The Mini-Mental State Examination (MMSE) is a standardised 30-point screening tool for global cognitive functioning, assessing orientation, immediate recall and learning, attention and calculation, delayed recall, and language and visuo-construction; scores are commonly interpreted as 27-30 normal cognitive performance, 25-26 possible mild cognitive impairment, 21-24 mild dementia, 10-20 moderate dementia, and <10 severe dementia [110, 111].

Buschke Memory Test

Buschke-Selektiver Erinnerungstest
neuropsychologische Messung

The Buschke Selective Reminding Test is a neuropsychological measure used to assess verbal learning and memory, with particular emphasis on differentiating storage, retention, and retrieval processes. In the Buschke subtest, participants are required to recall as many items as possible from a 10-word list presented sequentially on preprinted cards, with higher scores reflecting better uncued immediate memory performance [112].

2.11 Minimal Clinically Important Differences across Outcome Measures

MCIDs:
die kleinsten Veränderungen der Ergebnismaße, die Patient:innen als bedeutsam empfinden

nicht für jedes Ergebnisinstrument verfügbar und validiert

Minimal clinically important differences (MCIDs) represent the smallest changes in outcome measures that patients perceive as meaningful following a clinical intervention [113] and help determine whether observed treatment effects are clinically relevant [114]. For the outcome measures used in this review, no validated values were identified; however, empirically derived estimates have been reported in the literature. MCIDs are typically estimated using anchor-based and distribution-based methods [114]. Hengartner & Plöderl [114] reported MCID estimates for the MADRS ranging from 3 to 9 points, with values between 3 and 6 points deemed the most plausible. For the HDRS, estimates of the MCID differ based on the version of the scale employed. According to various methods, the estimates for the MCID of the HRDS-17 vary from 3 to 8 points, with values in the range of 3 to 5 points deemed most precise. An average MCID estimate of 3.7 points has been reported for the PHQ-9 [115]. For the MMSE, context-specific MCID estimates of 1-3 points have been described [116]. For the Buschke Memory Test no MCID estimates could be identified. Given the absence of validated MCID thresholds, proposed estimates were used to contextualise the magnitude of effects and not as criteria for clinical relevance. The MCID estimates across outcome measures are influenced by baseline disease severity and clinical context and should therefore be interpreted with caution.

2.12 Risk of Bias Assessment

RoB = Bewertung des Verzerrungspotentials der Evidenz

Risk of bias (RoB) was assessed by one reviewer (SF) separately for randomised and non-randomised studies. For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was applied to evaluate bias arising from the randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement, and selection of the reported results [117]. For NRCTs, the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool was used, assessing bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result [118]. An overall risk-of-bias judgement was generated for each study in accordance with the decision rules specified by the respective tools. For RoB 2, studies were rated as low, some concerns, or high risk of bias based on the tool's algorithm [117]. For ROBINS-I, overall judgements (low, moderate, serious, or critical) were assigned using the tool's recommended hierarchy, in which the overall rating cannot be higher than the most severe domain-level judgement [118]. Risk of bias assessments were only conducted for the main outcome. Visual summaries of risk of bias judgments were created using the *robvis* tool (online version [119]).

RCTs mit RoB2
NRCTS mit ROBINS-I

mit online tool *robvis* in low, moderate, serious, or critical eingeteilt

2.13 Effect Measures

Berichterstattung der Effektmaße

Effect measures were extracted and are reported as presented in the original studies. For continuous outcomes (e.g., symptom severity on MADRS, HDRS or PHQ-9), mean scores, mean changes, standard deviations, and corresponding test statistics (e.g. t-values, F-values, p-values, or 95% confidence intervals) were extracted. For binary outcomes (e.g. remission), proportions as reported by study authors were extracted. No transformations or conversions of effect measures were performed. Unadjusted between-group differences at follow-up were extracted when reported; otherwise, they were calculated by the review author (SF) from reported group-level follow-up means. No predefined thresholds for effect interpretation were applied, as the synthesis was narrative.

entsprechend der Ergebnismessungen

2.14 Synthesis Methods

Methode der Synthese der Evidenz

In line with the protocol, no meta-analysis was planned. Due to substantial methodological heterogeneity (RCTs and NRCTs) and clinical heterogeneity (different depression severity measures), results were synthesised by one reviewer (SF) narratively considering the Synthesis Without Meta-analysis (SWiM) guideline recommendations [120]. Studies were grouped by type of intervention according to the prespecified protocol. Heterogeneity was explored qualitatively by comparing study characteristics and results; no sensitivity analyses were conducted. Results were presented using direction of effect at the final follow-up (favouring the intervention, no clear difference, or favouring the control). Direction-of-effect judgements were based on whether

narrativ aufgrund Heterogeneität der Studien

the intervention group showed greater symptom reduction than the comparison group, without applying predefined thresholds or considering statistical significance. This does not provide information on the magnitude of the effect or the certainty of the evidence. Where multiple assessment time points were reported, results from the final follow-up were extracted for synthesis. Where study information was missing or unclear, assumptions were made to enable synthesis. In one study, dosage information was not fully specified and was therefore assumed based on the manufacturer's product information. In two other studies, the lower of the reported dose ranges was used for the synthesis to ensure a conservative and consistent approach. A table was created to visually present the main results which also includes the effect directions (Table 3-4).

2.15 Reporting Bias and Certainty Assessment

Berichterstattung des Verzerrungsrisikos und der Sicherheit der Ergebnisse

Formal methods to assess reporting bias were not applicable because no quantitative synthesis was conducted, and the heterogeneity of study designs and outcome measures precluded statistical assessment. Confidence in the main outcome was appraised by one reviewer (SF) by addressing considerations aligned with GRADE domains (limitation in study design and execution, inconsistency, indirectness, imprecision and dissemination bias [121], although no formal certainty assessment was undertaken.

3 Results

3.1 Study Selection

The database search yielded 1,037 records, which were exported into EndNote (Clarivate Analytics 2025; Desktop version). After removal of 76 duplicates in EndNote, the remaining records were imported into Rayyan (Rayyan Systems Inc., Doha, Qatar), where an additional 148 duplicates were identified and removed manually. Due to technical limitations, records retrieved from the ICTRP could not be imported into EndNote or Rayyan and were therefore screened outside these tools. A total of 805 records were excluded during title and abstract screening. Six studies identified through hand-searching were assessed directly for eligibility using the predefined screening sheet and were not screened in Rayyan. One ongoing trial (TCTR20250818014) that met the eligibility criteria based on the registered study protocol was identified; however, no results were available at the time of the review, and the study was therefore excluded. Characteristics are reported descriptively. A total of 13 full-text articles were examined, with eight excluded for documented reasons, as outlined in the Appendix A2. Due to limited evidence, studies evaluating combinations of ≥2 B vitamins and one NRCT were included, in line with the protocol. Five studies met the inclusion criteria and were included in the review. The complete study selection process, including the number of records screened and the reasons for exclusion at the full-text stage, is illustrated in the PRISMA flow chart (Figure 3-1).

1.037 Zitate, davon 805 ausgeschlossen im Abstract-Screening

6 Zitate in Handsuche gefunden
13 Zitate im Volltextscreening

letztendlich 5 Studien eingeschlossen

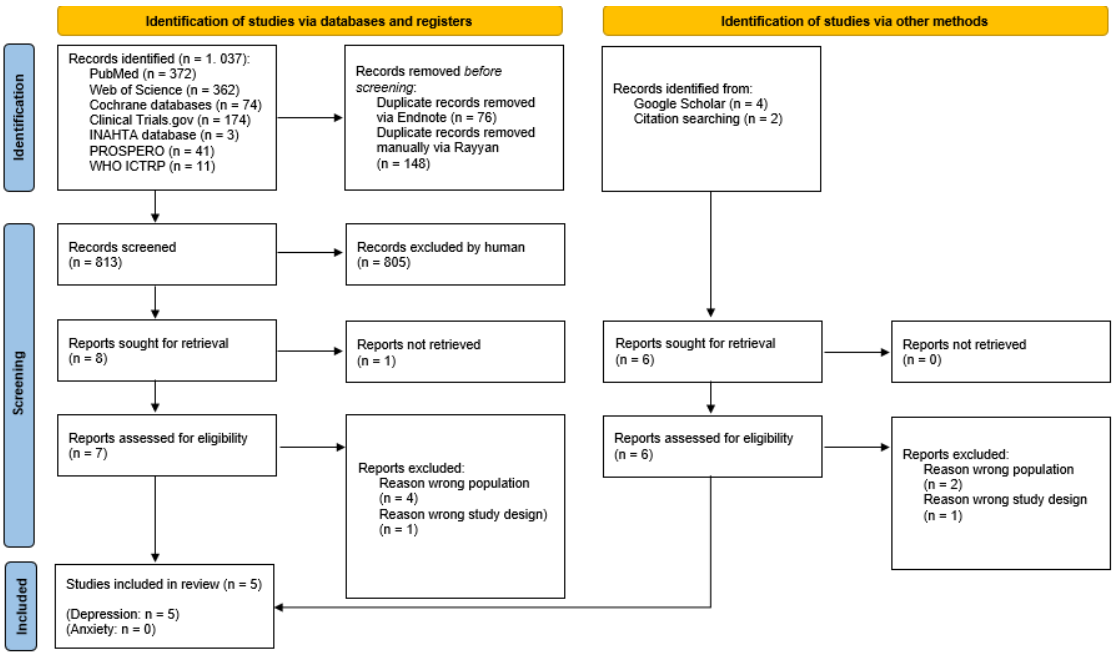

Figure 3-1: PRISMA 2020 Flow Diagram of the Study Selection Process, adapted from Page et al. [94]

3.2 Study Characteristics

Characteristics of the five included studies, including author, year and country, study design and sample size, follow-up duration, population characteristics (diagnosis, age, sex distribution, antidepressant status, setting), intervention, comparator, and primary outcome measures, are presented narratively and visually (Table 3-3), and baseline symptom severity is presented in Table 3-2. Additional relevant extracted information is reported only narratively.

Study Objectives

The prespecified primary outcome of this review was assessed in all five included studies. All included studies focused on depression, and none reported anxiety-related outcomes. Table 3-1 provides an overview of the aims of the included studies.

keine Studie zu Angststörungen

Table 3-1: Included Studies and their Primary Aims

Author, year, country	Study title	Aim
Almeida et al., 2014 [87], Australia	B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomized, double-blind, placebo-controlled trial	To examine whether supplementation with vitamins B6, B12, and folic acid improves antidepressant treatment response over a 52-week period.
Bell et al., 1992, [125] USA	Brief Communication: Vitamin B1, B2, and B6 Augmentation of Tricyclic Antidepressant Treatment in Geriatric Depression with Cognitive Dysfunction	To evaluate the impact of double-blind, placebo-controlled supplementation with vitamins B1, B2, and B6 at doses 5–8 times the recommended dietary allowance on affective symptoms and cognitive functioning in older adults with depression.
Gopalakrishnan et al., 2024 [122], India	Impact of Supplementation of Vitamin B12 and Folic Acid on Treatment Outcomes in Persons with Depression: A Comparative Study	To evaluate the effect of vitamin B12 and folic acid supplementation on depressive treatment outcomes relative to individuals who did not receive supplementation.
Kuchya et al., 2016 [123], India	Role of vitamin B supplementation with Fluoxetine in treatment of depression: A randomized controlled clinical trial	To investigate changes in fluoxetine's antidepressant efficacy when administered alongside vitamin B supplementation.
Unneh et al., 2025 [124], Nigeria	Effects of Supplementation with Folic Acid and Vitamin B12 Tablets as Adjunctive Therapy for People with Depression in Calabar, Cross River State, Nigeria	To evaluate the effects of folic acid and vitamin B12 supplementation as adjunctive therapy for individuals with depression.

Study Designs

Across the five included studies, two were double-blind, placebo-controlled RCTs [87, 125]. Three studies used open-label designs, comprising an NRCT [122], a parallel-group RCT [123], and a four-arm RCT [124]. Except for one study that was published only as a brief communication [125], all other included studies were available as full reports in the English language. The studies covered a wide temporal span, ranging from 1992 [125] to 2025 [124] and were conducted across four different countries (Australia, United States, India, Nigeria) on four continents.

5 Studien:
2 verblindete RCTs,
2 open-label RCTs
1 NRCT

1992 – 2025 durchgeführt

Population

Across the five included studies, a total of 364 participants with study populations ranging from 153 [87] to 14 [125], were enrolled, of whom 320 were included in the analysis, since Unneh et al. [124] used a four-arm design and only the relevant intervention-control comparison was included in the analysis. Almeida et al. [87] included a community-based sample, Bell et al. [125] recruited psychiatric inpatients, and Gopalakrishnan et al. [122], Kuchya et al. [123], and Unneh et al. [124] enrolled participants from psychiatric outpatient clinics. All participants across the included studies had a current diagnosis of depression, with one individual presenting bipolar depression [125]. Two studies used DSM-criteria [87, 125], two ICD-criteria [122] [123] and in the study by Unneh et al. [124] clinical diagnosis was made according to the depression level on the PHQ-9.

insgesamt 364 Patient:innen in den 5 Studien

alle mit Depression diagnostiziert

Baseline severity

Across studies, mean baseline depression scores were within the moderate severity range, in one case approaching the moderately severe range [124]. This classification is based on the respective cut-off values of the different depression rating scales used across studies (see section on Outcome Measures), as reflected by the reported mean and median scores in Table 3-2. For the study by Kuchya et al. [123], severity classification could not be determined because the authors did not specify which HDRS version was used, and cut-off scores differ across versions. Several studies applied minimum baseline score thresholds. Almeida et al. [87] required a MADRS score ≥20, indicating at least moderate depression. Bell et al. [125] and Gopalakrishnan et al. [122] did not specify a minimum threshold. Kuchya et al. [123] included participants with HDRS ≥14, which cannot be interpreted. Unneh et al. [124] enrolled participants with PHQ-9 scores between 5 and 25, capturing the full range from mild to moderately severe symptom levels.

Schweregrad: moderate Depression

bestimmt mit
MADRS
HDRS
PHQ-9

Age and Gender

Mean participant age across the included studies ranged from approximately 35 to 75 years. The youngest samples were reported by Gopalakrishnan et al. [122] with mean ages of 35.07 years (SD 11.01) in the intervention group and 34.82 years (SD 12.12) in the control group, while Bell et al. [125] reported the oldest sample with a mean age of 75 years (SD 7). One study [124] did not report mean age but provided age group distributions.

Ø Alter: 35 -75 Jahre

Sex distribution also varied across studies. In the study by Almeida et al. [87], females accounted for 63.2% in the intervention group and 49.3% in the control group. Bell et al. [125] reported a sample with 78.6% females. In the study by Gopalakrishnan et al. [122], the intervention group included 67.9% females, while the control group consisted of 71.4% females. In the study by Kuchya et al. [123], the intervention group consisted of 69.2% females, while the control group included 63.0% females. In the study by Unneh et al. [124], females accounted for 65.0% in the intervention group and 59.1% in the control group. For the studies by Bell et al. [125], Gopalakrishnan et al. [122], and Kuchya et al. [123], percentages were calculated by the author (SF) based on reported group sizes and rounded to one decimal place.

in allen 5 Studien deutlich mehr Frauen als Männer

Table 3-2: Symptom Severity at Baseline

		Intervention group		Control group		
Author, year U	Measure	Mean/median symptom severity at baseline[a]	SD/SEM/IQR[b]	Mean/median symptom severity at baseline[a]	SD/SEM/IQR[b]	Scale cut offs
Almeida et al., [87]	MADRS	Median 26	IQR 24-31	Median 27	IQR 22-32	0-6 none; 7-19 mild; 20-34 moderate; ≥35 severe[c]
Bell et al., [125]	MADRS	Mean 28	SD 3.7	Mean 25.3	SD 7.9	0-6 none; 7-19 mild; 20-34 moderate; ≥35 severe[c]
Gopalakrishnan et al., [122]	HDRS	Mean 21.18	SD 6.04	Mean 19.93	SD 2.29	0-7 none; 8-16 mild; 17-23 moderate; ≥24 severe[d]
Kuchya et al., [123]	HDRS	Mean 20.92	SEM 3.9	Mean 22.96	SEM 4.9	Cut-off scores not reported due to unclear HDRS version.
Unneh et al., [124]	PHQ-9	Mean 13.91	SD 5.63	Mean 14.64	SD 6.11	0-4 none/remission; 5-9 mild; 10-14 moderate; 15-19 moderately severe; ≥20 severe[c]

Note. HDRS: Hamilton Depression Rating Scale; IQR: interquartile range; MADRS: Montgomery–Åsberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; SEM: standard error of the mean

[a] *Higher scores indicate greater depressive symptom severity for all scales.*

[b] *Medians and interquartile range were reported for Almeida et al. [87]; Kuchya et al. [123] reported means and standard error of the mean and all other studies reported means and standard deviations.*

[c] *Symptom severity classifications are based on the established cut-off values for each respective scale.*

[d] *Severity cut-offs were provided in the publication, but the exact HDRS version could not be confirmed from the report.*

Antidepressant Use

Unneh et al. [124], had initiated antidepressant therapy prior to baseline (<2 weeks). In the remaining studies, antidepressant treatment was started concurrently with the B-vitamin intervention. Across the included studies, the antidepressants used fell into two major pharmacological classes. SSRIs were administered in four trials [87, 122-124]. One study [125] used TCA.

Beginn der Antidepressiva-Therapie zeitlich mit Vit B Verabreichung

Past diagnosis of Depression

Unneh et al. [124] and Gopalakrishnan et al. [122] reported that participants had no prior history of depression. Almeida et al. [87] provided explicit data, noting a past diagnosis of depression in 77.6% of participants in the intervention group and 76.3% in the control group. Bell et al. [125] and Kuchya et al. [123] did not report any information regarding past diagnoses.

Patient:innen hatten mehrheitlich Vorgeschichte an Depression

Co-Morbidities

Only Almeida et al. [87] provided baseline data on co-morbidities including cardiovascular disease, diabetes, chronic respiratory diseases, diabetes and hearing impairment. In the study by Bell et al. [125] of the 14 patients, three participants were diagnosed with dementia and two additional participants were classified as possibly having dementia with no statistically significant group difference. The remaining studies did not report co-morbidities.

Ko-Morbiditäten selten berichtet in Studien

Intervention

As only a limited number of studies investigated combinations of three or more B vitamins [87, 125] and [123], two studies examining supplementation with two B vitamins [122, 124] were included in accordance with the prespecified protocol.

3 Studien: ≥ 3 Vit B
2 Studien: 2 Vit B

Dosage of B-vitamins

Across the included trials, six of eight B-vitamins were used: vitamins B1, B2, B3, B6, B9, and B12. Vitamin B1 and B2 appeared in doses of each 10mg [123, 125]. Vitamin B3 was only reported by Kuchya et al. [123]. Vitamin B6 showed a broader spread, ranging from 3mg [123] to 10 mg [125]. Folic acid administered in doses ranging from 2mg (lowest dosage: [87]) to 5 mg (highest dosage: [122, 124]. Vitamin B12 exhibited the widest variation across studies, with doses ranging from 0.5 mg [87] to 10 mg [124].

Dosierungen:

Vit B1, B2, B3: 10mg
Vit B6: 3mg bis 10mg
Vit B9: 2mg bis 5mg
Vit B12: 0,5mg bis 10mg

Kuchya et al. [123] did not provide specific information on the individual B vitamin doses; however, given that the branded formulation was explicitly referenced, it is reasonable to assume that the study employed the standard Neurobion® Forte preparation. The branded preparation includes the dosages of vitamin B1 10mg, vitamin B2 10mg, vitamin B3 45mg, vitamin B6 3mg and vitamin B12 15μg [126].

Unneh et al. [124] reported inconsistent information on vitamin B12 dosage: the methods section described a dose of 100 mg/day, whereas the results tables listed 10 mg/day. Also, dosages of 4mg and 5mg of folic acid were reported. Similarly, Gopalakrishnan et al. [122] provided conflicting information, reporting vitamin B12 as 1500 mg in the flow chart but 1500μg in the methods section. Because higher vitamin B12 values are inconsistent with standard dosing ranges, the lower reported doses were judged more plausible and used in the review analyses.

nicht in allen Studien konsistente Informationen

Route and Frequency of Administration

orale Verabreichung 1-2 x täglich

All interventions were administered orally. Unneh et al. [124] and Gopalakrishnan et al. [122] report daily vitamin administration, while the frequency of the antidepressant remains not reported. Kuchya et al. [123] document once-daily antidepressant intake, whereas information on B vitamin intake frequency is not reported. Bell et al. [125] note a twice-daily vitamin schedule in divided doses, with antidepressant use frequency likewise not reported. According to Almeida et al. [87], vitamins are taken once daily, and a daily antidepressant regimen is described.

Intervention Duration and Timing of Follow-up

Nachbeobachtungszeiten zwischen 4 Wochen und 1 Jahr

In accordance with the prespecified protocol, follow-up categories were applied based on the final assessment time point of each study. Bell et al. [125] reached their final follow-up at 4 weeks, which falls into the early response category. Kuchya et al. [123] and Unneh et al. [124] concluded follow-up at 8 weeks, and Gopalakrishnan et al. [122] at 12 weeks, all of which correspond to the acute-phase response window. Of the included studies, only Almeida et al. [87] reported long-term (52-week) outcomes, which fall within the maintenance/relapse prevention window (≥6 months).

Endpunkt-Erhebungen: Baseline und mehrmalig je nach Nachbeobachtungszeit

Across studies, the timing of outcome assessments also varied. Kuchya et al. [123] assessed participants at baseline and at weeks 2, 6, and 8, whereas Bell et al. [125] collected data at baseline and at weeks 1, 2, 3, and 4. Unneh et al. [124] assessed outcomes at baseline and week 8, and Gopalakrishnan et al. [122] assessed outcomes at baseline and at 12 weeks. Almeida et al. [87] recorded outcomes at baseline and 4, 8, 12, 26, and 52 weeks.

Co-interventions

Ko-Interventionen

Co-interventions were reported in one study. In the study by Unneh et al. [124], the intervention group received printed handouts on depression and lifestyle modification, reminders via phone, email, and WhatsApp, and counselling sessions in the participants' preferred language that addressed depressive symptoms and provided lifestyle advice. The control group received only information leaflets at the end of the study.

Other relevant medication received

nur in 1 Studie weitere Medikamente berichtet

In the study by Bell et al. [125] one participant in the control group and two in the intervention group received perphenazine concurrently, and benzodiazepine use occurred in both groups without statistically significant group differences. No information on concomitant medication was provided in the remaining studies.

Adherence

Adhärenz mit Studienmedikation wurde in einigen Studien überprüft

In the study by Almeida et al. [87], participants were instructed to avoid additional vitamin supplements, and adherence was monitored through daily medication diaries, pill counts, and blood tests, with ≥75% tablet intake classified as adherent. Bell et al. [125] and Gopalakrishnan et al. [122] did not report adherence procedures. Kuchya et al. [123] evaluated medication compliance at each follow-up visit, although the method used for assessing adherence was not described and no results were reported. In the study by Unneh et al. [124], adherence was assessed using the Simplified Medication Adherence Questionnaire, with participants classified as non-compliant if any non-

adherence response was recorded or if more than two doses were missed in the previous week, but also did not report results.

Drop-outs, withdrawals and loss to follow up

In the study by Bell et al. [125], one participant attempted suicide, and another switched from a tricyclic antidepressant to lithium; both events occurred prior to randomisation. Almeida et al. [87] reported a loss to follow-up of 13.2% in the control group and 19.5% in the intervention group, with missing data assumed to be missing at random. The remaining studies did not provide information on loss to follow-up, withdrawals and drop-out rates.

wenig Informationen zu Drop-Outs etc. berichtet

Comparator

The two double-blind RCTs used antidepressant standard therapy at the same dosage as in the intervention arm, plus placebo as the comparator [87] [125], and the other three studies used antidepressant monotherapy as the comparator at the same dosage as in the intervention arm.

selbe Dosierung der Antidepressiva im Kontroll- wie im Interventionsarm

Outcomes

Primary and secondary outcomes

Across all included studies, the primary outcome of interest for this review was depressive symptom severity, as assessed using validated clinician- or patient-reported rating scales. Four of the five studies used clinician-reported scales such as MARDS [87, 125] and HDRS [122, 123]. One study [124] used the patient-reported instrument PHQ-9. Cognitive outcomes were uniquely examined in the study by Bell et al. [125], who assessed changes in MMSE and Buschke test scores. Clinical improvement metrics, such as response (≥50% symptom reduction) and remission rates, were reported by Almeida et al. [87]. Adverse events were assessed in two trials, including Almeida et al. [87] and Kuchya et al. [123].

Endpunkte
primäre:
MADRS, HDRS, PHQ-9

sekundäre:
MMSE, symptom reduction, remission rates

Ethical Approval, Informed Consent and Conflict of Interest

Except for Bell et al. [125], for which both the ethical review status and the procedures for obtaining informed consent were not reported and therefore remain unclear, all included studies stated that they had received ethical approval and obtained informed consent from participants. All study authors reported having no conflicts of interest.

Einverständniserklärungen kaum berichtet

Funding Sources

Almeida et al. [87]reported funding from the National Health and Medical Research Council of Australia. The authors specified that the sponsor was not involved in the study's design or conduct, nor in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript. In the study by Bell et al. [125], authors disclosed partial financial support from the Charles H. Farnsworth Trust and the USDA-Agricultural Research Service, and Gopalakrishnan et al. [122] reported funding from the Rajiv Gandhi University of Health Sciences, whereas the remaining authors reported receiving no funding.

Studienfinanzierung

3.3 Characteristics of Ongoing Trials

1 laufende Studie (Thailand) mit 40-60 Teilnehmer:innen

One ongoing clinical trial by Dianomo et al. titled "The Effect of Adjuvant Therapy with Folic Acid and Methylcobalamin on BDNF Levels and Cognitive Function in Patients with Depression Receiving Fluoxetine Therapy" was identified (Thai Clinical Trials Registry: TCTR20250818014, 2025). The study planned to recruit 40-60 adults aged 20-45 years, who were to be randomised to receive either fluoxetine alone or fluoxetine plus folic acid (1mg/day) and vitamin B12 (500μg/day). Assessments were scheduled at baseline and after six weeks. The trial is initiator-funded and conducted at the Department of Psychiatry, Universitas Hasanuddin (Indonesia). Ethical approval was contained. Eligible participants were required to be 20-45 years old, meet PPDGJ-III (Pedoman Penggolongan dan Diagnosis Gangguan Jiwa – III) criteria for depression, be receiving fluoxetine, have at least junior secondary education, and provide informed consent. Exclusion criteria included organic psychiatric disorders, substance abuse within the past year, chronic illnesses requiring anti-inflammatory drugs, antibiotics, or supplements, and severe psychiatric symptoms such as psychosis. The study uses an open-label, randomised, parallel-group design with an actual sample size of 36 participants. Cognitive function and depression severity are measured using a standardised rating scale and adverse events are monitored throughout the six-week treatment period. The study was completed on 16 July 2025, no study results have been published to date (status as of 04 December 2025; Thai Clinical Trials registry, 2025).

Table 3-3: Main Characteristics of the Included Studies

Author, year, country	Study design, N	FU (weeks)	Population[a] (diagnosis, baseline symptom severity, mean age in years, mean sex distribution, AD status, setting)	Pharmacological Intervention	Comparator	Outcome
Almeida et al., 2014, [87] Australia	DB-PC RCT, N= 153	52	DSM-IV-TR MDD, moderate, mean age 62, 56% female, AD-naïve, community	Citalopram (10-40mg) + vitamin B complex (B6: 25 mg, B9: 2 mg, B12: 0.5 mg)	Citalopram (20-40mg) + placebo	Change in MADRS score
Bell et al., 1992 [125], USA	DB-PC RCT, N= 14	4	DSM-III-R major/bipolar depression, moderate, mean age 75, 79% female, AD-naïve, inpatients	Nortriptyline or desipramine (initial 10 mg, titrated by 10-25 mg) + vitamin B complex (B1: 10 mg, B2: 10 mg, B6: 10 mg)	Nortriptyline or desipramine (initial 10 mg, titrated by 10-25 mg) + placebo	Change in MADRS score
Gopalakrishnan et al., 2024, [122], India	OL NRCT, N= 56	12	ICD-10 unipolar/bipolar depression, moderate, mean age 35, 68% female, AD-naïve, outpatients	Escitalopram (10mg) + folic acid (5mg) + vitamin B12 (1500µg/1500mg[c])	Escitalopram (10mg)	Change in HDRS score
Kuchya et al., 2016, [123] India	OL RCT, N= 53	8	ICD-10 depression, moderate, mean age 38, 64% female, AD-free ≥5 weeks, outpatients	Fluoxetine (20mg) + Neurobion® Forte[b] (B1: 10mg, B2: 10mg, B3: 45mg, B6: 3mg and B12: 15µg)	Fluoxetine (20mg)	Change in HDRS score
Unneh et al., 2025, [124] Nigeria	OL RCT, N= 44[d]	8	MDD (clinical diagnosis), moderate, mean age NR, 62% female, on fluoxetine <2 weeks, outpatients	Fluoxetine (20mg) + folic acid (4mg/5mg[c]) + vitamin B12 (100mg/10mg[c])	Fluoxetine (20mg)	Change in PHQ-9 score

Note. AD: antidepressant; vitamin B9: folic acid; CI: Confidence Interval; df: degrees of freedom; DB-PC: double-blind placebo-controlled; DSM (DSM-IV-TR, DSM-IIIR): Diagnostic and Statistical Manual of Mental Disorders; FU: follow-up, HDRS: Hamilton Depression Rating Scale; ICD-10: International Classification of Diseases, 10th Revision; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder, mg: milligrams; N: number of participants; NRCT: non-randomised controlled trial; OL: open-label; PHQ-9: Patient Health Questionnaire-9; RCT: randomised controlled trial; TCA: tricyclic antidepressant.

[a] Overall mean female proportions and mean ages were calculated from reported group when not reported directly and rounded for presentation (reported values per group with SD-values can be found in the extraction sheets). Mean symptom severity was categorised as minimal, mild, moderate, moderately-severe, or severe based on established cut-off scores (Table 3-2).

[c] Different dosages were reported within the same study.

[b] The specific dosages of the individual B vitamins were not reported. Dosage details were determined using the labelled composition of the branded Neurobion® Forte preparation.

[d] Unneh et al. [124] used a four-arm design; only the relevant intervention-control comparison was included in the analysis.

3.4 Risk of Bias (RoB) Assessment of the Included Studies

Risk of bias (RoB) for the four included RCTs [87, 123-125] was assessed using the RoB 2.0 tool [117], while the NRCT [122] was evaluated using the ROBINS-I tool [118]. All risk-of-bias assessments were conducted by one reviewer (SF) for the main outcome and are presented narratively and visually in Figure 3-2 (RoB 2.0) and Figure 3-3 (ROBINS-I), which were generated by the author using the robvis tool [119]. The narrative rationale focuses exclusively on domains in which the risk-of-bias judgement differed from low risk. In the Appendix A4 the authors' judgements about each risk of bias item can be found. Completed RoB 2.0 and ROBINS-I assessment sheets are available on request.

RoB 2.0
ROBINS-I

Risk of Bias in the Included RCTs

The study by Almeida et al. [87] showed some concerns in the selection of the reported result domain because the study was retrospectively registered and the protocol did not include a statistical analysis plan. According to the RoB 2.0 tool's decision algorithm, this leads to an overall judgement of some concerns.

2 RCTs:
"some concern"
1 RCT: high RoB

Almeida: some concern
Auswahl der berichteten Endpunkte etc.

For the study by Bell et al. [125], bias arising from the randomisation process was judged to be of some concern, as the randomisation process was described without further detail and allocation concealment was not described, yet the authors reported "no significant baseline differences". Missing outcome data was judged as high risk of bias, as the study reports that all participants were included in the final analysis, but "missing values were dropped from individual analyses" and no information on imputation of missing data was reported. Given the small sample size (n=14), even minimal attrition could meaningfully distort effect estimates. The domain measurement of the outcome was rated as having some concerns, as the study used an appropriate, validated measurement tool that was applied consistently at identical follow-up times. However, blinding of outcome assessors was not stated. Although there is no evidence of bias, observer-reported outcomes inherently involve some degree of judgment, so bias cannot be ruled out. No trial registration or pre-specified analysis plan was reported. Bias in the selection of the reported result was therefore judged as a concern. According to the tool's decision algorithm, this leads to an overall high risk of bias judgement.

Bell: high RoB
Randomisierung, Umgang mit fehlenden Daten
Verblindung

For the study by Kuchya et al. [123], the risk of bias arising from the randomisation process was judged as some concerns, as randomisation was stated only in the title and introduction, without a description of sequence generation or allocation concealment. The baseline statistics included age and gender, indicating a significant age difference ($p < 0.05$) and no major differences in sex distribution. Risk of bias due to deviations from the intended interventions was rated as some concerns, as neither participants nor carers or personnel delivering the intervention were blinded, as this was an open-label study. However, there was no information on deviations from the intended intervention. Outcome assessors were not blinded to group assignment, and although there is no evidence of bias, observer-reported outcomes involve some degree of judgment, so bias cannot be entirely ruled out. The domain measurement of the outcome was therefore rated as some concerns. No trial registration or pre-specified analysis plan was reported. Bias in the selection of the reported

Kuchya: some concern
Verblindung

result was therefore judged as some concerns. According to the tool's decision algorithm, this leads to an overall judgement of some concerns.

For the study by Unneh et al. [124] risk of bias due to deviations from intended interventions was rated as high, as the trial reported no blinding or study protocol, and applied co-interventions that likely influenced outcomes. Measurement of the outcome was judged as high risk, as depressive symptoms were self-reported, patients were not blinded, and knowledge of the assigned intervention likely influenced outcomes. Risk of bias in the selection of the reported result was judged as some concerns, as no pre-specified analysis plan or protocol was available. According to the tool's decision algorithm, this leads to an overall judgement of high risk of bias.

Unneh: high RoB
Verblindung, Ko-Interventionen

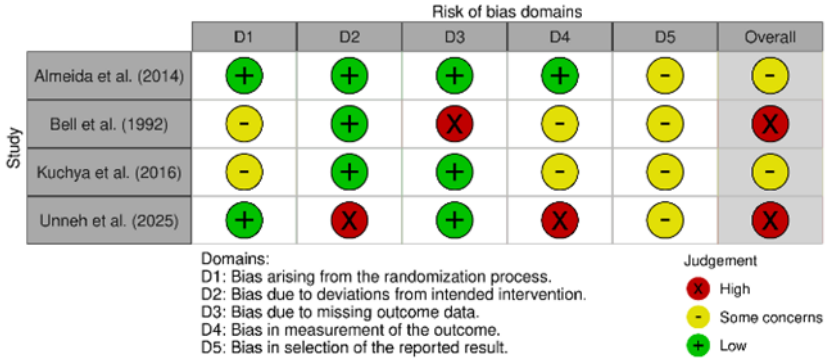

Figure 3-2: Risk of Bias in the included RCTs, generated using robvis

Risk of Bias in the Included NRCT

Bias due to confounding was judged as serious in Gopalakrishna's study [122], as no adjustment for confounders was reported. Bias in the measurement of outcomes was rated as serious, as the study used an open-label design with unblinded outcome assessors. Although there is no evidence of systematic error, the outcome measurement tool is not objective. No study protocol or pre-specified analysis plan or protocol was available, so selective reporting of analyses cannot be ruled out. The domain bias in the selection of the reported result was therefore judged as some concerns. According to the tool's decision algorithm, this leads to an overall judgement of a serious risk of bias.

Gopalakrishnan: serious RoB

open label
Endpunkt Messung

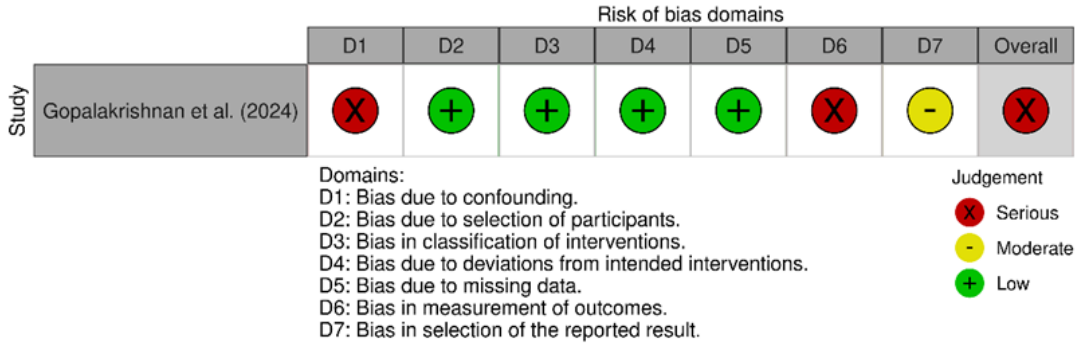

Figure 3-3: Risk of Bias in the included NRCT, generated using robvis

Sponsorship Bias

Although no direct sponsor involvement was indicated in either study [87, 122, 125], funding sources were considered as part of the risk-of-bias assessment, as financial support, particularly from sources with potential conflicts of interest, may influence study conduct or selective reporting.

keine Beeinflussung durch Sponsoren

3.5 Results for Effectiveness

Primary Outcome: Change in Symptom Severity

All the included studies evaluated depressive symptom severity using validated rating scales (MADRS, HDRS and PHQ-9). Categorisation of symptom severity, as well as any changes from baseline to follow-up, was determined by the author (SF) based on baseline scores and the corresponding cut-off values for the varying outcome measures, as presented in Table 3-2. Summary statistics for the intervention and control groups, including final follow-up means, standard deviations/standard errors of the mean, and precision measures, are presented in the summary of results table (Table 3-3). For Bell et al. [125], Kuchya et al. [123] and Unneh et al. [124], mean differences were calculated by the reviewer (SF) from reported group-level data (MD = mean at final follow-up in the intervention group minus mean at final follow-up in the control group), and estimates are unadjusted.

Ergebnisse
MADRS, HDRS, PHQ-9

Veränderung von Baseline zum letzten Datum der Nachbeobachtung

Symptom Severity at Final Follow-Up

Across studies, the direction of effect generally favoured the intervention. Two trials assessed depressive symptom severity using the MADRS and reported non-significant differences between the intervention and control groups at final follow-up. In the study by Almeida et al. [87], the mean difference was -0.4 (95% CI -2.6 to 1.8), and the between-group comparison was not statistically significant ($p = 0.739$). Similarly, Bell et al. [125] also found no statistically significant difference at the end of treatment (MD -5.0; $p = 0.11$). The reported MD of -5.0 points in the study by Bell et al. [125] lies within the range of proposed MADRS MCID estimates of approximately 3-6 points [114]; however, the lack of statistical significance and the imprecision of the estimate limit conclusions regarding clinical relevance.

MADRS (2 Studien): nicht signifikante Unterschiede zugunsten der Kombinationstherapie

Unterschied nicht klinisch relevant

In contrast, studies using other depression rating scales reported larger differences between the intervention and the control group. In the study by Gopalakrishnan et al. [122], in which outcomes were measured using the HDRS, a statistically significant mean difference in favour of the intervention (MD = -7.86; $p = 0.0001$) was reported. Although the authors reported cut-off values and symptom severity classifications, the HDRS version was not specified. Given that MCID estimates vary across scale versions, an MCID-based assessment was not performed. Unneh et al. [124], using the PHQ-9, likewise reported a statistically significant difference between groups (MD -8.72; $p < 0.0001$). This effect exceeds proposed MCID estimates for the PHQ-9 of approximately 3.7 points [115]; however, these thresholds are not validated.

HDRS, PHQ-9 (2 Studien): statistisch signifikante und klinisch relevante Unterschiede zugunsten der Kombinationstherapie

In the study by Kuchya et al. [123], which also assessed depression severity with the HDRS, a mean difference of -1.52 was reported; this difference was stated not to be statistically significant. No consideration of MCID estimates

HDRS (1 Studie): nicht signifikante Unterschiede

was possible, as the HDRS version was not specified and MCID estimates vary by scale version.

Changes in Symptom Severity Scales

Veränderungen im Schweregrad der Symptome von moderater zu milder Depression

Mean baseline depression severity was generally in the moderate range across studies, although instruments and reporting varied. In the study by Almeida et al. [87], baseline MADRS scores were comparable between groups, but endpoint values were reported graphically, precluding severity classification at follow-up. In the study by Bell et al. [125], baseline MADRS scores indicated moderate depression, and both groups improved to the mild range at 4 weeks. Approximate end-of-treatment scores were derived from reported change scores by the reviewer (SF), as endpoint values were not provided in the original publication. In the study by Gopalakrishnan et al. [122], baseline HDRS scores reflected moderate depression, with the intervention group reaching remission at 12 weeks and the control group improving to mild depression. Kuchya et al. [123] reported moderate baseline HDRS scores with marked improvement in both groups; however, severity classification at follow-up was not possible due to an unspecified HDRS version. In the study by Unneh et al. [124], PHQ-9 scores indicated moderate baseline depression, with the intervention group improving to mild depression at 8 weeks, while the control group remained in the moderate range.

Table 3-4: Summary of Findings on the Primary Outcome: Symptom Severity at Final Follow Up

			Intervention group			Control group					
Author, year	Length of FU	Outcome scale	N	Mean Symptom Severity (final FU)	SD/SEM	N	Mean Symptom Severity (final FU)	SD/SEM	MD Between groups (final FU)	Precision[a]	Effect direction[b]
Almeida et al., 2014 [87]	52 weeks	MADRS	77	NR (only graphically)	NR	76	NR (only graphically)	NR	-0.4	95% CI -2.6 to 1.8, z = -0.74 p = 0.739	↓
Bell et al., 1992 [125]	4 weeks	MADRS	8	-12.4[c]	SD=6.2	6	-7.4[c]	SD=7.9	-5.0[d]	t = -1.27 df = 11 p = 0.11	↓
Gopalakrishnan et al., 2024 [122]	12 weeks	HDRS	28	5.93	SD=3.16	28	13.79	SD=3.71	-7.86	t = 8.5344; p = 0.0001	↓
Kuchya et al., 2016 [123]	8 weeks	HDRS	27	4.95	SEM=1.8	26	6.47	SEM=2.3	-1.52[d]	t = 4.0; n.s.	↓
Unneh et al., 2025 [124]	8 weeks	PHQ-9	22	5.23	SD=3.19	22	13.95	SD=7.26	-8.72[d]	p < 0.0001	↓

Note. CI: confidence interval; df: degrees of freedom; FU: follow-up; HDRS: Hamilton Depression Rating Scale; IQR: interquartile range; MADRS: Montgomery–Åsberg Depression Rating Scale; MD: mean difference; n: sample size; NR: not reported; n.s.: non-significant; p: p-value; PHQ-9: Patient Health Questionnaire–9; SD: standard deviation; SEM: standard error of the mean; SSRI: selective serotonin reuptake inhibitor; t: t-statistic; z: z-statistic

[a] *Precision estimates were reported as provided in the original publications.*

[b] *Effect direction arrows: ↓ = favours intervention; ↑ = favours control; → = no difference.*

[c] *Bell et al. [125] reported change scores, while all other studies reported endpoint scores.*

[d] *Mean differences were calculated from reported group data, negative scores reflect improvement. MD = Mean (Intervention, FU) - Mean (Control, FU), unadjusted.*

Results of the Secondary Outcomes

Remissionsrate, Ansprechrate, kognitive Ergebnisse

The secondary outcomes of this review, as defined in the protocol, included response rate, remission rate, quality of life and cognitive outcomes. Response rate and remission were reported in one study [87]. Bell et al. [125] included cognitive outcomes. Adverse events were reported by Almeida et al. [87], and Kuchya et al. [123]. The remaining studies did not report data on the secondary outcomes specified in this review.

unerwünschte Ereignisse und Verträglichkeit

Remission of Symptoms

Remission (1 Studie): ca 10% höhere Raten in der Interventionsgruppe

Almeida et al. [87] assessed remission at weeks 12, 26, and 52, assessed by the Mini-International Neuropsychiatric Interview; a diagnostic interview based on DSM-IV and ICD-10 criteria [127]. Remission rates were similar in week 12 (79.4% vs 78.1%; p = 0.84) but were numerically higher in the intervention group at weeks 26 and 52 (85.3% vs 76.5% and 85.5% vs 75.8%). Adjusted estimates increased over time (week 12: OR 1.55, 95% CI 0.64-3.72; week 26: OR 2.32, 95% CI 0.91-5.97; week 52: OR 2.54, 95% CI 0.94-6.80). Analysis across time points suggested an overall benefit of the intervention after adjustment (OR 2.49, 95% CI 1.12-5.51).

Response Rate

Ansprechrate (1 Studie): geringer in der Interventionsgruppe, keine signifikanten Unterschiede

Almeida et al. [87] assessed response (≥50% reduction in MADRS) at weeks 4, 8, and 12. Response rates were consistently lower in the intervention group than the control group (week 4: 46.6% vs 51.3%; week 8: 63.9% vs 76.7%; week 12: 64.4% vs 76.7%). The adjusted between-group comparison was not statistically significant (OR 0.59, 95% CI 0.28-1.25). No response data was reported beyond week 12.

Quality of life

QoL: nicht berichtet

Quality of Life was not reported in any of the five studies.

Cognitive Outcomes

Change in MMSE

MMSE (1 Studie): unklare Ergebnisse, nicht signifikante Unterschiede

Bell et al. [125] reported MMSE scores as change from baseline at weeks 1, 2, 3 and 4. Baseline values were similar between groups (24.8 [SD 5.9] in the intervention group vs. 23.7 [SD 4.3] in the control group, p= 0.71). Over the four weeks, the intervention group showed small mean positive changes from baseline ranging from 0.43 in week 1 to 1.8 points in week 4, whereas the control group showed fluctuating values from 0.83 to -1.8 points. This lies within the range of non-validated MCID estimates of 1-3 points for the MMSE [116]. However, week-4 results indicated non-significant trend difference between groups (p = 0.07). Overall, the results indicate no clear evidence of a treatment-related effect on MMSE scores over the follow-up period.

Change in Buschke memory scores

Veränderungen im Buschke Score (1 Studie)

nicht signifikante Unterschiede

Bell et al. [125] reported changes from baseline in Buschke memory scores for weeks 1, 2, 3 and 4. Baseline values were similar between groups (mean 4.5 [SD 2.8] in the intervention group vs. 3.8 [SD 1.9] the control group, p= 0.64). Across the four weekly assessments, small mean positive changes from baseline in the intervention group ranged from -0.20 at week 1 to 1.3 points in week 4, while the control group showed changes between -0.5 and -0.25 points. Week-4 results indicated a non-significant difference between groups (p =

0.14). Overall, the results indicate no clear evidence of a treatment-related effect on memory performance over the follow-up period.

Synthesis of Effectiveness Results

für die Zusammenfassung der Ergebnisse

Gruppierung der Vit B Supplementierung:

For synthesis studies were grouped according to the type of B vitamin intervention: (1) formulations containing folic acid and vitamin B12, and (2) formulations containing ≥3 B-vitamins. This grouping was chosen in accordance with the prespecified protocol and because the review question concerned the effects of adjunctive B vitamin supplementation, and intervention characteristics (type and dose of vitamins) provided the most meaningful basis for comparing heterogeneous studies. In addition, a synthesis of adverse events was conducted, focusing on reported adverse events that overlapped across two studies (gastrointestinal adverse events and sexual dysfunction).

Formulations containing Folic Acid and Vitamin B12

Verabreichungen mit Folsäure und B12 (2 Studien)

In accordance with the PRISMA 2020 checklist, the following section summarises the key characteristics and risk of bias of the studies contributing to the synthesis.

ev. von Vorteil in der akuten Phase der Depression

allerdings basierend auf Studien mit hohem Verzerrungsrisiko und kleinen Fallzahlen

Across the two studies included in this synthesis [122, 124], participants presented with mean moderate baseline depression severity. The studies employed open-label designs, including one RCT [124] and one NRCT [122]. Both trials reported greater symptom improvement in the intervention groups compared with controls, considering the use of different depression rating scales (PHQ-9 and HDRS). In the study by Unneh et al. [124], the intervention group improved to mild depression at 8 weeks, in the study by Gopalakrishnan et al. [122], intervention participants achieved remission by 12 weeks; suggesting a benefit in the acute-phase response window. Reported between-groups mean differences were statistically significant and of potentially clinically relevant magnitude in both studies (-8.72 on the PHQ-9; $p < 0.0001$ and -7.86 on the HDRS, $p = 0.0001$). However, both studies were judged to be at high risk of bias: in the study by Unneh et al. [124], concerns were raised about deviations from the intended interventions due to co-interventions, while in the study by Gopalakrishnan et al. [122], the main issue was confounding. Together with small sample sizes ($n = 56$ vs. $n = 44$), open-label designs, heterogeneity in study designs and outcome measures, and short follow-up, the evidence addresses only a restricted segment of the review question, primarily in younger outpatient populations with moderate depression who were antidepressant-naïve or using antidepressants <2 weeks, and findings should be interpreted with considerable caution.

Kombinationstherapie mit SSRI und Vit B in unterschiedlicher Dosierung = eingeschränkte Aussagekraft

Both studies [122, 124] investigated a combination of folic acid and vitamin B12 as add-on therapy to SSRIs (escitalopram and fluoxetine). In both studies similar dosages of folic acid were applied (4mg and 5mg reported), but vitamin B12 dosage differed as Unneh et al. [124] administered a higher dose (10mg vs. 1500μg) than Gopalakrishnan et al. [122]. This heterogeneity in vitamin B12 exposure, together with differences in antidepressant regimens and treatment duration, further limits the comparability of the interventions.

Formulations Containing ≥3 B Vitamins

Verabreichungen mit ≥3 Vit B (3 Studien)

In accordance with the PRISMA 2020 checklist, the following section summarises the key characteristics and risks of bias of the studies contributing to this synthesis.

keine signifikanten Unterschiede zwischen den Gruppen

Almeida et al. [87] and Bell et al. [125] were conducted as double-blind RCTs, whereas Kuchya et al. [123] used an open-label randomised design. All three studies reported no statistically significant results. About risk of bias, Almeida et al. [87], was judged as having some concerns, primarily due to one downgraded domain related to a post-registered protocol. Bell et al. [125] was judged as having multiple concerns, including high risk of bias due to missing outcome data. Kuchya et al. [123] was judged as having some concerns overall, including downgrading in the domain deviations from intended interventions.

alle 3 Studien mit Verzerrungsrisiken kleinen Fallzahlen etc.

Almeida et al. [87], included participants with a mean age of approximately 65 years recruited from the community, Bell et al. [125] investigated a geriatric inpatient sample and Kuchya et al. [123] studied a younger outpatient population with a mean age of approximately 37 years. Multiple comorbidities were reported in the study by Bell et al. [125] and Almeida et al. [87]. Sample sizes ranged from moderate in the study by Almeida et al. (n = 153), small in study by Kuchya et al. (n = 53) and very small in the study by Bell et al. (n = 14).

...sehr unterschiedlichen Nachbeobachtungszeiten

Follow-up duration differed markedly across studies, ranging from 4 weeks in the study by Bell et al. [125] to 8 weeks in the study by Kuchya et al. [123] and 52 weeks in the study by Almeida et al [87]. Depression severity was assessed using the MADRS in two studies [87, 125] and the HDRS in the study by Kuchya et al. [123]. In the study by Bell et al. [125], both groups improved to the mild depression range by the end of treatment, and there was a non-significant improvement in depression severity (MD -5.0 points, p= 0.11). In the study by Almeida et al. [87], MADRS follow-up values were reported visually with a small reported mean change between groups (-0.4 points, p = 0.739). In the study by Kuchya et al. [123], interpretation of clinical severity at follow-up was not possible, as HDRS cut-off values were not specified; however, improvement is reported as small (-1.52 points) and not statistically significant.

Kombinationstherapie mit SSRI/TCA und Vit B in unterschiedlicher Dosierung = eingeschränkte Aussagekraft

The studies evaluated formulations containing ≥3 B vitamins in combination with SSRI (citalopram and fluoxetine) in two studies [87, 123] and TCA [125]. Across Almeida et al. [87] and Bell et al. [125], a combination of three B vitamins was used, whereas Kuchya et al. [123] administered a combination of five B vitamins. Overlaps were observed for vitamin B1 (10mg in [125] and [123]), vitamin B2 (10mg in [125] and [123]), and vitamin B6 across all three studies, albeit at different doses 25mg [87]; 10mg [125] and 3mg [123]). Folic acid (vitamin B9) overlapped between Almeida et al. (2mg) [87] and (10mg) [125], while vitamin B12 overlapped between Almeida et al. (0.5mg) [87] and Kuchya et al. (15μg) [123]. No dose-response analysis was undertaken; therefore, no conclusions can be made.

Ergebnisse lassen wegen Heterogenität der Studienpopulationen, Settings, methodischen Mängeln keine verallgemeinerbaren Schlüsse zu

Overall, findings across studies are difficult to compare due to substantial clinical and methodological heterogeneity (population age and setting, antidepressant background treatment, outcome measures, sample size, and follow-up duration). Given some concerns about the high risk of biased judgments and limited reporting, the evidence should be interpreted with caution.

3.6 Results for Safety

Adverse events and tolerability

Nebenwirkungen (2 Studien) vergleichbar zwischen den Interventions- und Kontrollgruppen

bei ca 5% der Patient:innen

Almeida et al. [87] reported adverse events occurring in more than 5% of participants at any assessment point between weeks 4 and 52. Across a wide range of neurological, gastrointestinal, sleep-related, and other symptoms, event rates were generally comparable between groups, and no statistically significant between-group differences were observed. Reported adverse events included tremor (10.8% vs. 8.3%), agitation/anxiety (30.0% vs. 28.6%), dry mouth (35.2% vs. 22.2%), headache (20.0% vs. 25.4%), constipation (13.1% vs. 12.7%), nightmares (18.6% vs. 11.5%), nausea (6.1% vs. 9.9%), and diarrhoea (10.9% vs. 5.7%) and sexual adverse events (19.5% vs. 11.1%) in the intervention and control groups. Reported odds ratios, confidence intervals and events per number of participants can be found in the extraction sheet (see Appendix 5). Kuchya et al. [123] reported adverse drug reactions at weeks 2, 6, and 8 following the intervention. Gastrointestinal symptoms occurred in one participant in each group (4.16% vs. 4.8%). Anorexia and insomnia were reported only in the control group (4.8% and 14.4%), whereas sexual dysfunction and skin rash were each reported in one participant (4.16%) in the intervention group. Vertigo was more frequently reported in the intervention group (12.48% vs. 4.8%). No statistical analyses were reported.

kaum Unterschiede zwischen den Gruppen

Across the included studies reporting adverse events, rates of gastrointestinal and sexual adverse events were similar between the intervention and control groups. However, conclusions are limited by low event rates and the absence of statistical analyses in one study.

Gastrointestinal adverse events

gastrointestinale Nebenwirkungen (2 Studien)

In the study by Almeida et al. [87], events were numerically more frequent in the intervention group than in the control group (diarrhoea: 10.9% vs. 5.7%; OR 2.03, 95% CI 0.56-7.28). Kuchya et al. [123] reported similarly low rates of gastrointestinal symptoms in both groups (4.8% vs. 4.16%) without providing statistical estimates.

Sexual dysfunction

sexuelle Funktionsstörung

Low to moderate rates of sexual dysfunction were observed. In the study by Almeida et al. [87], rates were numerically lower in the control group than in the intervention group (11.1% vs 16.2%; OR 1.55, 95% CI 0.59-4.05). Kuchya et al. [123] reported a single event in the intervention group (4.16%) and none in the control group, but no statistical analysis was reported.

All cause discontinuation rates

Therapieabbruch: nicht berichtet

All cause discontinuation rates was not reported in any of the five studies.

3.7 Certainty of Evidence

keine formale GRADE Bewertung, aber Einschätzung der Evidenz nach GRADE Kategorien

No formal assessment was undertaken. Instead, the relevant GRADE domains (risk of bias, inconsistency, indirectness, imprecision and dissemination bias [121]) were qualitatively considered to inform the interpretation of the main outcome.

The included studies comprised a mixture of blinded and unblinded RCTs and non-randomised designs, which weakens the overall quality of the evidence. Risk of bias was rated as moderate (some concerns) in two studies and high (RoB 2.0) or serious (ROBINS-I) in three studies. Common statistical measures used to assess inconsistency (e.g. I^2 or Cochran's Q test) were not used in this review, despite substantial clinical and methodological heterogeneity across studies. There were minor concerns regarding indirectness, as the populations, interventions, comparators, and outcomes examined in the included studies aligned well with the review question and no relevant discrepancies were identified. Overall confidence in the evidence was further weakened by imprecision, given the limited, often very small, sample sizes and the presence of wide or unreported confidence intervals. The completeness of the systematic literature search cannot be guaranteed, and statistical tests for publication bias were not possible. A dose-response gradient could not be detected, and follow-up periods were short in most studies.

Zuverlässigkeit der Evidenz wird als gering bis sehr gering eingeschätzt

Overall, the certainty of the evidence appears to be low to very low; however, no formal GRADE assessment was undertaken. The evidence is limited by imprecision, a small number of events, and risk of bias.

4 Discussion

4.1 Summary of the Main Findings

This systematic review included four randomised controlled trials - two of which were open-label - and one non-randomised controlled trial. The five studies reported a total of 364 participants, with data from 320 participants included in the analysis to evaluate the efficacy and safety of combining antidepressant therapy with ≥2 B vitamins on depressive and anxiety symptom severity. In accordance with the protocol, the originally planned restriction to B complex interventions containing ≥3 B vitamins and to RCTs only was broadened due to limited available evidence. All included studies addressed depressive disorders; no eligible evidence was identified for anxiety outcomes.

Systematische Übersicht umfasst 5 Studien (364 Pts):

4 RCTs (2 davon open-label) und
1 NRCT

zu Kombinationstherapie Antidepressiva mit ≥2 B Vitamine

One RCT and one NRCT [122, 124] evaluated folic acid plus vitamin B12 as add-on therapy and reported statistically significant improvements in depressive symptoms in the acute-phase response window; however, both were open label, judged at high risk of bias and included small samples.

The three remaining studies, including two double-blind RCTs and one open-label RCT, assessed supplementation with ≥3 B vitamins and did not report statistically significant benefits. Notably, the trial with the lowest risk of bias, the largest sample size, and the longest follow-up found no statistically significant between-group differences in symptom severity scores [87]. Comparability across those trials was limited by substantial clinical and methodological heterogeneity, including differences in study populations, antidepressant regimens, intervention formulations and doses, outcome measures and reporting and follow-up length. No serious adverse events were reported, and supplementation appeared generally well tolerated; however, safety conclusions are limited because adverse-event data were available from only two studies, statistical reporting was insufficient, and the number of events was small. One study suggested a longer-term benefit (52 weeks) for response [87]; cognitive outcomes showed no significant differences [125]. None of the included studies reported quality of life, serious adverse events or all-cause discontinuation rates as outcomes.

nur Studien mit Folsäure und Vit B12 zeigten Verbesserungen – aber kleine Studien mit hohem RoB

Studie mit geringstem RoB, größter Fallzahl und längstem FU findet keine Gruppenunterschiede

Nebenwirkungen vergleichbar zwischen den Gruppen

Overall, the evidence supporting the effectiveness and safety of combining antidepressant therapy with a B vitamin complex, reducing depressive symptom severity, remains very limited.

sehr limitierte Evidenz

4.2 Interpretation of the Results

Population Characteristics

All studies included in the present review focused exclusively on populations with depressive disorders exhibiting an average moderate level of symptom severity, although anxiety disorders show a slightly higher global prevalence [17]. Included studies comprised predominantly female populations, which is consistent with reports of a higher prevalence of depressive disorders among women compared with men worldwide [1, 17]. Two studies examined study

alle 5 Studien zu Depression, keine zu Angststörungen

mehr Frauen in den Studien, höhere Prävalenz

populations with a median age around 62 years [87], approaching the age group when DALY rates related to depression reach maximum [17] and in the case of Bell et al. [125], above 75 years, which is substantially older than the study populations in the other studies with a mean age of around 35-38 years [122-124]. These age distributions broadly overlap with age groups reported to have a high prevalence of depression in high- to middle-low SDI countries [16].

Interventions

Ergebnisse der Studien zu Folsäure und Vit B12

Both studies that reported statistically significant effects used formulations containing folic acid and vitamin B12 in combination with an SSRI [122, 124]. These findings contrast with the results of an RCT by Christensen et al. [128], conducted in Australia, which compared 400 μg/day folic acid and 100 μg/day vitamin B12 with placebo over a two-year period. In the subgroup of participants using antidepressants (n = 109), no significant interaction between vitamin B12 plus folic acid supplementation and antidepressant use was observed for PHQ-9 scores. Notably, patients with a clinical diagnosis of depression were excluded, resulting in lower baseline PHQ-9 scores compared with Unneh et al. [124] (7.82 vs. 13.91 in the intervention group) and the type of antidepressants was not reported. In addition, Unneh et al. [124] and Gopalakrishnan et al. [122] administered higher doses of both vitamin B12 and folic acid; the samples were younger on average, and the intervention period was limited to 8 weeks. An ongoing RCT (TCTR20250818014) was identified during this systematic review, evaluating a SSRI in combination with folic acid and vitamin B12, which may provide additional evidence. However, it is also open-label and involves a small sample size [128].

widersprechen australischer Studie – allerdings waren Teilnehmer:innen mit klinischer Diagnose ausgeschlossen

eine laufende Studie (Thailand) dazu könnte zusätzliche Evidenz bringen

keine Studie verabreichte ≥ 3 B-Vitamine

keine Effekte auch in weiterer Sekundäranalyse beobachtet

None of the studies included in this review that examined three or more B vitamins reported statistically significant effects [87, 123, 125]. While Kennedy has argued that multivitamin interventions may better capture the combined biological actions of B vitamins as a group [11], available trial evidence does not support a consistent clinical benefit in depression. The combination of folic acid, vitamin B6, and vitamin B12, a combination which was also used in the study by Almeida et al. [87], in addition to other micronutrients, was also found to be inferior to placebo in reducing depressive symptoms in MDD in a mixed sample of 158 patients with and without antidepressant therapy. Notably, there were substantially elevated placebo response rates and vitamin dosages differed [129]. In a secondary analysis of the SU.FOL.OM3 randomised secondary prevention trial, low-dose supplementation with 5-methyltetrahydrofolate, vitamins B6 and B12 also did not demonstrate a positive effect on depressive symptoms in a sample of cardiovascular disease survivors (n= 2000) with and without antidepressant use after a median follow-up of 4.7 years [130].

keine Überlegenheit von mehr B-Vitaminen

jedoch ev. bei Patient:innen mit genetischen Varianten, die den Homocystein-Stoffwechsel beeinflussen

oder verzögerten Effekten

Considering a combination of >3 B vitamins, Kuchya et al. [123] reported no superiority. An RCT investigating a vitamin B-complex formulation (Max Stress B) versus placebo in 60 patients with and without concurrent antidepressant and anti-anxiety medication use, containing vitamins B1, B2, B3, B5, B6, B9, B12 alongside other micronutrients, also reported non-significant improvements in depressive and anxiety symptoms over a period of 60 days [131]. Among other factors, the study populations, length of follow-up, and outcome measures differed. However, in another RCT, the authors reported that, in 159 patients with depression carrying genetic variants influencing homocysteine metabolism, a formulation containing vitamins B1, B2, B3, B6, B9 and B12, among other micronutrients, was found to be superior to the placebo

in terms of its efficacy in reducing homocysteine levels. Furthermore, a statistically significant response was observed in the majority of participants, with complete remission achieved in 42% of those receiving active treatment [132]. A three-arm RCT in individuals (n= 181) with bipolar disorder experiencing an acute depressive episode, compared adjunctive N-acetylcysteine within a micronutrient complex, which also contained vitamins B1, B2, B3, B5, B6, B7, B9, and B12, to placebo in one study arm. Participants received usual pharmacological treatment including mood stabilisers, antipsychotics, antidepressants and benzodiazepines. No significant between-group differences were observed in MADRS change scores. However, a significant difference was observed at the follow-up visit, which occurred four weeks after the conclusion of treatment. The authors conclude that this may point to either a delayed effect of the combination therapy or to improvement in symptoms after withdrawal [133].

Notably, findings from external trials derive from heterogeneous populations and interventions and are therefore not directly comparable with the present review; however, they highlight heterogeneous findings associated with the use of B vitamins.

wenig direkte Vergleichbarkeit zwischen den Studien

Secondary Outcomes

Remission, Response, Cognitive Outcomes

The predefined secondary outcomes of remission and response were assessed in one study [87]. Remission results showed no evidence of a short-term benefit but were consistent with a longer-term advantage of the intervention (52 weeks). Response rates did not differ significantly between groups, with no response data reported beyond week 12 [87]. However, Participants who had achieved remission by week 12 were followed up to assess relapse at weeks 26 and 52, and the risk of relapse of depressive symptoms was lower in the vitamin group than in the placebo group (OR 0.33, 95% CI 0.12-0.94) [87].
The study by Bell et al. [125] found no statistically significant benefit of a vitamin B complex on cognitive outcomes in a geriatric population that included patients with partial dementia [110, 112]. A meta-analysis also found that long-term homocysteine-lowering with B vitamins did not improve MMSE scores in cognitive domains [134]. However, RCTs including participants with a diagnosis of Alzheimer's disease, cognitive impairment, or depression were excluded from the analysis. Another meta-analysis that included older adults with Alzheimer's disease or dementia likewise found no significant difference in MMSE scores following vitamin B supplementation [135]. Vitamin B formulations varied across the included studies and did not consider comorbid depression; therefore, the results are not directly comparable with those of the study by Bell et al. [125].

keine signifikanten Gruppenunterschiede bei sekundären Endpunkten

auch in anderen Übersichtsarbeiten bestätigt,

allerdings wenig Vergleichbarkeit zwischen den Studien

Safety

Only two of five studies reported safety data on adverse events [87, 123]; the remaining studies did not provide such data. In the study by Almeida et al. [87], no statistically significant differences were observed between groups, while in the study by Kuchya et al. [123], only isolated events occurred in a small study population; no statistical measures were reported. One suicide attempt was reported by Bell et al. [125]; however, it occurred prior to randomisation and was therefore not attributable to the intervention and was not included in the safety analysis. The results regarding adverse events align with those of a meta-analysis, which found an association between the use of adjunctive nutraceuticals and numerically higher, but non-significant, rates

Nebenwirkungen kaum berichtet

nur einzelne Ereignisse

Übereinstimmung mit Meta-Analyse: geringfügig mehr NW mit Vit B

of adverse events compared to placebo. The authors suggest that this was likely due to limited statistical power, given the reduced number of studies and participants [90]. Sarris et al. [9] also reported in their meta-analysis that all nutraceuticals were generally well tolerated. However, these findings are based on meta-analyses of trials that investigated a wide range of different micronutrients and did not include all B vitamins.

in allen Studien wurden Vit-B-Dosierungen über den Grenzwerten verabreicht

Across all included studies, vitamin B dosages far exceeding the recommended daily intake were administered, as it appears to commonly be the case in other RCTs [129, 131, 132]. For many of the B vitamins, the EFSA has not established ULs. However, ULs have been defined for certain B vitamins and/or specific chemical forms, including vitamin B3 (with separate ULs for nicotinic acid and nicotinamide), vitamin B6, and folate [57]. An updated evaluation of the safety profiles of vitamins B1, B6, and B12 was prompted by findings from epidemiological cohort studies that raised concerns regarding high intakes of vitamin B6 and/or B12 and their potential association with an increased risk of hip fractures and lung cancer. However, no relevant studies addressing the selected safety aspects of vitamin B1 were identified and based on the currently available evidence, the authors concluded that a causal relationship between vitamin B6 and/or B12 intake and the risk of hip fracture or lung cancer cannot be established [136].

keine Studie adressierte diese Sicherheitsaspekte und das Risiko für Folgeerkrankungen

4.3 Limitations

Limitationen:

nur begrenzte Anzahl an Studien identifiziert

umfassendere Suche hätte ev. noch mehr gefunden

Limitations related to the literature search should be acknowledged. Only a limited number of databases and other sources were searched, and it is possible that relevant studies were missed. A single search string was applied across all databases; however, smaller databases may have benefited from a more concise and tailored search strategy. The use of additive combination terms in the search strategy may have reduced sensitivity in favour of higher specificity. Due to the limited evidence base, two open-label clinical trials and one NRCT were included, increasing the risk of confounding and bias and thereby reducing the certainty of the findings.

alle Arbeitsschritte eines systematischen Reviews wurden nur von einer Person durchgeführt

nur narrative Synthese der Evidenz wegen heterogener Evidenz

nicht für jeden Endpunkt konnte ein validierter MCID gefunden werden

einige Endpunkte mussten selbst berechnet werden

In contrast to recommendations, e.g., by Cochrane, key steps of the review process, including study selection, data extraction, and risk-of-bias assessment, were performed by a single reviewer (SF), which introduced a high likelihood of bias. No formal GRADE assessment was undertaken, meaning that the certainty of the evidence was not systematically evaluated. Owing to substantial heterogeneity across studies, a narrative synthesis was conducted instead of a meta-analysis, precluding quantitative estimation of treatment effects. Presenting results with arrows to illustrate effect direction may lead to overinterpretation, as this visual summary does not reflect effect sizes or confidence intervals. Also, the absence of validated MCID thresholds and incomplete reporting of outcome measure versions limited MCID-based interpretation; proposed estimates were therefore used cautiously to contextualise effect sizes rather than to define clinical relevance. In some studies, the reviewer (SF) calculated mean differences based on available statistics, as they were not directly reported. These may therefore be subject to uncertainty. Due to inconsistent reporting of B vitamin dosages in three studies, assumptions had to be made. This approach may have introduced additional uncertainty, as the exact doses administered cannot be confirmed, which represents a further

limitation. Authors were contacted to obtain missing information, and one author responded; however, the initial email sent by the reviewer (SF) contained incorrect information, resulting in no relevant data being obtained, and no second attempt was made to clarify the request.

vordefinierte Ein- und Ausschlusskriterien sind Vor- und Nachteile:

The predefined inclusion and exclusion criteria on the population can be viewed as both a strength and a limitation of this review. No specific age groups, considering adults, or comorbid conditions were excluded, and eligibility was based solely on a clinical diagnosis of depression or anxiety. However, the absence of age restrictions may have introduced heterogeneity, since depression characteristics, comorbidity profiles and responsiveness to the intervention may differ across age groups. The inclusion of participants with bipolar depression or comorbid conditions such as dementia, as well as concomitant therapies involving antipsychotics or benzodiazepines, may have also contributed to heterogeneity and could have influenced the results. No limitations were applied with respect to antidepressant class, which may have contributed to heterogeneity, as different antidepressant classes can vary in efficacy, onset of action, and side-effect profiles and may therefore interact differently with adjunctive B vitamin supplementation.

nur Erwachsene berücksichtigt

aufgrund der begrenzten Datenlage keine Auswertung für einzelne Antidepressiva-Klassen

die vorherige Dauer der Einnahme von Antidepressiva wurde nicht berücksichtigt

unterschiedliche Dosierungen der Vit B tragen zusätzlich zur Heterogenität der Studienlage bei

eine Dosis-Wirkungsanalyse war nicht möglich

einige Endpunkte wurden nur in einzelnen Studien berichtet,

ungleiche Nachbeobachtungszeiten

Concerning the intervention, eligibility required only the combination of B vitamins and antidepressant treatment, without distinguishing whether antidepressants were initiated before or concurrently with supplementation. Given the delayed onset of antidepressant efficacy, variation in treatment timing may have contributed to heterogeneity. In addition, the term vitamin B complex may not have been applied correctly: in this review it was used to denote combinations of more than two B vitamins, whereas the WHO ATC/DDD classification [137] defines B complex products as containing at minimum vitamin B1, B2, B3 and B6, with the possibility of additional B vitamins, and also distinguishes broader combinations that may include minerals or other substances mainly indicated as food supplements. Furthermore, inclusion of heterogeneous B vitamin formulations regardless of dose and composition may have increased clinical heterogeneity and limited formulation-specific conclusions on the dose-response relationship. The absence of a minimum follow-up requirement may have limited interpretation, given the delayed onset of antidepressant effects. Also, restricting the synthesis to final follow-up outcomes may inadequately reflect the clinical course of depression over time. The inclusion of studies published over a wide time span may represent a limitation, as diagnostic criteria and treatment standards have changed over time, potentially limiting comparability and applicability to current practice. Multiple outcome measurements were included, and one study [124] stated that depression was diagnosed clinically, guided by the PHQ-9 assessment. Although the PHQ-9 aligns with DSM symptom criteria, the extent to which a standardised diagnostic interview was used remained unclear, which may affect diagnostic consistency across studies.

Ko-Interventionen (Psychotherapie) können relevante Wirkungen haben,

wurden aber in den Studien nicht berichtet

An important limitation is the potential impact of co-interventions. In the study by Unneh et al. [124], participants in the supplementation arm also received educational handouts and counselling sessions targeting lifestyle factors and depressive symptoms, whereas the control group received antidepressant treatment alone. Throughout the remaining studies, psychotherapeutic or supportive care was either not reported or cannot be ruled out (e.g. inpatient setting in the study by Bell et al., [125]). Given evidence that adding psychotherapy to pharmacotherapy can improve outcomes in major depression, although the magnitude of benefit varies across meta-analyses [138, 139], unmeasured or unequally delivered psychosocial interventions represent a

plausible confounder. However, adherence is also a recognised challenge in antidepressant treatment and was not examined separately in this review. For example, the only small improvement in the antidepressant-only group in the study by Unneh et al. [124] may also reflect suboptimal adherence to pharmacotherapy.

Studien in Ländern mit unterschiedlichem Hintergrund durchgeführt:

Nigeria, Indien, Australien, USA

Unterschiedlicher Zugang zur Gesundheitsversorgung

It is important to consider that the included studies were conducted in countries with different economic backgrounds. The United States and Australia are classified as high-income economies, whereas Nigeria and India are considered lower-middle-income economies [140]. Differences in access to antidepressant treatment and interventional practices between high-income and lower-middle-income countries may also contribute to the heterogeneity of findings across the included studies. For example, the stronger intervention effects observed in Nigeria [124] and India [122] compared with Australia [125] and the USA [87] may partly reflect contextual differences, including access to standard care.

einige Variablen nicht berücksichtigt:

Biomarker und Homocystein-Konzentrationen als Surrogatendpunkte

Ernährungsgewohnheiten

Ko-Morbiditäten

In this review, several variables relevant to interpreting treatment effects were not addressed. Data on B vitamin blood levels were not considered, although they may serve as objective markers of supplementation effectiveness [87]. Vitamin deficiency at baseline was not assessed at baseline, although it could influence how well the intervention works. Homocysteine levels were not predefined as an outcome, despite evidence suggesting that homocysteine is relevant to depression [50, 66]. For example, Almeida et al. [87] reported a significant reduction in total homocysteine and suggested that remission benefits were confined to participants above a specific baseline cut-off (OR = 3.47. 95% CI 1.22-9.84). Dietary intake was not systematically assessed or extracted in this review, despite appetite loss resulting in decreased nutrient intake being a common symptom of depression [35] and a vegan diet was associated with vitamin B12 deficiency and elevated tHcy in a recent meta-analysis [141]. Comorbidities were extracted but not addressed separately, despite several of them, such as diabetes and cardiovascular disease, being known to be associated with depression [142, 143] or B vitamin deficiency, such as gastric disease [144]. Finally, cross-study comparisons may be further complicated by regional differences in micronutrient inadequacies [145] and by national food fortification policies [146, 147]. The considerations largely align with patterns reported in the background systematic reviews, including Almeida et al., (2015, [88]); Young et al., (2019, [82]); Borges-Vieira & Cardoso, (2023, [89]); suggesting that the fundamental conclusions remain consistent.

alle Studien hatten Verzerrungsrisiko:

inkomplette Daten, fehlende statistische Analysen

fehlende Festlegung von Schwellwerten

fehlende Informationen zu exakten Dosierungen

All included studies were at moderate or high risk of bias and exhibited additional limitations beyond their study designs. Several studies reported key information incompletely: Bell et al. [125], Kuchya et al. [123] and Unneh et al. [124] did not fully describe participant characteristics. Gopalakrishnan et al. [122], Kuchya et al. [123] and Unneh et al. [124] reported insufficient information on statistical values. Only Almeida et al. [87] conducted an ITT analysis, adjusted for several confounders and provided details on patient recruitment. Kuchya et al. [123] provided no information on the version of the outcome assessment used and did not report scale-based cut-off values, whereas Gopalakrishnan et al. [122] reported cut-off values and categorised symptom severity but also did not explicitly state the version of the scale used. Reporting of vitamin dosages was also inconsistent: Unneh et al. [124] and Gopalakrishnan et al. [122] did not consistently report the same dosing details, and Kuchya et al. [123] did not report exact dosages. In addition, eligibility criteria limited generalizability in several trials, as some excluded patients with clinically relevant comorbidities (e.g. diabetes, anaemia, alcohol intake in the

study by [122] or excluded patients with any comorbidities [124]. Almeida et al. [87] restricted inclusion to English-speaking participants and did not meet the planned sample size (388 targeted vs. 153 randomised). Finally, Bell et al. [125] provided no clear information on ethics approval or informed consent despite involving a vulnerable study population.

4.4 Further Implications

Future research should prioritise high-quality, adequately powered, double-blind RCTs with longer follow-up to capture the clinical course of depression across its different phases and to determine the optimal composition and dose of B-vitamin supplementation as an adjunctive therapy. This should be accompanied by improved and standardised reporting. Objective measures (e.g. baseline and follow-up blood levels of B vitamins and Hcy) and adherence to treatment should be systematically assessed. Given the limited evidence on safety, studies should include comprehensive adverse-event collection and longer-term safety monitoring, particularly for chronic high-dose use, in line with existing EFSA guidance and established ULs for specific B vitamins.

hoch-qualitative klinische Studien mit ausreichend langen Nachbeobachtungszeiten fehlen
ebenso wie standardisierte Ergebnismessung

To improve applicability, future trials should enrol clinically relevant populations, including patients with more severe or persistent depression, and consider adjunctive supplementation among antidepressant users suffering from other mental disorders, such as anxiety. Stratified study designs may be particularly informative, for example by targeting subgroups defined by age, baseline B-vitamin status, or homocysteine levels, as for example vitamin B12 deficiency is known to be prevalent in older adults [148]. Given that the burden of depression and anxiety has been increasing among younger people [1], there is also a need for timely evaluation of intervention strategies in adolescents. Also, quality of life was not assessed in any included study; future trials should include validated quality-of-life outcomes to capture patient-relevant benefits beyond symptom reduction.

um Übertragbarkeit und Aussagekraft der Evidenz zu gewährleisten:

Einschluss relevanter Patient:innen-Populationen mit schwerer und persistierender Depression

hohe Prävalenz

Finally, trials should better control for confounding by measuring and adjusting for relevant clinical and contextual factors (e.g. age, psychotherapy, comorbidities, diet, and socioeconomic and geographic determinants), as inadequate confounder adjustment has been a common limitation in prior research [50].

Kontrolle von Störfaktoren in wichtig

5 Conclusion

Mental disorders, including anxiety and depressive disorders, represent a major and growing global public health burden. Access to effective treatment remains limited in many settings, and antidepressant therapy poses challenges, underscoring the need for strategies to improve care. With respect to the present review question, the available evidence was insufficient to answer whether combination of B vitamin complex with antidepressant therapy is effective and safe for reducing depressive symptom severity. Further high-quality research is required to clarify whether vitamin B supplementation offers an accessible and safe adjunct in the management of depression and anxiety.

psychische Krankheiten wie Depression und Angststörungen: große Belastung für die globale öffentliche Gesundheit
insuffiziente Datenlage, um Forschungsfrage abschließend zu beantworten

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Appendix

Appendix A1: Documentation of the Literature search in Databases and Registries

Search Query #	PICO elements	Search tearms and Bool'sche operators
Search query #1	Population: patients with depression or anxiety	Depressive Disorder OR Depressive Disorder, Major OR Dysthymic Disorder OR Anxiety Disorders OR Panic Disorder OR Social Anxiety Disorder OR depressi* OR major depressive disorder OR MDD OR depressive episode OR recurrent depressive disorder OR chronic depression OR persistent depressive disorder OR PDD OR dysthymi* OR anxiet* OR generalized anxiety disorder OR GAD OR panic disorder OR social anxiety OR mixed anxiety and depressive disorder
Search query #2	treated with antidepressant medication	antidepressive agents OR antidepressive agents, tricyclic OR antidepressive agents, second-generation OR monoamine Oxidase Inhibitors OR Serotonin Uptake Inhibitors OR antidepressant* OR antidepressiv* OR antidepressive agent* OR SSRI OR selective serotonin reuptake inhibitor* OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR serotonin norepinephrine reuptake inhibitor* OR serotonin noradrenaline reuptake inhibitor* OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR tricyclic antidepressant* OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR monoamine oxidase inhibitor* OR monoamine oxidase A inhibitor* OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine
Search query #3	Intervention: vitamin B complex	vitamin b complex OR vitamins OR dietary supplements OR micronutrients OR nutritional supplements OR thiamine OR riboflavin OR niacin OR pantothenic acid OR pyridoxine OR biotin OR folic acid OR cobalamins OR b vitamin* OR vitamin b complex OR micronutrient* OR nutritional supplement* OR vitamin supplement* OR dietary supplement* OR nutritional intervention* OR dietary intervention* OR thiamin* OR thiamine OR aneurin OR vitamin b1 OR riboflavin OR lactoflavin OR vitamin b2 OR niacin OR nicotinamide OR nicotinic acid OR niacinamide OR vitamin b3 OR pantothenic OR dexpanthenol OR vitamin b5 OR pyridoxin* OR pyridoxal OR pyridoxamine OR plp OR pyridoxal-5-phosphate OR vitamin b6 OR biotin OR vitamin b7 OR vitamin h OR coenzyme r OR folic acid OR folat* OR l-methylfolate OR 5-mthf OR levomefolate OR folinic acid OR leucovorin OR vitamin b9 OR cobalamin* OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR coenzyme b12 OR vitamin b12
Search query #4	Combination terms	drug therapy, combination OR drug synergism OR combination therap* OR combined therap* OR combined treatment OR combined modality therap* OR combination regimen* OR add-on OR addon OR add on OR co-treatment OR cotreatment OR co treatment OR additive OR adjuvant OR augmentation OR augmentative OR augmentation strateg* OR adjunctive OR supplementation OR co-therapy OR cotherapy OR co therapy OR co-administration OR coadministration OR co administration OR co-intervention OR cointervention OR co intervention OR concomitant OR booster OR concurrent therap*
Search query #5		#1 AND #2 AND #3 AND #4

Database	Search string	Date of search	Hits	Notes
Pubmed via MEDLINE	((Depressive Disorder[MeSH Terms] OR Depressive Disorder, Major[MeSH Terms] OR Dysthymic Disorder[MeSH Terms] OR Anxiety Disorders[MeSH Terms] OR Panic Disorder[MeSH Terms] OR Social Anxiety Disorder[tiab] OR depressi*[tiab] OR major depressive disorder[tiab] OR MDD[tiab] OR depressive episode[tiab] OR recurrent depressive disorder[tiab] OR chronic depression[tiab] OR persistent depressive disorder[tiab] OR PDD[tiab] OR dysthymi*[tiab] OR anxiet*[tiab] OR generalized anxiety disorder[tiab] OR GAD[tiab] OR panic disorder[tiab] OR social anxiety[tiab] OR mixed anxiety and depressive disorder[tiab])) AND ((Antidepressive Agents[MeSH Terms] OR Antidepressive Agents, Tricyclic[MeSH Terms] OR Antidepressive Agents, Second-Generation[MeSH Terms] OR Monoamine Oxidase Inhibitors[MeSH Terms] OR Serotonin Uptake Inhibitors[MeSH Terms]) OR (antidepressant*[tiab] OR antidepressiv* [tiab] OR antidepressive agent*[tiab] OR SSRI[tiab] OR selective serotonin reuptake inhibitor*[tiab] OR fluoxetine[tiab] OR	15.10.2025	372	No filters applied.

	citalopram[tiab] OR escitalopram[tiab] OR paroxetine[tiab] OR sertraline[tiab] OR fluvoxamine[tiab] OR SNRI[tiab] OR serotonin norepinephrine reuptake inhibitor*[tiab] OR serotonin noradrenaline reuptake inhibitor*[tiab] OR venlafaxine[tiab] OR desvenlafaxine[tiab] OR duloxetine[tiab] OR milnacipran[tiab] OR levomilnacipran[tiab] OR TCA[tiab] OR tricyclic antidepressant*[tiab] OR imipramine[tiab] OR clomipramine[tiab] OR trimipramine[tiab] OR amitriptyline[tiab] OR nortriptyline[tiab] OR doxepin[tiab] OR MAOI[tiab] OR monoamine oxidase inhibitor*[tiab] OR monoamine oxidase A inhibitor*[tiab] OR phenelzine[tiab] OR tranylcypromine[tiab] OR moclobemide[tiab] OR NaSSA[tiab] OR mirtazapine[tiab] OR SARI[tiab] OR trazodone[tiab] OR nefazodone[tiab] OR NARI[tiab] OR reboxetine[tiab] OR NDRI[tiab] OR bupropion[tiab] OR vilazodone[tiab] OR vortioxetine[tiab] OR agomelatine[tiab])) AND ((Vitamin B Complex[MeSH Terms] OR Vitamins[MeSH Terms] OR Dietary Supplements[MeSH Terms] OR Micronutrients[MeSH Terms] OR Thiamine[MeSH Terms] OR Riboflavin[MeSH Terms] OR Niacin[MeSH Terms] OR Pantothenic Acid[MeSH Terms] OR Pyridoxine[MeSH Terms] OR Biotin[MeSH Terms] OR Folic Acid[MeSH Terms] OR Cobalamins[MeSH Terms]) OR (B vitamin*[tiab] OR vitamin B complex[tiab] OR micronutrient*[tiab] OR nutritional supplement*[tiab] OR vitamin supplement*[tiab] OR dietary supplement*[tiab] OR nutritional intervention*[tiab] OR dietary intervention*[tiab] OR thiamin*[tiab] OR thiamine[tiab] OR aneurin[tiab] OR vitamin B1[tiab] OR riboflavin[tiab] OR lactoflavin[tiab] OR vitamin B2[tiab] OR niacin[tiab] OR nicotinamide[tiab] OR nicotinic acid[tiab] OR niacinamide[tiab] OR vitamin B3[tiab] OR pantothenic[tiab] OR dexpanthenol[tiab] OR vitamin B5[tiab] OR pyridoxin*[tiab] OR pyridoxal[tiab] OR pyridoxamine[tiab] OR PLP[tiab] OR pyridoxal-5-phosphate[tiab] OR vitamin B6[tiab] OR biotin[tiab] OR vitamin B7[tiab] OR vitamin H[tiab] OR coenzyme R[tiab] OR folic acid[tiab] OR folat*[tiab] OR l-methylfolate[tiab] OR 5-MTHF[tiab] OR levomefolate[tiab] OR folinic acid[tiab] OR leucovorin[tiab] OR vitamin B9[tiab] OR cobalamin*[tiab] OR cyanocobalamin[tiab] OR methylcobalamin[tiab] OR hydroxocobalamin[tiab] OR adenosylcobalamin[tiab] OR coenzyme B12[tiab] OR vitamin B12[tiab])) AND ((Drug Therapy, Combination[MeSH Terms] OR Drug Synergism[MeSH Terms]) OR (combination therap*[tiab] OR combined therap*[tiab] OR combined treatment[tiab] OR combined modality therap*[tiab] OR combination regimen*[tiab] OR add-on[tiab] OR addon[tiab] OR add on[tiab] OR co-treatment[tiab] OR cotreatment[tiab] OR co treatment[tiab] OR additive[tiab] OR adjuvant[tiab] OR augmentation[tiab] OR augmentative[tiab] OR augmentation strateg*[tiab] OR adjunctive[tiab] OR supplementation[tiab] OR co-therapy[tiab] OR cotherapy[tiab] OR co therapy[tiab] OR co-administration[tiab] OR coadministration[tiab] OR co administration[tiab] OR co-intervention[tiab] OR cointervention[tiab] OR co intervention[tiab] OR concomitant[tiab] OR booster[tiab] OR concurrent therap*[tiab]))			
Web of Science Core Collection	Search query #1: TS=("Depressive Disorder" OR "Major Depressive Disorder" OR "Dysthymic Disorder" OR "Anxiety Disorders" OR "Panic Disorder" OR OR "Social Anxiety Disorder" OR depressi* OR MDD OR "depressive episode" OR "recurrent depressive disorder" OR "chronic depression" OR "persistent depressive disorder" OR PDD OR dysthymi* OR anxiet* OR "generalized anxiety disorder" OR GAD OR "panic disorder" OR "social anxiety" OR "mixed anxiety and depressive disorder"): 1,118,346 hits Search query #2: TS=("Antidepressive Agents" OR "Antidepressive Agents, Tricyclic" OR "Antidepressive Agents, Second-Generation" OR "Monoamine Oxidase Inhibitors" OR "Serotonin Uptake Inhibitors" OR antidepressant* OR "antidepressiv*" OR SSRI OR "selective serotonin reuptake inhibitor*" OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin noradrenaline reuptake inhibitor*" OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR "tricyclic antidepressant*" OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR "monoamine oxidase inhibitor*" OR "monoamine oxidase A inhibitor*" OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine): 196,698 hits Search query #3: TS=("Vitamin B Complex" OR Vitamins OR "Dietary Supplements" OR Micronutrients OR "Nutritional Supplements" OR Thiamine OR Riboflavin OR Niacin OR "Pantothenic Acid" OR Pyridoxine OR Biotin OR "Folic Acid" OR Cobalamins OR "B vitamin*" OR "vitamin B complex" OR micronutrient* OR "nutritional supplement*" OR "vitamin	15.10.2025	362	No filters

	supplement*" OR "dietary supplement*" OR "nutritional intervention*" OR "dietary intervention*" OR thiamin* OR thiamine OR aneurin OR "vitamin B1" OR riboflavin OR lactoflavin OR "vitamin B2" OR niacin OR nicotinamide OR "nicotinic acid" OR niacinamide OR "vitamin B3" OR pantothenic OR dexpanthenol OR "vitamin B5" OR pyridoxin* OR pyridoxal OR pyridoxamine OR PLP OR "pyridoxal-5-phosphate" OR "vitamin B6" OR biotin OR "vitamin B7" OR "vitamin H" OR "coenzyme R" OR "folic acid" OR folat* OR l-methylfolate OR 5-MTHF OR levomefolate OR "folinic acid" OR leucovorin OR "vitamin B9" OR cobalamin* OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR "coenzyme B12" OR "vitamin B12"): 714,290 hits Search query #4: TS=("Drug Therapy, Combination" OR "Drug Synergism" OR "combination therap*" OR "combined therap*" OR "combined treatment" OR "combined modality therap*" OR "combination regimen*" OR add-on OR addon OR "add on" OR co-treatment OR cotreatment OR "co treatment" OR additive OR adjuvant OR augmentation OR augmentative OR "augmentation strateg*" OR adjunctive OR supplementation OR co-therapy OR cotherapy OR "co therapy" OR co-administration OR coadministration OR "co administration" OR co-intervention OR cointerventions OR "co intervention" OR concomitant OR booster OR "concurrent therap*"): 1,747,687 hits Search query 5: #1 AND #2 AND #3 AND #4			
Cochrane Library via Ovid including: **Cochrane Database of Systematic Reviews** **Cochrane Central Register of Controlled Trials** **Cochrane Clinical Answers**	((exp "Depressive Disorder"/ OR exp "Depressive Disorder, Major"/ OR exp "Dysthymic Disorder"/ OR exp "Anxiety Disorders"/ OR exp "Panic Disorder"/ OR "Social Anxiety Disorder".tw. OR depressi*.tw. OR "major depressive disorder".tw. OR MDD.tw. OR "depressive episode".tw. OR "recurrent depressive disorder".tw. OR "chronic depression".tw. OR "persistent depressive disorder".tw. OR PDD.tw. OR dysthymi*.tw. OR anxiet*.tw. OR "generalized anxiety disorder".tw. OR GAD.tw. OR "panic disorder".tw. OR "social anxiety".tw. OR "mixed anxiety" AND "depressive disorder".tw.)) AND ((exp "Antidepressive Agents"/ OR exp "Antidepressive Agents, Tricyclic"/ OR exp "Antidepressive Agents, Second-Generation"/ OR exp "Monoamine Oxidase Inhibitors"/ OR exp "Serotonin Uptake Inhibitors"/) OR (antidepressant*.tw. OR antidepressiv*.tw. OR "antidepressive agent*".tw. OR SSRI.tw. OR "selective serotonin reuptake inhibitor*".tw. OR fluoxetine.tw. OR citalopram.tw. OR escitalopram.tw. OR paroxetine.tw. OR sertraline.tw. OR fluvoxamine.tw. OR SNRI.tw. OR "serotonin norepinephrine reuptake inhibitor*".tw. OR "serotonin noradrenaline reuptake inhibitor*".tw. OR venlafaxine.tw. OR desvenlafaxine.tw. OR duloxetine.tw. OR milnacipran.tw. OR levomilnacipran.tw. OR TCA.tw. OR "tricyclic antidepressant*".tw. OR imipramine.tw. OR clomipramine.tw. OR trimipramine.tw. OR amitriptyline.tw. OR nortriptyline.tw. OR doxepin.tw. OR MAOI.tw. OR "monoamine oxidase inhibitor*".tw. OR "monoamine oxidase A inhibitor*".tw. OR phenelzine.tw. OR tranylcypromine.tw. OR moclobemide.tw. OR NaSSA.tw. OR mirtazapine.tw. OR SARI.tw. OR trazodone.tw. OR nefazodone.tw. OR NARI.tw. OR reboxetine.tw. OR NDRI.tw. OR bupropion.tw. OR vilazodone.tw. OR vortioxetine.tw. OR agomelatine.tw.)) AND ((exp "Vitamin B Complex"/ OR exp Vitamins/ OR exp "Dietary Supplements"/ OR exp Micronutrients/ OR exp Thiamine/ OR exp Riboflavin/ OR exp Niacin/ OR exp "Pantothenic Acid"/ OR exp Pyridoxine/ OR exp Biotin/ OR exp "Folic Acid"/ OR exp Cobalamins/) OR ("B vitamin*".tw. OR "vitamin B complex".tw. OR micronutrient*.tw. OR "nutritional supplement*".tw. OR "vitamin supplement*".tw. OR "dietary supplement*".tw. OR "nutritional intervention*".tw. OR "dietary intervention*".tw. OR thiamin*.tw. OR thiamine.tw. OR aneurin.tw. OR "vitamin B1".tw. OR riboflavin.tw. OR lactoflavin.tw. OR "vitamin B2".tw. OR niacin.tw. OR nicotinamide.tw. OR "nicotinic acid".tw. OR niacinamide.tw. OR "vitamin B3".tw. OR pantothenic.tw. OR dexpanthenol.tw. OR "vitamin B5".tw. OR pyridoxin*.tw. OR pyridoxal.tw. OR pyridoxamine.tw. OR PLP.tw. OR pyridoxal-5-phosphate.tw. OR "vitamin B6".tw. OR biotin.tw. OR "vitamin B7".tw. OR "vitamin H".tw. OR "coenzyme R".tw. OR "folic acid".tw. OR folat*.tw. OR l-methylfolate.tw. OR 5-MTHF.tw. OR levomefolate.tw. OR "folinic acid".tw. OR leucovorin.tw. OR "vitamin B9".tw. OR cobalamin*.tw. OR cyanocobalamin.tw. OR methylcobalamin.tw. OR hydroxocobalamin.tw. OR adenosylcobalamin.tw. OR "coenzyme B12".tw. OR "vitamin B12".tw.)) AND ((exp "Drug Therapy, Combination"/ OR exp "Drug Synergism"/) OR ("combination therap*".tw. OR "combined therap*".tw. OR "combined treatment".tw. OR "combined modality therap*".tw. OR "combination regimen*".tw. OR add-on.tw. OR addon.tw. OR "add on".tw. OR co-treatment.tw. OR cotreatment.tw. OR "co treatment".tw. OR additive.tw. OR adjuvant.tw. OR augmentation.tw. OR augmentative.tw. OR "augmentation strateg*".tw.	15.10.2025	74	No filters

	OR adjunctive.tw. OR supplementation.tw. OR co-therapy.tw. OR cotherapy.tw. OR "co therapy".tw. OR co-administration.tw. OR coadministration.tw. OR "co administration".tw. OR co-intervention.tw. OR cointervention.tw. OR "co intervention".tw. OR concomitant.tw. OR booster.tw. OR "concurrent therap*".tw.))			
International Network of Agencies for Health Technology Assessment (INAHTA) database	(("Depressive Disorder" OR "Depressive Disorder, Major" OR "Dysthymic Disorder" OR "Anxiety Disorders" OR "Panic Disorder" OR "Social Anxiety Disorder" OR depressi* OR "major depressive disorder" OR MDD OR "depressive episode" OR "recurrent depressive disorder" OR "chronic depression" OR "persistent depressive disorder" OR PDD OR dysthymi* OR anxiet* OR "generalized anxiety disorder" OR GAD OR "panic disorder" OR "social anxiety" OR "mixed anxiety" AND "depressive disorder")) AND (("Antidepressive Agents" OR "Antidepressive Agents, Tricyclic" OR "Antidepressive Agents, Second-Generation" OR "Monoamine Oxidase Inhibitors" OR "Serotonin Uptake Inhibitors") OR (antidepressant* OR antidepressiv* "antidepressive agent*" OR SSRI OR "selective serotonin reuptake inhibitor*" OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin noradrenaline reuptake inhibitor*" OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR "tricyclic antidepressant*" OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR "monoamine oxidase inhibitor*" OR "monoamine oxidase A inhibitor*" OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine)) AND (("Vitamin B Complex" OR Vitamins OR "Dietary Supplements" OR Micronutrients OR "Nutritional Supplements" OR Thiamine OR Riboflavin OR Niacin OR "Pantothenic Acid" OR Pyridoxine OR Biotin OR "Folic Acid" OR Cobalamins) OR ("B vitamin*" OR "vitamin B complex" OR micronutrient* OR "nutritional supplement*" OR "vitamin supplement*" OR "dietary supplement*" OR "nutritional intervention*" OR "dietary intervention*" OR thiamin* OR thiamine OR aneurin OR "vitamin B1" OR riboflavin OR lactoflavin OR "vitamin B2" OR niacin OR nicotinamide OR "nicotinic acid" OR niacinamide OR "vitamin B3" OR pantothenic OR dexpanthenol OR "vitamin B5" OR pyridoxin* OR pyridoxal OR pyridoxamine OR PLP OR pyridoxal-5-phosphate OR "vitamin B6" OR biotin OR "vitamin B7" OR "vitamin H" OR "coenzyme R" OR "folic acid" OR folat* OR l-methylfolate OR 5-MTHF OR levomefolate OR "folinic acid" OR leucovorin OR "vitamin B9" OR cobalamin* OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR "coenzyme B12" OR "vitamin B12")) AND (("Drug Therapy, Combination" OR "Drug Synergism") OR ("combination therap*" OR "combined therap*" OR "combined treatment" OR "combined modality therap*" OR "combination regimen*" OR add-on OR addon OR "add on" OR co-treatment OR cotreatment OR "co treatment" OR additive OR adjuvant OR augmentation OR augmentative OR "augmentation strateg*" OR adjunctive OR supplementation OR co-therapy OR cotherapy OR "co therapy" OR co-administration OR coadministration OR "co administration" OR co-intervention OR cointervention OR "co intervention" OR concomitant OR booster OR "concurrent therap*"))	15.10.2025	3	No filter
WHO International Clinical Trials Registry Platform (ICTRP)	(("Depressive Disorder" OR "Depressive Disorder, Major" OR "Dysthymic Disorder" OR "Anxiety Disorders" OR "Panic Disorder" OR OR "Social Anxiety Disorder" OR depressi* OR "major depressive disorder" OR MDD OR "depressive episode" OR "recurrent depressive disorder" OR "chronic depression" OR "persistent depressive disorder" OR PDD OR dysthymi* OR anxiet* OR "generalized anxiety disorder" OR GAD OR "panic disorder" OR "social anxiety" OR "mixed anxiety" AND "depressive disorder")) AND (("Antidepressive Agents" OR "Antidepressive Agents, Tricyclic" OR "Antidepressive Agents, Second-Generation" OR "Monoamine Oxidase Inhibitors" OR "Serotonin Uptake Inhibitors") OR (antidepressant* OR antidepressiv* OR "antidepressive agent*" OR SSRI OR "selective serotonin reuptake inhibitor*" OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR "serotonin norepinephrine reuptake inhibitor*" OR "serotonin noradrenaline reuptake inhibitor*" OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR "tricyclic antidepressant*" OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR "monoamine oxidase inhibitor*" OR "monoamine oxidase A inhibitor*" OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine)) AND (("Vitamin B Complex" OR Vitamins OR "Dietary Supplements" OR Micronutrients OR	15.10.2025	11	No filter

	"Nutritional Supplements" OR Thiamine OR Riboflavin OR Niacin OR "Pantothenic Acid" OR Pyridoxine OR Biotin OR "Folic Acid" OR Cobalamins) OR ("B vitamin*" OR "vitamin B complex" OR micronutrient* OR "nutritional supplement*" OR "vitamin supplement*" OR "dietary supplement*" OR "nutritional intervention*" OR "dietary intervention*" OR thiamin* OR thiamine OR aneurin OR "vitamin B1" OR riboflavin OR lactoflavin OR "vitamin B2" OR niacin OR nicotinamide OR "nicotinic acid" OR niacinamide OR "vitamin B3" OR pantothenic OR dexpanthenol OR "vitamin B5" OR pyridoxin* OR pyridoxal OR pyridoxamine OR PLP OR pyridoxal-5-phosphate OR "vitamin B6" OR biotin OR "vitamin B7" OR "vitamin H" OR "coenzyme R" OR "folic acid" OR folat* OR l-methylfolate OR 5-MTHF OR levomefolate OR "folinic acid" OR leucovorin OR "vitamin B9" OR cobalamin* OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR "coenzyme B12" OR "vitamin B12")) AND (("Drug Therapy, Combination" OR "Drug Synergism") OR ("combination therap*" OR "combined therap*" OR "combined treatment" OR "combined modality therap*" OR "combination regimen*" OR add-on OR addon OR "add on" OR co-treatment OR cotreatment OR "co treatment" OR additive OR adjuvant OR augmentation OR augmentative OR "augmentation strateg*" OR adjunctive OR supplementation OR co-therapy OR cotherapy OR "co therapy" OR co-administration OR coadministration OR "co administration" OR co-intervention OR cointervention OR "co intervention" OR concomitant OR booster OR "concurrent therap*")			
ClinicalTrials.gov	(depression OR depressive disorder OR major depressive disorder OR MDD OR depressive episode OR recurrent depressive disorder OR chronic depression OR persistent depressive disorder OR PDD OR dysthymia OR anxiety OR anxiety disorder OR generalized anxiety disorder OR GAD OR panic disorder OR social anxiety OR mixed anxiety and depressive disorder) AND (antidepressant OR antidepressiv* OR antidepressive agent OR SSRI OR selective serotonin reuptake inhibitor OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR serotonin norepinephrine reuptake inhibitor OR serotonin noradrenaline reuptake inhibitor OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR tricyclic antidepressant OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR monoamine oxidase inhibitor OR monoamine oxidase A inhibitor OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine) AND (B vitamin OR vitamin B complex OR micronutrient OR nutritional supplement OR vitamin supplement OR dietary supplement OR nutritional intervention OR dietary intervention OR thiamine OR aneurin OR vitamin B1 OR riboflavin OR lactoflavin OR vitamin B2 OR niacin OR nicotinamide OR nicotinic acid OR niacinamide OR vitamin B3 OR pantothenic acid OR dexpanthenol OR vitamin B5 OR pyridoxine OR pyridoxal OR pyridoxamine OR PLP OR pyridoxal-5-phosphate OR vitamin B6 OR biotin OR vitamin B7 OR vitamin H OR coenzyme R OR folic acid OR folate OR vitamin B9 OR L-methylfolate OR 5-MTHF OR levomefolate OR folinic acid OR leucovorin OR cobalamin OR vitamin B12 OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR coenzyme B12) AND (combination therapy OR combined therapy OR combined treatment OR combined modality therapy OR combination regimen OR add-on OR addon OR add on OR co-treatment OR cotreatment OR co treatment OR additive OR adjuvant OR augmentation OR augmentative OR augmentation strategy OR adjunctive OR supplementation OR co-therapy OR cotherapy OR co therapy OR co-administration OR coadministration OR co administration OR co-intervention OR cointervention OR co intervention OR concomitant OR booster OR concurrent therapy)	15.10.2025	174	No filters
PROSPERO	(("Depressive Disorder" OR "Depressive Disorder, Major" OR "Dysthymic Disorder" OR "Anxiety Disorders" OR "Panic Disorder" OR "Social Anxiety Disorder" OR depressi* OR "major depressive disorder" OR MDD OR "depressive episode" OR "recurrent depressive disorder" OR "chronic depression" OR "persistent depressive disorder" OR PDD OR dysthymi* OR anxiet* OR "generalized anxiety disorder" OR GAD OR "panic disorder" OR "social anxiety" OR "mixed anxiety" AND "depressive disorder")) AND (("Antidepressive Agents" OR "Antidepressive Agents, Tricyclic" OR "Antidepressive Agents, Second-Generation" OR "Monoamine Oxidase Inhibitors" OR "Serotonin Uptake Inhibitors") OR (antidepressant* OR antidepressiv* OR "antidepressive agent*" OR SSRI OR "selective serotonin reuptake inhibitor*" OR fluoxetine OR citalopram OR escitalopram OR paroxetine OR sertraline OR fluvoxamine OR SNRI OR "serotonin	15.10.2025	41	No filter

	norepinephrine reuptake inhibitor*" OR "serotonin noradrenaline reuptake inhibitor*" OR venlafaxine OR desvenlafaxine OR duloxetine OR milnacipran OR levomilnacipran OR TCA OR "tricyclic antidepressant*" OR imipramine OR clomipramine OR trimipramine OR amitriptyline OR nortriptyline OR doxepin OR MAOI OR "monoamine oxidase inhibitor*" OR "monoamine oxidase A inhibitor*" OR phenelzine OR tranylcypromine OR moclobemide OR NaSSA OR mirtazapine OR SARI OR trazodone OR nefazodone OR NARI OR reboxetine OR NDRI OR bupropion OR vilazodone OR vortioxetine OR agomelatine)) AND (("Vitamin B Complex" OR Vitamins OR "Dietary Supplements" OR Micronutrients OR "Nutritional Supplements" OR Thiamine OR Riboflavin OR Niacin OR "Pantothenic Acid" OR Pyridoxine OR Biotin OR "Folic Acid" OR Cobalamins) OR ("B vitamin*" OR "vitamin B complex" OR micronutrient* OR "nutritional supplement*" OR "vitamin supplement*" OR "dietary supplement*" OR "nutritional intervention*" OR "dietary intervention*" OR thiamin* OR thiamine OR aneurin OR "vitamin B1" OR riboflavin OR lactoflavin OR "vitamin B2" OR niacin OR nicotinamide OR "nicotinic acid" OR niacinamide OR "vitamin B3" OR pantothenic OR dexpanthenol OR "vitamin B5" OR pyridoxin* OR pyridoxal OR pyridoxamine OR PLP OR pyridoxal-5-phosphate OR "vitamin B6" OR biotin OR "vitamin B7" OR "vitamin H" OR "coenzyme R" OR "folic acid" OR folat* OR l-methylfolate OR 5-MTHF OR levomefolate OR "folinic acid" OR leucovorin OR "vitamin B9" OR cobalamin* OR cyanocobalamin OR methylcobalamin OR hydroxocobalamin OR adenosylcobalamin OR "coenzyme B12" OR "vitamin B12")) AND (("Drug Therapy, Combination" OR "Drug Synergism") OR ("combination therap*" OR "combined therap*" OR "combined treatment" OR "combined modality therap*" OR "combination regimen*" OR add-on OR addon OR "add on" OR co-treatment OR cotreatment OR "co treatment" OR additive OR adjuvant OR augmentation OR augmentative OR "augmentation strateg*" OR adjunctive OR supplementation OR co-therapy OR cotherapy OR "co therapy" OR co-administration OR coadministration OR "co administration" OR co-intervention OR cointervention OR "co intervention" OR concomitant OR booster OR "concurrent therap*"))			

Appendix A2: Reasons for exclusion of studies after full-text screening

NO.	AUTHOR (YEAR)	STUDY TITLE	REASON FOR EXCLUSION
1	Almeida et al. (2010)	B-Vitamins Reduce the Long-Term Risk of Depression After Stroke: The VITATOPS-DEP Trial	Wrong population (with/without antidepressants)
2	Andreeva et al. (2012)	Supplementation with B vitamins or n23 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids (SU.FOL.OM3) randomized trial	Wrong population (no clinical diagnosis of depression or anxiety; with/without antidepressants)
3	Christensen et al. (2010)	No clear potentiation of antidepressant medication effects by folic acid+vitamin B12 in a large community sample	Wrong population (participants with a high likelihood of depressive symptoms were excluded)
4	Ford et al. (2010)	The B-VITAGE trial: a randomized trial of homocysteine lowering treatment of depression in later life	Wrong study design (= study protocol)
5	Klemp et al. (2010)	B vitamin supplementation in treating depression	Wrong population (with/without antidepressants)
6	Lewis et al. (2013)	The effect of methylated vitamin B complex on depressive and anxiety symptoms and quality of life in adults with depression	Wrong population (with/without antidepressants)
7	Okereke et al. (2015)	Effect of long-term supplementation with folic acid and B vitamins on risk of depression in older women	Wrong population (no clinical diagnosis of depression)
8	Skarupski et al. (2010)	Longitudinal associations of vitamin B-6, folate and vitamin B-12 with depressive symptoms among older adults over time	Wrong study design (No experimental design)

Appendix A3: Documentation of author contact

Reference, date of contact	Date of response	Final status	Comments / responses
Bell et al. (1992), 18 Oct 2025	No response	Data extraction, RoB 2.0 assessment performed	Old study, pre-registration era
Kuchya et al. (2016), 30 Oct 2025	Yes 30 Oct 2025	Data extraction, RoB 2.0 assessment performed	No additional information included.
Unneh et al. (2025), 29 Oct 2025	No response	Data extraction, RoB 2.0 assessment performed	
Gopalakrishnan et al. (2024), 28 Oct 2025	No response	Data extraction, RoB 2.0 assessment performed	

Appendix A4: Review of authors' judgements about each risk of bias item

Risk of Bias Domain	Author's judgement
ALMEIDA ET AL. (2014)	
1: Randomisation process	Computer-generated randomisation was carried out by the hospital's pharmacy. Allocation was concealed (pharmacy dispensed identical vitamins and placebo), manufactural institute stated. Groups were well balanced for most measured variables; baseline tHcy was higher in the vitamin group (Table 1; $p \approx 0.039$) with no clear indication of randomisation failure.
2: Deviations from the intended interventions	Investigators and participants remained masked to treatment assignment and to biochemical results until final data collection. Analyses were performed according to the intention-to-treat principle.

3: Missing outcome data	All participants were included in ITT.
4: Measurement of the outcome	The study authors used an appropriate and validated tool. All participants were assessed at the same pre-specified time points. Outcomes assessors were blinded until the final collection.
5: Selection of the reported result	Protocol was retrospectively registered. No information on statistical analysis plan in protocol.
BELL ET AL. (1992)	
1: Randomisation process	Authors state randomisation was performed, no description of random-sequence generation. No description of allocation concealment. Authors report "no significant baseline differences".
2: Deviations from the intended interventions	The study was reported as double-blind. No information on ITT, but all randomised participants were included in the analysis. One participant changed to a different TCA with another active substance. No trial protocol is available, but this change can be judged as usual treatment of consequences.
3: Missing outcome data	All participants were included in the analysis. However, since missing values were dropped without reporting information on imputation or sensitivity analysis and given the very small sample size (n=14), bias due to missing outcome data cannot be ruled out.
4: Measurement of the outcome	A validated outcome measure was used, and assessments were conducted uniformly in a hospital setting. Blinding of outcome assessors was not reported, and although there is no evidence of bias, observer-reported outcomes inherently involve some degree of judgement, so bias cannot be ruled out.
5: Selection of the reported result	No trial registration or pre-specified analysis plan was reported. Analysis intentions are not available.
KUCHYA ET AL. (2016)	
1: Randomisation process	Authors state randomisation was performed, no description of random-sequence generation. No description of allocation concealment. Only age and sex reported as baseline values. Authors state "equal age distribution", but statistics show p-value <0.05. The sex distribution was comparable in both study arms (control 1:1.7, intervention 1:1.63).
2: Deviations from the intended interventions	The study was open label with no blinding of participants or personnel, and no evidence of deviations from assigned interventions. Although ITT was not reported, all randomised participants were analysed.
3: Missing outcome data	All randomised participants were included in the analysis and tables suggest complete data for all randomised participants.
4: Measurement of the outcome	The study authors used an appropriate and validated tool. Blinding of outcome assessors was not reported, and although there is no evidence of bias, observer-reported outcomes inherently involve some degree of judgement, so bias cannot be ruled out.
5: Selection of the reported result	No trial registration or pre-specified analysis plan was reported. Analysis intentions are not available.
UNNEH ET AL. (2025)	
1: Randomisation process	Randomisation was computer-generated. Amber, serially labelled bottles used. The consistently high p-values (≈1) across baseline variables indicate excessive similarity between groups, which is interpreted as by chance.
2: Deviations from the intended interventions	The study was open-label with no blinding of participants or personnel. The co-interventions (counseling sessions and individualised lifestyle advice), which were not provided to the control group, are likely to influence depression outcomes due to lack of blinding and absence of a prespecified protocol. Although ITT was not reported, all randomised participants were analysed.
3: Missing outcome data	All randomised participants were included in the analysis and tables suggest complete data for all randomised participants.
4: Measurement of the outcome	The study authors used an appropriate and validated tool. Depressive symptoms were self-reported, patients were not blinded and knowledge of the assigned intervention likely influenced outcomes.
5: Selection of the reported result	No trial registration or pre-specified analysis plan was reported. Analysis intentions are not available.
GOPALKRISHNA ET AL. (2024)	
1: Confounding	The study used no adjustment for confounders. Only a few baseline variables were measured. Several important confounders were unmeasured.

2: Selection of participants into the study	Selection of participants was completed before the start of the intervention. There is no indication of delayed or staggered follow-up periods.
3: Classification of interventions	Group assignments were determined before the intervention began.
4: Deviations from intended interventions	There was no evidence on deviations from intended interventions.
5: Missing outcome data	All participants were included in the analysis.
6: Measurement of outcomes	Open-label design with unblinded outcome assessors, and although there is no evidence of systematic error, the outcome measure is not an objective tool.
7: Selection of the reported result	The absence of a pre-specified analysis plan or study protocol means that selective reporting of analyses cannot be ruled out.

Appendix A5: Data Extraction Sheets

Data extraction sheets are based on the Good Practice Data Extraction Form published by Cochrane's Effective Practice and Organisation of Care (EPOC) group and adapted to the needs of the review (n.d). For abbreviations see List of Abbreviations.

GENERAL INFORMATION	
Date of extraction	23/09/2025
Performed by	Susanne Fasching
Reference	**Almeida, O. P., Ford, A. H., Hirani, V., Singh, V., vanBockxmeer, F. M., McCaul, K., & Flicker, L. (2014). B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. The British journal of psychiatry : the journal of mental sci-ence, 205(6), 450–457. https://doi.org/10.1192/bjp.bp.114.145177**
Publication status	Published
Publication type	Full report
Country	Australia
Conflict of interest	No conflict of interest declared by the authors.
Funding	Funded by the NHMRC (grant no. 572594); funder had no role in design, conduct, analysis, interpretation, or reporting.
POPULATION AND SETTING	
Description	Middle-aged adults with depression, recruited from the community.
Setting	At home setting.
Inclusion/exclusion criteria for participation in the study	Inclusion: adults ≥50 yrs., MDE in context to MDD (single episode/recurrent) according to DSM-IV-TR criteria, MADRS score ≥20, fluent in English (written/spoken), AUDIT ≤ 15, MMSE ≥24 Exclusion: history of stroke, neurodegenerative or severe/life-threatening illness (<1yr. survival), psychosis, suicidality, schizophrenia, schizoaffective or bipolar disorder, allergy to citalopram/escitalopram, current antidepressant use, or electroconvulsive therapy.
Methods of participant recruitment	Participants were recruited via the Australian electoral roll using mailed study information and a PHQ-9 screening questionnaire, with additional referrals provided by local general practitioners (n=35). Adults who returned the screening questionnaire and scored ≥10 on the PHQ-9 and ≤15 on the AUDIT were invited to a face-to-face diagnostic assessment at the Royal Perth Hospital using the MINI interview in line with DSM-IV-TR criteria.
Informed consent (Yes/No/Unclear)	Yes.
METHODS	
Aim of study	To assess whether supplementation with vitamins B6, B12, and folic acid improves the effectiveness of antidepressant therapy over one year
Study Design	Parallel, randomised, double-blind controlled trial
Unit of allocation	By individuals
Participation duration	52 weeks
Ethical approval	Approved by: Human Ethics Committee of the Royal Perth Hospital
PARTICIPANTS	
Total no. randomised	153
Baseline imbalances	Groups comparable, except for homocysteine levels ($p = 0.039$).
Withdrawals and exclusions	Withdrawals due to loss to follow-up assumed as random occurrence, no exclusions or dropouts reported.

Age (mean)	Intervention group: 63.4 years (SD 8.2) Control group: 61.7 years (SD 7.4)
Gender distribution	Intervention group: 38 females (63.2%) Control group: 48 females (49.3%)
Type of disorder	Depression
Baseline symptom severity	Intervention group: MADRS median 26 (IQR 24-31) Control group: MADRS median 27 (22-32)
Co-morbidities	Intervention group: cardiovascular diseases (n=9, 11.7%), chronic respiratory diseases (n=15, 19.5%), diabetes (n=10, 13.0%), hearing impairment (n= 16, 20.8%) Control group: cardiovascular diseases (n=11, 14.5%), chronic respiratory diseases (n= 19, 25.0%), diabetes (n=8, 10.5%), hearing impairment (n=16, 21.0%)
Past diagnosis of depression/anxiety	Intervention group: n= 59, 77.6% Control group: n= 58, 76.3%
Other treatment received (add. to study intervention)	NR
Subgroups measured	Age, gender, plasma homocysteine, red cell folate, serum B12.
Subgroups reported	Baseline tHcy, red cell folate, serum B12
INTERVENTION GROUP	
Group name	Vitamins group
No. randomised to group	N= 77 participants
Description	Participants received citalopram + 0.5mg of vitamin B12, 2mg of folic acid and 25mg of vitamin B6. Citalopram: starting dose 10 mg/day, increased to 20 mg after 2 weeks; flexible adjustment up to max. 40 mg by weeks 4 and 8.
Duration of treatment	Vitamins maintained for 52 weeks.
Timing	Vitamins administered as one daily capsule after breakfast.
Delivery	Vitamins dispensed by hospital pharmacy at baseline, 4, 8, 12, and 26 weeks.
Providers	Guidance in dosage of citalopram by certified psychiatrist. After 12 weeks guidance by GPs.
Co-interventions	NR
Integrity of delivery	NR
Compliance	Objective measures of adherence included blood tests and pill count; participants who took ≥75% of prescribed tablets were considered adherent.
CONTROL GROUP	
Group name	Placebo group
No. randomised to group	N= 76 participants
Description	Participants received citalopram + placebo (identical size, shape, colour, texture, smell, taste as vitamins). Citalopram: starting dose 10 mg/day, increased to 20 mg after 2 weeks; flexible adjustment up to 40 mg by week 8.
Duration of treatment	Placebo maintained for 52 weeks.
Timing	Placebo administered as one daily capsule after breakfast.
Delivery	Placebo dispensed by hospital pharmacy at baseline, 4, 8, 12, and 26 weeks.
Providers	Guidance in dosage of citalopram by certified psychiatrist. After 12 weeks guidance by GPs.
Co-interventions	NR
Compliance	Participants received instructions not to use vitamin supplements during the study. Objective measures of adherence included blood tests and pill count; participants who took ≥75% of prescribed tablets were considered adherent. Participants kept a medication diary during the study (record of all medications/day).
OUTCOMES	
Primary outcome: change in symptom severity	
Outcome name	Change in MADRS score
Timing	Measured from start of intervention. Reported baseline and after 4, 8,12, 26 and 52 weeks
Outcome definition	Mean change in MADRS scores (desirable)
Unit of measurement Scales	Unit of measurement: MADRS score Scales (upper/lower limits): NR
Person measuring	NR
Is outcome/tool validated?	Yes (according to reference cited no. 31)
Imputation of missing data	Outcomes analysed as panel data. ITT analysis including all available observations. No assumptions about missing data; authors assumed loss to follow-up occurred at random (MAR).
Assumed risk estimate	MADRS median 27 (IQR 22-32)
Power	NA
Secondary outcome: response rate	
Outcome name	Response rate
Timing	Measured from start of intervention. Reported weeks 4, 8 and 12.
Outcome definition	Reduction of 50% in baseline symptom scores

Unit of measurement	Unit of measurement: MADRS. Scales (upper/lower limits): NR					
Person measuring	NR					
Is outcome/tool validated?	Yes (according to reference cited no. 35).					
Imputation of missing data	Outcomes analysed as panel data. ITT analysis including all available observations. No assumptions about missing data; authors assumed loss to follow-up occurred at random (MAR).					
Assumed risk estimate	MADRS median 27 (IQR 22-32)					
Power	NA					
Secondary outcome: remission rate						
Outcome name	Remission of MDE					
Timing	Measured from start of intervention. Reported weeks 12, 26 and 52.					
Outcome definition	Remission according to DSM-IV-TR (binary outcome, desirable)					
Unit of measurement	Unit of measurement: MINI assessment. Scales (upper/lower limits): NR					
Person measuring	NR					
Is outcome/tool validated?	Yes (according to reference cited no. 35).					
Imputation of missing data	ITT analysis using panel data models including all available observations. No imputation performed; authors assumed loss to follow-up occurred at random (MAR).					
Assumed risk estimate	NA					
Power	80% at n = 310 planned; reduced n mitigated by repeated measures / ITT (power calculation was based on remission as the trial's original primary outcome, not on the primary outcome of this review). Only 153 randomised. Additional follow-up points (26 & 52 weeks) added to mitigate power loss via panel-data modelling.					
Secondary outcome: adverse events						
Outcome name	Adverse effects at any time.					
Timing	Measured from start of intervention. Reported weeks 4, 8, 12, 26, 52; baseline complaints not attributed to treatment.					
Outcome definition	Adverse effects questioned included "tremor of the hands, muscle stiffness, involuntary muscle contractions, muscle cramps, feeling of pins and needles in the body, difficulty concentrating, agitation or restlessness, irritability, dizzy of faint, headache, other pain, arthritis orpain in the joints, nausea, diarrhoea, constipation, vomiting, anorexia, weight loss, weight gain, skin rash, nightmares, excessive somnolence, poor sleep, palpitations, dry mouth, others (e.g. delayed ejaculation or anorgasmia (binary outcome, undesirable)"; p. 451-452					
Unit of measurement Scales: upper and lower limits	Unit of measurement: 4-point severity scale, face-to-face assessments Scales (upper/lower limits): "not at all" (best) or "a little" or "quite a bit" or "a lot" (worst)					
Person measuring	NR					
Is outcome/tool validated?	NR					
Imputation of missing data	ITT analysis using panel data models including all available observations. No imputation performed; authors assumed loss to follow-up occurred at random (MAR).					
Assumed risk estimate	NA					
Power	NA					
Other reported outcomes (not extracted)	Relapse of major depressive symptoms following remission by 12 weeks (26 and 52 weeks), change from citalopram to another antidepressant, adherence to citalopram/vitamins, blood samples (changes in tHcy, red cell, folate, serum B12 relative to baseline)					
RESULTS						
Primary outcome: change in MADRS score						
Comparison	Citalopram + B vitamins vs. citalopram + placebo					
Outcome	Mean changes of MADRS scores over time					
Subgroup	NR					
Time point	Weeks 4, 8, 12, 26, 52 (graphical presentation) from start of intervention					
Post intervention/ change from baseline?	Change from baseline					
Results Change from baseline (Adjusted for baseline MADRS and gender)	Intervention			Comparison		
	Mean	SD	No. pts.	Mean	SD	No. pts.
	Fig. 2	Fig. 2	Fig. 2	Fig. 2	Fig. 2	Fig. 2
Baseline data	Intervention			Comparison		
	Mean	IQR	No. pts.	Mean	IQR	No. pts
	26	24-31	77	27	22-32	76
No. missing participants and reasons	15/77 lost during follow up in intervention group.			10/76 lost during follow up in control group.		
Other results	Mean difference –0.4 MADRS points (95% CI –2.6 to 1.8, z = –0.74, p = 0.739).					
Statistical methods used	Xtmixed (multilevel mixed-effects linear regression) for change in MADRS over time					

RESULTS				
Secondary outcome: response rate				
Comparison	Citalopram + B vitamins vs. citalopram + placebo			
Outcome	reduction of 50% in MADRS baseline symptom scores			
Subgroup	NR			
Time point	Week 4, 8, 12 from start of intervention			
Post intervention/ change from baseline?	Change from baseline			
Results (Adjusted for gender and baseline tHcy) 1. week 4 2. week 8 3. Week 12	Intervention		Comparison	
	No. events	No. pts	No. events	No. pts
	34 46 47	73 72 73	38 56 56	74 73 73
Baseline data	Intervention		Comparison	
	No. events	No. pts.	No. events	No. pts.
	NA	NA	NA	NA
Missing participants	Missing participants due to loss to follow-up.		Missing participants due to loss of follow-up.	
Any other results reported	Effect of vitamins between group: OR = 0.59 (95% CI 0.28-1.25). Adjusted for gender and baseline tHcy.			
Statistical methods used	Binary outcomes analysed with xtlogit (= panel logistic regression model for dichotomous outcomes with repeated measures, OR, 95% CI).			
RESULTS				
Secondary outcome: remission of MDE				
Comparison	Citalopram + B vitamins vs. citalopram + placebo			
Outcome	Remission of MDE			
Subgroup	Baseline tHcy			
Time point	Week 12, 26, 52 from start of intervention			
Results Post intervention 1. week 12 2. week 26 3. Week 52 (Adjusted for gender and baseline tHcy)	Intervention		Comparison	
	No. events	No. pts.	No. events	No. pts.
	58 58 53	73 68 62	57 52 50	73 68 66
Baseline data	Intervention		Comparison	
	No. events	No. pts.	No. events	No. pts.
	NA	NA	NA	NA
Missing participants	Missing participants due to loss to follow-up.		Missing participants due to loss of follow-up.	
Any other results reported	Week 12: OR 1.55 (95% CI 0.64–3.72) Week 26: OR 2.32 (95% CI 0.91–5.97) Week 52: OR 2.54 (95% CI 0.94–6.80) Adjusted for gender and tHcy. Effect of vitamins between group: OR 2.49 (95% CI 1.12–5.51). No significant time-group interaction, ARR 6.5%, NNT 16 (33 in worst-case scenario). Subgroup (high tHcy): OR 3.47 (95% CI 1.22–9.84).			
Statistical methods	Binary outcomes analysed with xtlogit (= panel logistic regression model for dichotomous outcomes with repeated measures, OR, 95% CI)			
RESULTS				
Secondary outcome (2): adverse effects at any time				
Comparison	Citalopram + B vitamins vs. citalopram + placebo			
Outcome	Adverse effects (≥5% prevalence, binary, not desirable)			
Time point	Weeks 4, 8, 12, 26, 52 from start of intervention			
Adverse effect	Intervention (events/n)	Comparison (events/n)	Effect estimate (95% CI)	
Tremor	7/65	6/72	OR 1.33 (95% CI 0.42–4.18)	
Agitation, anxiety	9/30	10/35	OR 1.07 (95% CI 0.37–3.13)	
Headache	10/50	16/63	OR 0.74 (95% CI 0.30–1.80)	
Nausea	4/66	7/71	OR 0.59 (95% CI 0.16–2.12)	
Diarrhoea	7/64	4/70	OR 2.03 (95% CI 0.56–7.28)	
Constipation	8/61	8/63	OR 1.04 (95% CI 0.36–2.97)	
Nightmares	11/59	7/61	OR 1.77 (95% CI 0.63–4.92)	
Dry mouth	19/54	14/63	OR 1.90 (95% CI 0.84–4.29)	
Sexual	12/74	8/72	OR 1.55 (95% CI 0.59–4.05)	
Other results	NR			

Statistical methods	Binary outcomes analysed with xtlogit (= panel logistic regression model for dichotomous outcomes with repeated measures, OR, 95% CI).

GENERAL INFORMATION	
Date of extraction	27/10/2025
Performed by	Susanne Fasching
Reference	**Bell, I. R., Edman, J. S., Morrow, F. D., Marby, D. W., Perrone, G., Kayne, H. L., Greenwald, M., & Cole, J. O. (1992). Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction. Journal of the American College of Nutrition, 11(2), 159–163.**
Publication status	Published
Publication type	Brief communication
Country	United States of America
Conflict of interest	NR
Funding	Supported in part by a grant from the Charles H. Farnsworth Trust, Boston, MA, and by the USDA–Agricultural Research Service, Contract No. 53-3K06-5-10.
POPULATION AND SETTING	
Description	Geriatric patients recruited from the hospital setting.
Setting	McLean Geriatric Inpatient Service
Inclusion/exclusion criteria for participation in the study	Inclusion: hospitalised nonalcoholic inpatient volunteers meeting DSM-III-R criteria for major depression or bipolar depression, MMSE ≥16, had to be medically stable inpatients eligible for open trial of the secondary-amine tricyclic antidepressant nortriptyline as part of clinical treatment
Methods of participant recruitment	Hospitalised geriatric patients identified during inpatient clinical care. No further information.
Informed consent (Yes/No/Unclear)	Unclear
METHODS	
Aim of study	The study aimed to evaluate, under double-blind and placebo-controlled conditions, whether adding vitamins B_1, B_2, and B_6 at approximately 5–8 times the recommended dietary allowance could enhance depressive and cognitive outcomes in older adults receiving standard tricyclic antidepressant therapy for depression.
Study Design	Randomised, double-blind, placebo-controlled trial.
Unit of allocation	By individuals
Participation duration	4 weeks
Ethical approval	NR
PARTICIPANTS	
Total no. randomised	14
Baseline imbalances	Authors state "so significant baseline differences in age, gender distribution, martial status, education, weight differential from age-appropriate standard weights between groups" (p. 160). Table 1 and 2: no significant baseline imbalances were observed between groups in blood vitamin enzyme activity coefficients, depression severity (MADRS), or cognitive performance (MMSE, Buschke test, serum nortriptyline. No tabular presentation of participant characteristics.
Withdrawals & exclusions	Two excluded (1 suicide attempt; 1 switched to lithium due to bipolar diagnosis, not included in data analyses) before randomisation; one switched to desipramine remained in analysis.
Age (mean)	Mean Age 75 ± 7 Jahre Intervention group: NR Control group: NR
Gender distribution	3 Males, 11 Females Intervention group: NR Control group: NR
Type of disorder	Depression
Baseline symptom severity	Intervention group: MADRS median 28 (SD 3.7) Control group: MADRS median 25 (SD 7.9)
Co-morbidities	Some patients are diagnosed with definite or possible dementia at discharge (2/8 intervention; 3/6 control). No further information on co-morbidities.
Past diagnosis of depression/anxiety	NR
Other treatment received (add. to study intervention)	Adjunctive medications (excl. B vitamins) were allowed and recorded (NR); clinical treatment aside from vitamin/placebo administration was not standardised for ethical and practical reasons as stated. Concomitant use included perphenazine (1/6 placebo, 2/8 active; p = 1.0) and benzodiazepines (3/6 placebo, 7/8 active; p = 0.24).
Subgroups measured	NR

Subgroups reported	NR
INTERVENTION GROUP	
Group name	Active group
No. randomised to group	N= 8 participants
Description	TCA was titrated clinically into the therapeutic range (50–150 ng/ml) in 10–25 mg increments as tolerated. Participants received opaque capsules containing vitamin B_1 10 mg, B_2 10 mg, and B_6 10 mg.
Duration of treatment	Vitamins maintained for 28 days.
Timing	Vitamins administered twice daily in divided doses (9 a.m. and 5 p.m.).
Delivery	NR
Providers	NR
Co-interventions	NR
Compliance	NR
CONTROL GROUP	
Group name	Placebo group
No. randomised to group	N= 6 participants
Description	TCA was titrated clinically into the therapeutic range (50–150 ng/ml) in 10–25 mg increments as tolerated. Participants received opaque capsules containing lactose.
Duration treatment period	Placebo maintained for 28 days.
Timing	Placebo administered twice daily (9 a.m. and 5 p.m.).
Delivery	NR
Providers	NR
Co-interventions	NR
OUTCOMES	
Primary outcome: change in symptom severity	
Outcome name	Change in MADRS score
Timing	Measured from start of intervention. Reported baseline and after 1, 2, 3 and 4 weeks
Outcome definition	Mean change in MADRS scores (desirable)
Unit of measurement Scales	Unit of measurement: MADRS score. Scales (upper/lower limits): Each item (n= 10) is scored from 0 to 6, with higher scores reflecting more severe depressive symptoms.
Person measuring	NR
Is outcome/tool validated?	Yes (according to reference cited no. 14).
Imputation of missing data	NR
Assumed risk estimate	Baseline MADRS 28.0 (SD 3.7) in the active group.
Power	NR
Secondary outcome: Cognitive Outcomes	
Outcome name	Change in MMSE
Timing	Measured from start of intervention. Reported baseline and after 1, 2, 3 and 4 weeks
Outcome definition	Cognitive dysfunction
Unit of measurement	Unit of measurement: MMSE score. Scales (upper/lower limits): maximum score of 30; higher scores indicate better cognition.
Person measuring	NR
Is outcome/tool validated?	Yes (according to reference cited no. 14).
Imputation of missing data	NR
Assumed risk estimate	Baseline MMSE 24.8 (SD 5.9) in the intervention group.
Power	NR
Secondary outcome: Cognitive Outcomes	
Outcome name	Free recall subtest of the Buschke Memory Test
Timing	Measured from start of intervention. Reported baseline and after 1, 2, 3 and 4 weeks
Outcome definition	Free recall subtest of the Buschke Memory Test
Unit of measurement Scales: upper and lower limits	Unit of measurement: Buschke Memory Test. Scales (upper/lower limits): "requires subjects to recall as many words as possible from a 10-word list of items presented one at a time on pre-printed cards; higher scores indicate better uncued immediate memory" (p.160). Maximum score = 10.
Person measuring	NR
Is outcome/tool validated?	Yes (according to reference cited no. 20).
Imputation of missing data	NR
Assumed risk estimate	Baseline BUSCHKE 4.5 (SD 2.8) in the intervention group.
Power	NR
Other reported outcomes (not extracted)	Total protein, albumin, weight, blood vitamins, NTP levels.
RESULTS	
Primary outcome: change in MADRS score	

Comparison	TCA + B vitamins vs. TCA + placebo					
Outcome	Change in MADRS score (mean difference between current weeks's score and baseline value)					
Subgroup	NR					
Time point	Weeks 1, 2, 3, 4 from start of intervention					
Post intervention/change baseline?	Change from baseline					
Results (change scores)	Intervention			Comparison		
	Mean	SD	No. subjects	Mean	SD	No. subjects
Week 1	-3.4	3.7	8	-1.0	4.7	6
Week 2	-6.3	5.1	8	-3.8	7.2	6
Week 3	-7.9	5.9	8	-6.6	6.4	6
Week 4	-12.4	6.2	8	-7.4	7.9	6
Baseline data	Intervention			Comparison		
	Mean	SD	No. partici-pants	Mean	SD	No. participants
	28	3.7	8	25.3	7.9	6
Missing participants	NA (no loss to follow-up reported)			NA (no loss to follow-up reported)		
Other results reported	NR					
Statistical methods	Two tailed t-tests for measures but change scores (one-tailed, potentially problematic). Miss-ing values were dropped from individual analyses.					
RESULTS						
Secondary outcome: Cognitive outcomes						
Comparison	Nortriptyline + B vitamins vs. Nortriptyline + placebo					
Outcome	Change in MMSE (mean difference between current weeks' score and baseline value)					
Subgroup	NR					
Time point	Weeks 1, 2, 3, 4 from start of intervention					
Post intervention/change baseline?	Change from baseline					
Results (change scores)	Intervention			Comparison		
	Mean	SD	No. subjects	Mean	SD	No. subjects
Week 1	0.43	2.0	8	0.83	2.4	6
Week 2	0.38	1.8	8	-0.17	3.3	6
Week 3	1.1	2.9	8	0.40	3.4	6
Week 4	1.8	2.7	8	-1.8	5.5	6
Baseline data	Intervention			Comparison		
	Mean	SD	No. subjects	Mean	SD	No. participants
	24.8	5.9	8	23.7	4.3	6
Missing participants	NA (no loss to follow-up reported)			NA (no loss to follow-up reported)		
Other results reported	NA					
Statistical methods	Two tailed t-tests for measures but change scores (one-tailed, potentially problematic). Miss-ing values were dropped from individual analyses.					
RESULTS						
Secondary outcome: Cognitive outcomes						
Comparison	TCA + B vitamins vs. TCA + placebo					
Outcome	Change in BUSCHKE (mean difference between current week's score and baseline value)					
Subgroup	NA					
Time point	Weeks 1, 2, 3, 4 from start of intervention					
Post intervention/change baseline?	Change from baseline					
Results (Change scores)	Intervention			Comparison		
	Mean	SD	No. subjects	Mean	SD	No. subjects
Week 1	-0.20	1.1	8	-0.50	1.8	6
Week 2	-0.20	1.5	8	-0.67	1.6	6
Week 3	0.75	0.96	8	0.8	1.5	6
Week 4	1.3	2.1	8	-0.25	1.5	6
Baseline data	Intervention			Comparison		
	Mean	SD	No. Subjects	Mean	SD	No. participants
	4.5	2.8	8	3.8	1.9	6
Missing participants	NA (no loss to follow-up reported)			NA (no loss to follow-up reported)		
Other results reported	NA					
Statistical methods	Two tailed t-tests for measures but change scores (one-tailed, potentially problematic). Miss-ing values were dropped from individual analyses.					

GENERAL INFORMATION	
Date of extraction	03/11/2025
Performed by	Susanne Fasching
Reference	**Gopalakrishnan, V. V., Parameshwaraiah, S. T., Sannappa, A. C., Malyam, V., Channaveeradevaru, C., Ghanate, G., & Tiwary, S. (2024). Impact of supplementation of vitamin B12 and folic acid on treatment outcomes in persons with depression: A comparative study. The Journal of Medical Sciences, 10(1–4). https://doi.org/10.5005/jp-journals-10045-00249**
Publication status	Published
Publication type	Full report
Country	India
Conflict of interest	No conflict of interest declared by the authors.
Funding	Grant from Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India.
POPULATION AND SETTING	
Population description	Outpatients who were diagnosed with depression.
Setting	Psychiatry Department and Central Research Lab of RajaRajeswari Medical College and Hospital, Bengaluru, Karnataka, India and a laboratory in Bengaluru.
Inclusion/exclusion criteria for participation in the study	Inclusion criteria: adults aged 18–60 years (all genders) with a first episode of unipolar or bipolar depressive disorder diagnosed according to ICD-10; drug-naïve at enrolment; depression severity assessed using HAM-D. Exclusion criteria: patients with altered sensorium; comorbid psychotic disorders; hypothyroidism, anaemia, renal failure, hypertension, diabetes, pregnancy, or on hormonal therapy; and those with alcohol use.
Methods of participant recruitment	Participants were recruited from the psychiatry outpatient clinic.
Informed consent (Yes/No/Unclear)	Yes.
METHODS	
Aim of study	To evaluate the effect of vitamin B12 and folic acid supplementation on treatment outcomes in individuals with depression compared with those who did not receive supplementation.
Study Design	Prospective open-labelled comparative study.
Unit of allocation	By individuals
Participation duration	3 months
Ethical approval	Obtained ethical committee clearance.
PARTICIPANTS	
Total no. randomised	N= 56
Baseline imbalances	No significant differences.
Withdrawals and exclusions	NR
Age (mean)	Intervention group: 35.07 ± 11.01 years Control group: 34.82 ± 12.12 years
Gender distribution	Intervention group: 20 females, 8 males Control group: 19 females, 9 males
Type of disorder	Depression
Baseline symptom severity	Intervention group: HAM-D score: 21.18 ± 6.04 Control group: HAM-D score: 19.93 ± 2.29
Co-morbidities	Intervention group: NR Control group: NR
Past diagnosis of depression/anxiety	Intervention group: NR Control group: NR
Other treatment received (add. to study intervention)	NR
Subgroups measured	NR
Subgroups reported	NR
INTERVENTION GROUP	
Group name	With supplementation (group II)
No. randomised to group	N= 28 participants
Description	Treatment with escitalopram (10mg) + vitamin B12 (1500µg) + folic acid (5mg)
Duration of treatment	Treatment maintained for 3 months.
Timing	Tablets administered once daily.
Delivery	NR
Providers	NR

Co-interventions	NR					
Compliance	NR.					
CONTROL GROUP						
Group name	Group I (no supplementation)					
No. randomised to group	N= 28 participants					
Description	Participants received escitalopram 10mg tablets.					
Duration of treatment	Treatment maintained for 3 months.					
Timing	NR					
Delivery	NR					
Providers	NR					
Co-interventions	NR					
Compliance	NR					
OUTCOME						
Primary outcome: change in symptom severity						
Outcome name	Change in HAM-D score.					
Timing	Measured from start of intervention. Reported baseline and after 3 months.					
Outcome definition	Remission of depressive symptoms scores (desirable).					
Unit of measurement Scales	Unit of measurement: HAM-D score. Scales (upper/lower limits): NR					
Person measuring	NR					
Is outcome/tool validated?	Yes (according to reference no. 13)					
Imputation of missing data	NR					
Assumed risk estimate	Baseline HAM-D score: 19.93 ± 2.29					
Power	NR					
Other reported outcomes (not extracted)	Blood levels (folate, vitamin B12, homocysteine)					
RESULTS						
Primary outcome: change in symptom severity						
Comparison	Escitalopram + B vitamins vs. escitalopram alone					
Outcome	Change of HAM-D scores over time					
Subgroup	NR					
Time point	3 months					
Post intervention/change from baseline?	Change from baseline					
Results Change from baseline.	Intervention			Comparison		
	Mean	SD	No. pts.	Mean	SD	No. pts.
	5.93	3.16	28	13.79	3.71	28
Baseline data	Intervention			Comparison		
	Mean	IQR	No. pts.	Mean	IQR	No.pts.
	21.18	NR	28	19.93	NR	28
No. missing participants	NA (no loss to follow-up)			NA (no loss to follow-up)		
Other results reported	Change in blood levels.					
Statistical methods	Unpaired t-test for comparing continuous outcomes between two independent groups. Table 3 is labelled as a correlation analysis, but no correlation coefficients (e.g., Pearson or Spearman) were reported.					
GENERAL INFORMATION						
Date of extraction	10/11/2025					
Performed by	Susanne Fasching					
Reference	**Kuchya, S., Gedam, S., & Lakhwani, L. (2016). Role of vitamin B supplementation with fluoxetine in treatment of depression: A randomized controlled clinical trial. International Journal of Medical Research and Review, 4(1), 90–96. https://europub.co.uk/articles/-A-227496**					
Publication status	Published					
Publication type	Full report					
Year of Publication	2016					
Country	India					
Conflict of interest	No conflict of interest declared by the authors.					
Funding	"Nil"					
POPULATION AND SETTING						
Description	Outpatients who were newly diagnosed with depression.					
Setting	Department of Psychiatry at MGM medical college and MY hospital Indore, outpatient clinics.					
Inclusion/exclusion criteria for participation in the study	Inclusion: psychiatrist's diagnosis for moderate to severe depression (ICD-10 criteria & HDRS ≥14) > 2 weeks, patients 18-65 yrs old,					

	Exclusion: psychotic symptoms; pregnancy/lactation; recent antidepressant/fluoxetine use (<5 weeks); need for ECT; untreated hypertension (BP ≥ 150/90); renal, cardiac, diabetic, or liver disease; fluoxetine contraindication; inability for adequate follow-up.
Methods of participant recruitment	Open-ended recruitment from outpatient clinic: first fluoxetine-only group, later fluoxetine + vitamin B.
Informed consent obtained (Yes/No/Unclear)	Yes.
METHODS	
Aim of study	"To explore the change in antidepressant efficacy of Fluoxetine with vitamin B supplementation." (p.90)
Study Design	"Single centre, open label, active controlled, parallel, and single period 8- week study." (p.90)
Unit of allocation	By individuals
Participation duration	8 weeks
Start/End point	NR
Ethical approval	Approval of study protocol by the Ethics Review Committee of MGMC medical college and MY hospital Indore.
PARTICIPANTS	
Total no. randomised	N= 53
Baseline imbalances	Unequal age distribution, equal gender distribution.
Withdrawals and exclusions	NR
Age (mean)	Intervention group: 35.68 years (SD 9.86) Control group: 39.66 years (SD 9.83)
Gender distribution	Intervention group: 18 females, 11 males (Ratio 1.0:1.7) Control group: 17 females, 10 males (Ratio 1.0:1.63)
Type of disorder	Depressive disorder
Baseline symptom severity	Intervention group: 20.92 ± 3.9 HDRS score Control group: 22.96 ± 4.9
Co-morbidities	Intervention group: NR Control group: NR
Past diagnosis of depression/anxiety	Intervention group: NR Control group: NR
Other treatment received (add. to study intervention)	NR
Subgroups measured	NR
Subgroups reported	NR
INTERVENTION GROUP	
Group name	Fluoxetine plus vitamins group
No. randomised to group	N= 27 participants
Description	Patients received 20mg Fluoxetine hydrochloride (=Fluoxetine IP) –oral capsules and NEUROBION FORTE tablets (vitamin B1, vit B2, vit B3, vit B6 and vit B12)
Duration of treatment	Treatment maintained for 8 weeks.
Timing	Fluoxetine once daily with food. NR for NEUROBION FORTE.
Delivery	NR
Providers	NR
Co-interventions	At each follow-up visit, participants underwent a general and clinical examination, assessment of adverse drug reactions, evaluation of medication compliance, and measurement of vital parameters.
Compliance	Evaluation of medication compliance at each follow-up.
CONTROL GROUP	
Group name	Fluoxetine alone group
No. randomised to group	N= 26 participants
Description	Patients received 20mg Fluoxetine hydrochloride (=Fluoxetine IP) – 20 mg oral capsules.
Duration	Treatment maintained for 8 weeks.
Timing	Once daily with food.
Delivery	NR
Providers	NR
Co-interventions	At each follow-up visit, participants underwent a general and clinical examination, assessment of adverse drug reactions, evaluation of medication compliance, and measurement of vital parameters.
Compliance	Evaluation if medication compliance at each follow-up.
OUTCOMES	
Primary outcome: change in symptom severity	
Outcome name	Change in HDRS
Timing	Measured from start of intervention. Reported baseline and after 2, 6, 8 weeks.
Outcome definition	Reduction in HDRS to ≤ 10 at 8th -10th week of follow up
Unit of measurement Scales	Unit of measurement: HDRS. Scales (upper/lower limits): NR

Person measuring/ reporting	NR					
Is outcome/tool validated?	Yes (according to reference 30-31)					
Imputation of missing data	NR					
Assumed risk estimate	Mean baseline HDRS = 22.96					
Power	NR					
Secondary outcome: adverse events						
Outcome name	Safety data (adverse drug reactions observed)					
Timing	Measured from start of intervention (at each follow-up), reported: timepoint unclear					
Outcome definition	Gastrointestinal disorders (abdominal discomfort/ cramps/diarrhoea), anorexia, psychiatric disorders (insomnia), reproductive systems disorders (sexual dysfunction), skin and subcutaneous tissue disorders (skin rash), CNS disorders (vertigo)					
Unit of measurement, Scales	Unit of measurement: NR. Scales (upper/lower limits): NR					
Person measuring/ reporting	NR					
Is outcome/tool validated?	NR					
Imputation of missing data	NR					
Assumed risk estimate	NR					
Power	NR					
RESULTS						
Primary Outcome: change in symptom severity						
Comparison	Fluoxetine + B vitamins vs. fluoxetine alone					
Outcome	Mean change in HDRS					
Subgroup	NR					
Time point	Weeks 2, 6, 8					
Post intervention/change from baseline?	Change from baseline					
Results	Intervention			Comparison		
	Mean	SD	No. pts.	Mean	SD	No. pts.
Week 2 Week 6 Week 8	16.90 10.81 4.95	± 6.9 ± 4.8 ± 1.8	27 27 27	18.53 13.30 6.47	± 7.2 ± 4.4 ± 2.3	26 26 26
Baseline data	Intervention			Comparison		
	Mean	IQR	No. pts.	Mean	IQR	No. pts.
	20.92	NR	27	22.96	NR	26
No. missing participants	NR			NR		
Any other results	NR					
Statistical methods	Between-group comparison performed using unpaired t-test; categorical variables expressed as percentages with 95% CI; statistical significance set at two-tailed $p < 0.05$.					
RESULTS						
Secondary outcome: adverse events						
Comparison	Fluoxetine + B vitamins vs. fluoxetine alone					
Outcome	Safety data (adverse drug reactions observed)					
Subgroup	NR					
Time point	Weeks 2, 6, 8					
Post intervention/ change from baseline?	Post intervention					
Adverse drug reactions	Intervention group (n= 27)			Control Group (n= 26)		
Gastrointestinal disorders: abdominal discomfort/cramps/diarrhoea	1 (4.16%)			1 (4.8%)		
Anorexia	0			1 (4.8%)		
Psychiatric Disorders: insomnia	0			3 (14.4%)		
Reproductive Systems Disorders: sexual dysfunction	1 (4.16%)			0		
Skin and subcutaneous tissue disorders: skin rash	1(4.16%)			0		
CNS disorders: vertigo	3 (12.48%)			1 (4.8%)		
No. missing participants	NR			NR		
Any other results	NR			NR		
Statistical methods	NR					

GENERAL INFORMATION	
Date of extraction	03/11/2025
Performed by	Susanne Fasching
Reference	**Unneh, Egena & Efut, Joseph & Ejemot-Nwadiaro, Regina & Esu, Ekpereonne & Nja, Glory & Rao, Laxmi. (2025). Effects of Supplementation with Folic Acid and Vitamin B12 Tablets as Adjunctive Therapy for People with Depression in Calabar, Cross River State, Nigeria. The Review of Contemporary Scientific and Academic Studies. 5. 10.55454/rcsas.5.04.2025.006.**
Publication status	Published
Publication type	Full report
Country	Nigeria
Conflict of interest	No conflict of interest declared by the authors.
Funding	The authors declare that no grants were received to support this research; it was entirely self-funded.
POPULATION AND SETTING	
Description	"Clinically diagnosed" persons with major depressive disorder using PHQ-9.
Setting	Out-patient clinic of Federal Neuro-psychiatric Hospital, Calabar, Cross River State.
Inclusion/exclusion criteria for participation in the study	Inclusion: diagnosis of MDD <2 weeks, PHQ-9 scores 5-25, age ≥ 18 years, no complications, visits of study sites, treated with Fluoxetine, stay in area during study, return-to-function scores 25-44 (WHODAS 2.0), signation of consent forms. Exclusion: patients < 18 years, people with depression previously on folic acid or vitamin B12 tablets, psychotic/manic features, untreated hypothyroidism, suicide or homicide risk, substance use disorder, treatment with other antidepressant than fluoxetine, pregnant or breast-feeding women, complications, thyroid dysfunctions, severe medical illness (bedridden, physical, mental handicaps), antidepressant use > 2 weeks. People with depression with co-morbidities, intake of multivitamins, stay outside of Calabar city, lack of consent.
Methods of participant recruitment	Participants were recruited from the out-patient clinic of Federal Neuro-psychiatric Hospital, Calabar, Cross River State.
Informed consent obtained (Yes/No/Unclear)	Yes.
METHODS	
Aim of study	To evaluate the impact of folic acid and vitamin B12 supplementation as an adjunct treatment in individuals with depression in Calabar, Cross River State.
Study Design	Four-arm randomised controlled trial involving one control and three intervention groups.
Unit of allocation	By individuals
Duration	8 weeks
Ethical approval	Approved by hospitals' Research and Ethics Committee.
PARTICIPANTS	
Total no. randomised	N= 88 Intervention group 1: n= 22 folic acid tablets only Intervention group 2: n= 22 vitamin B12 tablets only Intervention group 3: n= 22 folic acid + vitamin B12 Control group: n= 22
Baseline imbalances	No statistically significant difference with regards to age, gender, marital status, education, depressive symptoms. Imbalances in dietary history NR.
Withdrawals and exclusions	NR
Age (mean)	Intervention group 3: NR Control group: NR
Gender distribution	Intervention group 3: 14 females (65.0%), 8 males (35.0%) Control group: 13 females (59.1%), 9 males (40.9%)
Type of disorder	Depression
Baseline symptom severity	Intervention group 3: 13.91±5.63 PHQ-9 score Control group: 14.64±6.11 PHQ-9 score
Co-morbidities	Intervention group: NA Control group: NA
Past diagnosis of depression/anxiety	Intervention group: n= 0 Control group: n= 0
Other treatment received (add. to study intervention)	NR
Subgroups measured	NR
Subgroups reported	NR
INTERVENTION GROUP	
Group name	Intervention group 3
No. randomised to group	N= 22 participants

Description	Participants in the intervention group were administered Fluoxetine tablets (20mg), folic acid tablets (4mg and 5mg reported) and vitamin B12 tablets (100mg and 10mg reported). Amber coloured serially labelled bottles for allocation and concealment of drugs.					
Duration of treatment	Treatment maintained for 8 weeks.					
Timing	Vitamins administered daily.					
Delivery	Delivered by principal investigator.					
Providers	NR					
Co-interventions	Intervention group received printed handouts (English language) on depression and lifestyle modification. Participants were reminded via phone calls, email, and WhatsApp.Counselling sessions conducted in participants' preferred language. Researcher discussed depressive symptoms. Lifestyle advice included exercise, smoking cessation, and alcohol reduction.					
Compliance	Measurement by Simplified Medication Adherence Questionnaire. Participants were considered non-compliant if they gave any non-adherence response or missed more than two doses in the previous week / more than two full days of medication during the intervention.					
CONTROL GROUP						
Group name	Control group					
No. randomised to group	N= 22 participants					
Description	Participants received fluoxetine 20mg tablets.					
Duration of treatment	Treatment maintained for 8 weeks.					
Timing	NR					
Delivery	Delivered by principal investigator.					
Providers	NR					
Co-interventions	Information leaflets at the end of the study.					
Compliance	Measurement by Simplified Medication Adherence Questionnaire Conducted by psychiatrist. Participants were considered non-compliant if they gave any non-adherence response or missed more than two doses in the previous week / more than two full days of medication during the intervention.					
OUTCOMES						
Primary outcome: change in symptom severity						
Outcome name	Change in PHQ-9 score					
Timing	Measured from start of intervention. Reported baseline and after 8 weeks.					
Outcome definition	Remission of depressive symptoms scores (desirable), handled as continuous outcome.					
Unit of measurement Scales	Unit of measurement: PHQ-9 score. Scales (upper/lower limits): none (0-4), mild (5-9) moderate (10-14), moderately severe (15-19), 20-27 (severe)					
Person measuring	Psychiatrist trained to use PHQ-9. Documentation by research assistants (n=4, degrees in public health, psychiatric nursing and psychiatric medicine, trained on questionnaire handling, distribution, assessment of items of PHQ-9)					
Is outcome/tool validated?	Yes (according to reference WHO (2023))					
Imputation of missing data	NR					
Assumed risk estimate	Mean baseline PHQ-9 = 14.64±6.11 in the control group					
Power	A priori power calculation indicated that a total of 88 participants (22 per group) would provide 90% power at a 5% significance level to detect a minimum clinically important difference of 4 points in PHQ-9 scores, assuming a standard deviation of 4.1. Achieved power not reported.					
Other reported outcomes (not extracted)	Return to function (WHODAS 2.0)					
RESULTS						
Primary outcome: change in symptom severity						
Comparison	Fluoxetine + B vitamins vs. fluoxetine alone					
Outcome	Change of PHQ-9 scores over time					
Subgroup	NR					
Time point	Week 8					
Post intervention/change from baseline?	Change from baseline					
Results	Intervention			Comparison		
	Mean	SD	No. pts.	Mean	SD	No. pts.
Change from baseline.	5.23	±3.19	22	13.95	±7.26	22
Baseline data	Intervention			Comparison		
	Mean	IQR	No. pts.	Mean	IQR	No. pts.
	13.91±5.63	NR	22	14.64±6.11	NR	22
No. missing participants and reasons	NR			NR		
Any other results	NR					
Statistical methods	Independent t-test for continuous outcome. Data were analysed using descriptive statistics (mean, standard deviation, frequency). Statistical significance was set at $p < 0.05$ (95% CI).					

Appendix A6: Screening and Selection Tool

Review title: Combination Therapy with Antidepressants and Vitamin B Complex Compared to Antidepressant Monotherapy: A Systematic Review

Review question:
In patients with depression and anxiety treated with antidepressant medication, does combination therapy with antidepressants and vitamin B complex lead to a greater improvement in symptoms compared to antidepressant monotherapy?

Reviewer: Susanne Fasching

Author/Year:

Study Title:

Date:

Inclusion Criteria:

Criterion	Yes	No
Adults (≥18 years) with depression or anxiety (DSM-5, ICD-10 or validated assessment)	☐	☐
Treated with antidepressants	☐	☐
Adjunctive vitamin B complex (≥3 vitamins; if insufficient ≥2)	☐	☐
Primarily oral supplementation (IM/IV acceptable if limited evidence)	☐	☐
Comparator: antidepressant monotherapy or antidepressant + placebo	☐	☐
Outcome includes validated symptom severity scales (e.g. HDRS, MADRS, BDI, HAMA, GAD-7)	☐	☐
Randomised controlled trial (non-randomised only if < 5 RCTs identified)	☐	☐
Language: English or German	☐	☐

Exclusion Criteria:

Exclude if …	Check
Population without depression/anxiety (e.g. healthy participants, other psychiatric/neurological disorders)	☐
Children only, or no separate adult data	☐
Not involving antidepressant + vitamin B complex (≥2–3 vitamins)	☐
Unequal co-medication (e.g. mood stabilisers, antipsychotics not balanced)	☐
No relevant comparator (not antidepressant ± placebo)	☐
Ineligible design (observational, case reports/series, qualitative, review, meta-analysis)	☐

Eligible Outcomes

Primary Outcome

☐ Change in symptom severity (e.g. HDRS, MADRS, BDI, HAMA, GAD-7)

Secondary Outcomes
☐ Response rate (defined as a ≥50% reduction in baseline symptom scores, based on validated depression or anxiety scales)
☐ Remission rate (defined according to validated cut-offs of the assessment tools used (e.g., HDRS ≤7, MADRS ≤10)

☐ Quality of life (assessed with validated, generic instruments; e.g., SF-36, WHOQOL-BREF)
☐ Cognitive outcomes (validated tools)
☐ Adverse events / tolerability (including the frequency and type of reported adverse events and

dropout rates due to side effects)
☐ All-cause discontinuation

Final Decision

☐ INCLUDED ☐ EXCLUDED

Reason for exclusion (if applicable):
……
……

Notes

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