The Role of Dietary Supplements in Depression and Anxiety – A Narrative Review

Authors
Knut Hoffmann[1, 2], Barbara Emons[2], Stefan Brunnhuber[3], Sedya Karaca[2], Georg Juckel[1, 2]

Affiliations
1 LWL University Hospital for Psychiatry, Psychotherapy and Preventive Medicine, Bochum, Germany
2 LWL Institute for Mental Health, Bochum, Germany
3 Diaconic Clinics Zschadrass, Colditz, Germany

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Correspondence
Knut Hoffmann
LWL-University Hospital for Psychiatry
Psychotherapy and Preventive Medicine,
Alexandrinenstraße 1,
44791 Bochum,
Germany
knut.hoffmann@lwl.org

ABSTRACT

Introduction Dietary supplements are very widely used in the general population and there is a growing market for them, which is against the recommendations of the German Society for Nutrition. There is some evidence that dietary supplements are useful additions in the treatment of psychiatric disorders. This review is an overview of available practical knowledge regarding the use of supplements in psychiatric treatment. In particular, the review focused on the diagnosis of depression and anxiety in terms of supplement treatment.

Methods This is a narrative review of the evidence regarding supplements for treating anxiety and depression. We searched PubMed to 2018. Two reviewers screened the citations and abstracted the data. Phytopharmaceutical attends and animal-based data were excluded.

Results There are strong indications regarding the impact of supplements on the selected psychiatric disorders, but at this time, there only a few randomized clinical studies available, so evidence for these findings is quite low. However, it must be noted that there are strong hints for a relationship between vitamin D level and depression. Furthermore, various supplements have got potentially an influence on the characteristics of depression.

Discussion This review summarizes the current knowledge about supplements when used for some psychiatric conditions, but the data does not provide compelling evidence in any direction. There are only indications that there is an influence of supplements on psychiatric diseases. In support of this, there is further need for high-quality studies in this field. Reviews on other diagnoses, such as schizophrenia and dementia, will be part of further work.

Introduction

According to European and German law, dietary supplements are defined as chemical substances like minerals, vitamins, and antioxidants, which are part of normal nutrition but also can added to normal nutrition in the shape of more or less pure substances. Vitaminoids such as coenzyme Q10, carnitine, and inositol are also subsumed under the group of dietary supplements. In Germany, there is also a special regulation called the Dietary Supplement Act (Nahrungsergänzungsmittelverordnung, NemV). According to the recommendations of the German Society for Nutrition, and also the German Federal Institute for Risk Rating (Bundesinstitut für Risikobewertung, BfR), dietary supplements are not necessary for healthy persons who have a normal nutritional intake [1]. Despite this, there is a huge industry supplying the population with these products and a sales volume of $1.2 billion USD a year [2, 3], and this does not include sales from supermarkets. These products are usually used without any medical consultation, and advertisement in newspapers, TV, or other media is legal in opposition to genuine pharmaceutical drugs. Magnesium is one of the most popular dietary supplements, followed by calcium and iron, and vitamin A, D, and B formulations are increasing at the highest rates the in Germany [2]. It is also well known that although the fat-soluble vitamins (vitamin A, vitamin D, vitamin E, and vitamin K) can possibly enrich in the fatty tissues of the human being, overdoses and in-

toxications of vitamin A have been reported sporadically. In general reports of adverse effects and poisoning due to consuming dietary supplements are increasing [4, 5].

Despite this nonmedical application of dietary supplements they are also used for specific medical conditions. Deficiencies in vitamins and minerals may be caused by special forms of diet, such as a strict vegetarian or vegan diet. These deficiencies can lead to specific medical conditions that can be identified via blood tests or may lead to distinct neurological or hematological symptoms. A Cochrane review in 2012 involved a meta-analysis of 78 clinical studies with nearly 300 000 probands and found that the continuous supplementation of antioxidants such as beta carotene, vitamin E, and probably vitamin A has raised mortality significantly with a relative risk of 1.0006, p = 0.002 [6].

There are also psychiatric conditions that are sometimes treated with dietary supplements. The most common are depression and anxiety disorders. There are a few hospitals in Germany that have added treatment with dietary supplements routinely to classical psychopharmacological and psychotherapeutic treatment in their therapeutic repertoire. The core aim of this study is to reveal the possible evidence of such substances in the treatment of depression and anxiety. The selection of the search topics was carried out after a primarily, not systematic, informative search in PubMed these topics where the only once with an expected big enough outcome.

Methods

A narrative review on the effect of supplements on different psychiatric disorders is provided, which explicitly does not match the criteria of a meta-analysis. The included studies were found via PubMed.

Search strategy

We searched the electronic databases PubMed without language restriction from January 2012 to April 2018 to identify effect of supplements on different psychiatric disorders. Our search was limited to peer-reviewed literature.

Eligibility criteria

The inclusion and exclusion criteria for this narrative review were developed using the frame of participants, kind of supplement, and psychiatric diagnosis.

Participants

Studies in adults, male and female, with a psychiatric diagnosis.

Supplement

Studies on the supplements vitamin D (Vit D), polyunsaturated fatty acids (PUFA), vitamin C, N-acetylcysteine (NAC), inositol, folic acid, and citicholine were selected.

Psychiatric diagnosis

Psychiatric diagnosis depression and anxiety were selected. Also, therapeutic aspects have been used for selection in case of depression.

Search terms

The search was conducted on a combination of the supplement and psychiatric diagnosis of interest. Also, the search was conducted in an open manner with view of supplements in general.

Data extraction

Data from selected studies were extracted in tabular form including the basic information on the study, study design, study time, supplements, psychiatric diagnosis, participants, results, and limitations.

Descriptive analysis

Descriptive analysis was based on the summary of the effects of supplements on the selected psychiatric diagnosis.

Results

The effects of dietary supplement will be sorted by diagnosis below.

The role of supplements in depressive disorder

Most studies used in this review refer to depressive disorder. The findings of these studies are summarized in ▶ **Tables 1** and ▶ **2**. The studies are divided into 2 approaches: those referring to diagnostic approaches to supplements and those referring to therapeutical approaches. The diagnostic approaches are summarised in ▶ **Table 1**

Vid D and depressive disorder

Many studies refer to reduced Vit D serum levels in populations suffering from depressive disorder [8–16]. Belzeaux et al. found that hypovitaminosis of Vit D was generally more severe in patients with depression than patients with schizophrenia [7]. Furthermore, a positive association between anhedonia and low Vit D [17] was found, and significant reduction in cognitive functioning in people suffering from MDE associated with lower Vit D levels were reported [18]. Lee at al. refers to a cross-dependency between Vit D levels and serum cholesterol [19]. Brouwer-Brolsma et al. [20] used data from the B-PROOF study (n = 2 839, age 65 +) and found that long-term Vit D substitution had a significant effect on depressive symptoms, but there could be no interaction with Vit D regulating genes found in elderly people with elevated homocysteine levels. Pregnant Afro-American women aged 18–44 seemed to have a higher risk of postpartum depression relating to low Vit D levels in the second trimester, and there was also lower inflammatory cytokine activity [21]. Johansson et al. [22] found a positive relationship between reduced Vit D levels and depression in 506 patients with chronic heart disease. BDI-II scores in 126 patients with stroke were significantly negatively correlated with low Vit D levels, but not PHQ-9 scores [23]. Rabenberg et al. [24] stated that the higher association of Vit D deficiency and depression during summertime in a sample of 6 331 participants may be a consequence and not a cause of depression. Kerr et al. [25] investigated Vit D levels in relation to light exposure (measurement over autumn, winter, and spring) and found that the incidence of depression was higher with low Vit D levels independent of season. Elstgeest et al. [26] could demonstrate that over a period of 6 years, natural changes in Vit D

▶ **Table 1** Diagnostic approaches due to dietary supplements in depression.

Authors (Year)	Second mental health condition	Probands	Parameter	Design	Results	Limitations
Accortt et al. [21]		Female (18–44, pregnant, Afro-American)	Vit D	prospective study; in the second trimester of pregnancy, n = 91, Serum 25-OHD was measured during the first prenatal visit women had a second trimester blood sample assayed for inflammatory markers. Depressive symptoms were assessed at a postpartum visit	Sign. inverse association between prenatal log 25(OH)D and Postpartum Depression symptoms, interleukin-6 and IL-6/IL-10 ratio moderated the effect higher levels of inflammatory markers, lower prenatal log 25(OH)D were associated with sign. higher Postpartum Depression symptoms -> increasing Vit D status in pregnant women with elevated pro-inflammatory cytokines can help to reduce PPD symptoms	drop outs = some missing data on depression 74 % of women in this sample reported use of a Vit D supplement -might have raised mean serum levels of 25(OH)D were measured between 9 and13 weeks gestation with supplementation prescribed thereafter. -Inflammatory markers were measured between 13–28 weeks of gestation
Almeida et al. [28]		Male (71–88)	Vit D	Observational study examining the retrospective, cross-sectional and prospective associations between Vit D concentration and depressed mood. n = 3 105	Vit D does not play a role in the causation of depression	diagnosis of depression through WADLS, limited assessment of Vit D concentration definition of clinically significant depression not equate to a diagnosis according to DSM or ICD criteria
Belzeaux et al. [7]	Schizophrenia	Adults	Vit D (< 50 nmol/L)	monocentric-cross-sectionaland observational study, retrospective chart review, n = 82, n = 53 mood disorder, n = 29 schizophrenia	Vit D deficiency was higher in patients with mood disorders than in patients with schizophrenia	Retrospective study No causal link Low level of evidence No healthy control group No data on sun exposure
Belzeaux et al. [18]	Hypovitaminosis D (< 50 nmol/L)	Adults (18–65, depression, no medication)	Vit D (< 50 nmol/L)	n = 91 (MDE, non-medicated patients with and without hypovitaminosis), cross-sectional study, Measurements: Stroop Color test, Trail Making Test, Hayling Sentence Completion Test, Iowa Gambling Task, Verbal fluency Test, WAIS-IV, Digital Span Test, National Adult Reading Test	association between hypo-VD in patients with MDE and cognitive impairment --> significant difference in groups in Stoop test	small sample size - only medication free patients with MDE causal relationship between Hypo Vit D and cognitive function need to be proven, no control of dietary and physical activity
Brouwer-Brolsma et al. [20]		Adults (65 + Dutch)	Vit D	"B-PROOF" study, a randomized, double-blind, placebo-controlled trial design (n = 2 839 at baseline; n = 2 544 at follow-up)	association between serum 25(OH)D and score of depressive symptoms (measured with 15 point Geriatric Depression scale) No associations between Vit D-related genetic make-up and the depressive symptoms observed no significant interactions between Vit D-related genes and 25(OH)D concentrations	no measurement of Vit D levels after 2 years, not possible to say something about causality within 2 years self-supplementation of Vit D possible / other medications that affect metabolism
Callegari et al. [29]	Anxiety	Females (16–25)	Vit D	n = 353 healthy woman mental health was measured by several instruments (PHQ-9, GAD-7, K10, SF-12 MCS Serum 25OHD was measured real-time sun exposure was measured using UV dosimeters	Vit D serum levels not associated with mental health scores. Vit D status was not associated with depression or anxiety.	low prevalence of severe Vit D deficiency and mental health symptoms
Can et al. [27]		Adults (18–65)	Vit D	cross-sectional-healthy control group design, n = 175 (n = 86 patients MMD; n = 89 healthy controls)	no relationship between depression & Vit D levels/ Fok1 polymorphism of Vit D Receptor Gene	confounding factors may affect Vit D levels 3 times more female participants

▶ **Table 1** Continued.

Authors (Year)	Second mental health condition	Probands	Parameter	Design	Results	Limitations
Chu et al. [8]	Anxiety	Adults (18+, Canada)	Vit D	cross-sectional study conducted every 2 years; n = 7518 (adults, non-pregnant), blood samples (25(OH)D concentrations (expressed in nmol/L)); measures of depression, anxiety and stress	positive associations between serum 25(OH)D concentrations and indicators of mental health (depression/anxiety) higher serum 25(OH)D concentrations associatioted with a good mental health and general health state	no assessment from a mental health professional (too impractical/costly) response bias to raise Vit D levels individuals would need an intake of 1000–4000 IU/day-only possible: 200–300 IU/day from food sources -->need for supplements over a long period of time to see benefits
Collin et al. [9]		Adults	Vit D	nested case–control study, longitudinal design, n = 1196	25(OH)D concentrations above 10 ng/mL: related to a lower probability of recurrent depressive symptoms no significant results in comparing individuals with concentrations < versus ≥ 20 or < versus ≥ 30 ng/mL among participants with low dietary quality, a better Vit D status is related to a lower probability of recurrent depressive symptoms preventive role of plasma Vit D against recurrent depressive symptoms (especially among individuals with poor dietary quality)	Limited statistical power Caucasian individuals (no generalization)
Dana-Alamdari et al. [31]		Adults (18–63)	Vit D	n = 84 (n = 44 non-medicated with MDD; n = 41 healthy control), cross-sectional-healthy control group design	no sign. protective role of Vit D inverse relationship between the levels of Vit D and depressive symptoms in current depression episodes (but not statistically significant)	
Elstgeest et al. 2017			Vit D	Dutch older adults (65–88), n = 173; snd. Cohort 6 years later (n = 450, 55–65)	Over 6 years a increase of Vit D-levels leads to a small decrease of depressive symptoms.	study population are different, second was much younger (55–65), not comparable
Hashimoto et al. [35]		Adults; older	Vit C	metabolomics analysis of cerebrospinal fluid (CSF) from cognitively intact elderly patients n = 28 with MDD, n = 18 healthy controls	abnormalities in the brain levels of ascorbic acid might play a role in the depressive symptoms of elderly MDD patients	small sample size no measurement of plasma ascorbic acid
Johansson et al. [22]	Chronic heart disease	Adults with chronic heart disease	Vit D	n = 506 HF (heart failure) patients, depressive symptoms measured with the Centre for Epidemiological Studies Depression Scale, physical function were measured using the physical function scale from the RAND-36. Vit D was measured in blood samples	in HF patients with Vit D < 50 nmol/L, Vit D is associated to depressive symptoms during follow-up and this association is mediated by physical function. This relationship is not found in patients with Vit D level > 50 nmol/L.	study was not designed to assess the association between Vit D and depression. Mostly self-reported scores the time of the year when Vit D levels was measured was not recorded parathyroid hormone (PTH) was not measured
Jovanova et al. [12]		Adults (55+)	Vit D	population-based cohort designed study, embedded in the Rotterdam study n = 3251	low serum Vit D levels were associated with more depressive symptoms, but not with a change of depressive symptom	Unmeasured confounding factors, no account for parathyroid hormone (PTH). Reverse causality between Vit D and Depression

▶ **Table 1** Continued.

Authors (Year)	Second mental health condition	Probands	Parameter	Design	Results	Limitations
Jääskeläinnen et al.		Adults 30–79	Vit D	cross-sectional study, n = 5371; n = 354 diagnosed with depression, n = 222 diagnosed with anxiety disorder	higher serum 25(OH)D concentrations associated with reduced risk of depression & a lower prevalence of depressive disorder (especially among men, younger, divorced and those who had an unhealthy lifestyle or suffered from the metabolic syndrome)	
Kerr et al. [25]		Female (18–25)	Vit D	n = 185 female participants living in the Pacific Northwest during fall, winter, and spring. Center for Epidemiologic Studies Depression (CES-D) scale weekly for 4 weeks (W1–W5). serum levels of Vit D3 and C (as a control variable) in blood samples collected at W1 and W5	Lower W1 Vit D3 predicted significant depressive symptoms across W1–W5. Lower levels of depressive symptoms in fall participants (vs. Winter and Spring) were explained by their higher levels of Vit D3. W1 depressive symptoms did not predict change in Vit D3 levels from W1 to W5. association between low levels of Vit D and depressive symptoms	Single geographic location and single gender. Self-report measures. No screening for health factors that may affect Vit D levels
Van den Berg et al. [30]		Adults 60+	Vit D	prospective cohort study n = 367 depressed older persons; n = 132 non-depressed older persons. depression measured using Composite International Diagnostic Interview, a structured clinical interview and the Inventory of Depressive Symptoms (self-Report); Vit D levels were assessed at baseline	Vit D had no effect on the course of depression or remission, except for a trend towards lower remission. lower Vit D levels predicted mortality among depressed older persons	
Kim et al. [23]	Stroke	Adults, stroke	Vit D	n = 126 stroke patients, 25-hydroxyVit D (25-OHD) concentration was used to determine their Vit D status. Depressive symptoms were assessed using BDI2 and PHQ9; functional status was evaluated wit K-MBI	Vit D-deficient group: BDI-II and PHQ-9 scores were significantly higher than control group. Sign. negative correlation between serum 25-OHD levels and BDI-II, but not PHQ-9 or K-MBI. Vit D deficiency was correlated with depressive symptoms in stroke patients	Cross-sectional design – progression/ change of Vit D was not measured. No classification of stroke severity in patients
Lee et al. [19]		Adults (20–88, Korea)	Vit D	population-based cross-sectional study, n = 7198 (n = 6503 Individuals without depressive symptoms; n = 695 Ind. with depressive symptoms)	Association between Vit D deficiency and depressive symptoms weakened by high serum total cholesterol status. Vit D and total cholesterol are important for the prevention and treatment of depression. Vit D-deficient participants with normal-to-borderline serum total cholesterol had an increased risk of depressive symptoms. This association was absent in a sub-population of individuals with high serum total cholesterol	no causality of relationship, no clinical measurements of depression: depressive group if they answered 'yes' to a questionnaire. no temporal or causal association between Vit D deficiency and depression in stroke patients. no generalization of results

▶ **Table 1** Continued.

Authors (Year)	Second mental health condition	Probands	Parameter	Design	Results	Limitations
Lui et al. 2013	Anxiety	Adults (18–73)	PUFA (docosahax-aenacid, eicosapen-tenacid, methylester)	cross-sectional study, healthy control group, 2 patient groups. n = 121 adults, n = 18 MDD with comorbid anxiety disorder, n = 41 MDD, n = 62 healthy controls	presence and severity of comorbid anxiety were associated with the lowest EPA and DHA levels	small sample of patients with MDD and comorbid anxiety -> anxiety contained a variety of subtypes of anxiety. young age of sample Measures limited to DHA, EPA, and the AA to EPA
Mizoue et al. [10]		Adults (19–69, Japan, worker)	Vit D	cross-sectional study. n = 1786 (92 % had suboptimal Vit D status), Serum 25-hy-droxyVit D [25(OH)D] concentrations were measured - Depressive symptoms were measured with CES-D scale	lower levels of circulating Vit D are associated with increased likelihood of having depressive symptoms	cross-sectional study does not necessarily indicate causality. there could be more factors influencing hypovitaminosis D -> Workers with depression may have decreased appetite / reject outdoor activi-ties
Otoki et al. [33]		Adults (18–65)	PUFA	n = 9 medication-free participants, MDD with seasonal pattern, uncontrolled within-subject design. 2 times of measurements	quantification of plasma plasmalogen and diacyl-phospholipid species, and fatty acids within total phospholipids, cholesteryl esters, triacylglycerols and free fatty acids during euthymia in summer or fall, and during depression in winter in order to screen for potential high sensitivity lipid biomarkers. Triacylglycerol alpha-linolenic acid concentration was significantly decreased, and myristoleic acid concentration was significantly increased, during winter depression compared to summer-fall euthymia."	small sample size, absence of dietary or physical activity information
Payne et al. [36]						
Raben-berg et al. [24]		Adults (18–79)	Vit D	cross-sectional analysis n = 6331 partici-pants representative German Health Interview and Examination Survey for Adults (2008–2011)	Vit D status were inversely associated with current depressive symptoms in summer (not in winter). association is stronger in summer time: Vit D deficiency may be a consequence not a cause of depression	self-reports, wide range of confounding factors
Rakofsky & Dunlop [34]				literature search for randomized, controlled clinical trials using nutritional supplements in the treatment of Bipolar Depression (PubMed and Ovid MEDLINE)	inconsistent results for nutritional supplements (O3FAs, vitamin C, NAC, inositol or citicholine). No evidence for folic acid, choline, and O3FA-cytidine	
Shin et [14]		Adults (20–70)	Vit D	n = 52228 participants from the employee health screening, measurement of Serum 25-hydroxyVit D level & C-reactive protein / assessment of depressive symptoms	Vit D deficiency associated with depressive symptoms, but elevated serum C-reactive protein (CRP) level was not. CRP level does not account for the association between Vit D deficiency and the presence of depressive symptoms	No indication of causality level of physical activity was not assessed depression was not clinically diagnosed (use of CES-D scale). Possible unadjusted confounders

▲ **Table 1** Continued.

Authors (Year)	Second mental health condition	Probands	Parameter	Design	Results	Limitations
Thomas & Al Anouti [15]		Female	Vit D	cross-sectional study design assessing seasonal variation in depressive symptoms (measured by BDI) and Vit D levels. Assessing the relationship between Vit D deficiency and mood in female university students in the United Arab Emirates	depressive symptoms were positively correlated with 25 (OH)D levels summer cohort : highest levels of Vit D deficiency and greater depressive symptoms	correlational study, relationships statistical, not causal or temporal female participants
Parker et al. [16]			Vit D	Review: empirical papers published in recent years were identified	association between Vit D insufficiency and depression, and for Vit D supplementation and augmentation in those with clinical depression who are Vit D deficient	more randomized controlled longitudinal trials to clarify the role of Vit D in the pathogenesis of depression and its treatment
von Känel et al. [17]		Adults	Vit D	n = 380 depressed participants (n = 27 drop out) Depression measured using: HADS-D, BDI2 and Brief Symptom Inventory serum levels of 25-hydroxyVit D3 (25-OH D) were measured	Vit D deficiency is associated with cognitive/affective depressive symptoms, especially anhedonia symptoms	observational design/retrospectively collected data. confounding factors cannot be excluded. no measurement of physical activity, sun exposure, nutrition depressive symptoms not measured by a clinical interview method of Vit measurement changed through the study

levels were related to depressive symptoms, independent of the age of the patient. Other studies did not find a relationship between Vit D and affective disorder [27–30] or any protective effect of Vit D on depression [31]. In summary, it can be emphasized that there are reduced Vit D levels in populations suffering from depressive disorders [8–16, 21–23]. Further, many studies indicate that Vit D levels refer to depressive symptoms and their incidence [24–26], but also there are studies that did not find any relationship between depression an Vit D levels [27–30].

The role of PUFA, Vit C, NAC, inositol, folic acid, and citicholine in affective disorders

The effect of PUFA on depression was also investigated. Low levels of PUFA were associated with higher levels of both depression and anxiety [32, 33]. Both studies refer only to small sample sizes. Rakofsky et al. undertook a literature search on PUFA, Vit C, NAC, inositol, folic acid, and citicholine and found inconsistent correlation between PUFA, Vit C, and citicholin and bipolar disorder, no correlation between folic acid, choline and cytidine-PUFA and bipolar disorder [34]. Hashimoto et al. also found significantly ($p = 0.0029$) higher levels of Vit C in the cerebrospinal fluid CSF of elderly people with depression, but no cognitive decline in comparison with healthy controls [35]. The elevation was interpreted as a result of increased oxidative stress in the central nervous system. Payne et al. studies the nutrition habits of depressed people with a lower intake of fruits and vegetables, resulting in lower Vit C levels. In this study, natural Vit C intake seems to be beneficial for depression, but Vit C from dietary supplements has no effect [36]. This implicates that various supplements have influence on depression or being influenced by depression [32–36].

Supplements and therapeutical approaches

Therapeutical approaches are summarized in ▶ **Table 2**.

Vit D

Again, most of the literature refers to Vit D, and the findings regarding therapeutical aspects are also contradictory. A possible positive effect was found in a review by Mulcahy et al., but it was also noted that depression-associated behavior (e. g., social withdrawal, diminished cognitive capacity) may lead to poor diet and the measured effects are not caused by influencing depression, but depression-associated behavior [37]. Stokes et al. [38] investigated 278 patients with chronic liver disease (144: MDD, 134: no MDD) and found a significant improvement in depressive symptoms in a group supplemented with 20 000 UI Vit D per week [38], and there was a similar finding by Penkhofer et al. in 82 depressive females with comorbid DM II 50 000 IU/week) [39]. Gowda et al. undertook a meta-analysis of RCTs in this field (n = 4 923) and found no significant effect in the reduction of depressive symptoms: most studies focused on mild depressive disorders [40]. Muosa et al. conducted an RCT of Vit D vs. placebo (n = 33 vs. 17) and found no effect on depression and anxiety in both arms [41], and a very similar study design with comparable findings was used by Marsh et al. [42] and Kjaegaard et al. [43]. In a supplementation-study (50 000 IU/week), Sephermanesh et al. (2016) only found a trend in reduction of BDI scores [44]. In a randomized pilot study, Rolf et al. treated 20 patients suffering from MS with 14 000 IU Vit D/d, controlled by

▶ **Table 2** Dietary supplements in treatment of depression.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Smith et al. [49]		Docosahaxaenacid (DHA) (260 oder 520 mg/d)		Adults	n = 28 mild to moderate MMD, non-responsive to medication/ psychotherapy. 8-week open-label pilot trial of low-dose DHA, (260 mg or 520 mg/day), no placebo control	54 % of patients had a ≥ 50 % reduction on the HAM-D. 45 % were in remission. Significant reduction in the HAMD score for middle insomnia no significance in reduction in excessive daytime somnolence on the total Epworth Sleepiness Scale (ESS). No significant adverse reactions to DHA. Improvement of CGI. Adjunctive benefits in patients with mild to moderate depression	lack of a placebo small sample size serum and RBC fatty acid status not examined smoking was not controlled (modifies the metabolism of omega 3)
Sahraian et al. [61]	Suicidality	Vit C (1000 mg/d)		Adults	8-week randomized double-blind placebo-controlled clinical trial. adult patients with MMD n = 78, n = 21 treatment (vitamin c) group, n = 22 placebo group 35 drop outs treatment group received Citalopram + Vit C; placebo group received Citalopram + placebo	Depression symptoms decreased in both groups, no statistically significant difference between the 2 groups	small sample size short duration fixed dose of Vit C no control of dietary intake of Vit C
Stokes et al. [38]	Chron. Liver disease	Vit D (20,000 UI/ Week)		Adults	cross-sectional analysis, n = 111 patients with chronic liver disease. n = 34 depression. n = 77 no depression	results indicate that Vit D substitution might significantly improve depressive symptoms in CLD (in particular in women with low baseline Vit D)	intervention was not an RCT, small sample size
Payne et al. [36]		Antioxidants	Vit C	Adults	case-control study, longitudinal clinical examination, n = 278, n = 144 partici- pants with depression, n = 134 participants without depression	Participants with depression: significantly lower intake of fruits, vegetables, vitamin C, and ß-cryptoxan- thin than participants without depression	Sample size. No confirmation of causal relationship between depression and nutrition -> antidepressants may have an effect on appetite an diet. Severely depressed persons were excluded. Self-report of dietary intake = not objective. generalization only to older adults (outicipants older than 60) from Europe with non-severe depression receiving psychiatric treatment
von Känel et al. 20105				Adults	n = 380 depressed participants (n = 27 drop out). Depression measured using: HADS-D, BDI2 and Brief Symptom Inventory. Serum levels of 25-hydroxyVit D3 (25-OH D) were measured	Vit D deficiency is associated with cognitive/affective depressive symptoms, especially anhedonia symptoms	observational design/retrospectively collected data. confounding factors cannot be excluded No measurement of physical activity, sun exposure, nutrition depressive symptoms not measured by a clinical interview. method of Vit measurement changed through the study
Gowda et al. [40]		Vit D		Adults	meta-analysis of randomized controlled trials, n = 4923, Vit D supplementation to reduce depression/depressive symptoms MEDLINE, EMBASE, psych INFO, CINAHL plus, and Cochrane library	no significant effect was seen, no significant reduction in depression	most studies focused on participants with mild depressive symptoms and sufficient serum Vit D

▶ **Table 2** Continued.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Mousa et al. [41]		Vit D (Calciol 4000 IU/d)		Adults (18–60; obese; Vit D ≤ 50 nmol/L)	randomized, placebo-controlled cross-sectional analyses, n = 63 (48 completed trial) (n = 33 Vit D group) (n = 32 placebo)	no association between increased risk of depression and Vit D deficiency in persons without clinically significant depression	small sample size short duration (16-week intervention) BDI scores in normal range. Healthy young individuals. No measurement of factors influencing depressing symptoms
Marsh et al. [42]		Vit D (5000 IU/d)		Adults (18–70 years)	double blind placebo-controlled trial n = 230 (randomized n = 33; n = 16 Vit D, n = 17 placebo)	both treatments (Vit D/placebo) did not improve reduction in mood elevation or anxiety symptoms	small sample size low Vit D levels in the supplementation group at conclusion
Kiecolt-Glaser et al. [50]	Depression	Omega-3 (2,5 g/d, 2085 mg Eicosapentac-id + 348 mg Docosahaxaenac-id)		Adults (21–29)	Placebo-controlled, double-blind 12-week RCT. n = 68 (medical students, 6 visits -> alternating between lower stress an higher stress (non-exam and major exam)	Participants that received n-3 showed a decrease in lipopolysaccharide (LPS) stimulated interleukin 6 (IL-6) productions and a reduction in anxiety symptoms, without a change in depressive symptoms. n-3 supplementation can reduce inflammation and anxiety in young healthy adults. reduction in anxiety is associated with n-3 supplementation. n-3 may have potential anxiolytic benefits (healthy individuals without an anxiety diagnosis)	Not shown that n-3 supplemented participants would show smaller exam-related increments in inflammation and distress among compared to controls. absence of systematic stress-related changes in control group. possible side effects
Kjærgaard et al. [43]		Vit D3 (40 000 IU/ week)		Adults (30–75); 25 (OH)D Level < 55 nmol/L, > 70 nmol/L	nested case–control study and randomized clinical trial. n = 357 (n = 243 case group (splited in treatment and placebo)/n = 114 control group) 3 groups -> participants with low 25(OH)D levels were randomized to treatment group (40 000 IU Vit D3 per week for 6 months or placebo. Participants with high 25(OH)D levels -> nested controls	participants with low Vit D levels were significantly more depressed (at baseline). No effect of Vit D supplementation was found on depressive symptoms -> low levels of Vit D may be the results instead the cause of depressive symptoms	short duration to investigate depression . participants were informed about if they had high or low Vit D levels -> may biased their self-report of depressive symptoms. individuals with severe depressive symptoms were excluded from the intervention -> participants had no or mild depressive symptoms. possible side effects of supplementation
Jovanova et al. [12]				Adults (55 +)	population-based cohort designed study, embedded in the Rotterdam study; n = 3251	Low serum Vit D levels were cross-sectionally associated with more depressive symptom, but not with a change of depressive symptoms	unmeasured confounding factors no account for parathyroid hormone a(PTH) reverse causality between Vit D and Depression
Nguyen et al. [63]		Retinol	Retinla equivalent	Adults (65 +)	cross-sectional study (based on “Shika Study” Measurements: interviews, self-administered questionnaires and comprehensive health examination) investigation between vitamin intake and depressive symptoms (n = 1634)	except for retinol and Vit D, the consumption of all vitamins, was lower among depressed participants. no associations between the 15 vitamins in depressed male or underweight participants. relationship between Vit Deficiencies and depressive symptoms in female and overweight elderly participants	cross-sectional design does not provide evidence for causality. self-reported dietary assessment methods to measure vitamin intake -> subjective. some confounding factors (physical activity, economic income, history of drug use, diseases, history of vitamin supplements etc could not be excluded

▶ **Table 2** Continued.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Sepehr-manesh et al. [44]	Oxidative stress	Vit D (50 kIU/ week)		Adults (18–65)	A Randomized, double blind, placebo-controlled Clinical Trial; n = 40 with MDD -> 1 group (n = 20) received 50 kIU Vit D/ week the other group (n = 20) received placebo for 8 weeks. fasting blood samples were taken at baseline and after intervention Measurements: BDI and glucose homeostasis variables, lipid profiles, hs-CRP, and biomarkers of oxidative stress	trend towards a greater decrease in the BDI was observed in the Vit D group than in the control group Vit D supplementation of individuals with MDD -> showed beneficial effects on BDI, indicators of glucose homeostasis, and oxidative stress	Short duration. all participants had Vit D deficiency - no examination of individuals without Vit D deficiency
Rolf et al. [45]	Multiple sclerosis	Vitamin (14.000 IU/d)		Adults; multi-ple sclerosis	randomized pilot study n = 40 relapsing remitting (RR)MS patients received Vit D3 supplementation (n = 20) or placebo (n = 20) during 48 weeks	no significantly different reductions between treatment and controls no reductions in pro- and anti-inflammato-ry cytokine balances, secreted by stimulated leukocytes and CD8 + T cells were found in the Vit D3 compared to the controls. no evidence for a reduction of depressive symptoms or related biomarkers	
Masoumi et al. [52]		Omega-3 (1 g/d)		Female (45–65 years)	triple-blind randomized controlled trial n = 60 women with post-menopausal depression Group 1: 20 mg citalopram & placebo. Group 2: 20 mg citalopram 1 g omega-3	Trend of decreasing depression scores in intervention group (2) Sign. difference in depression scores between the groups	Small sample size
Penckofer et al. [39]	Anxiety	Vit D (25-hydroxy-Vit D) (50,000 IU/ week		Female 18 + ; DM II	open-label, proof-of-concept study to assess the effect of Vit D2 supplementa-tion on depression, anxiety, and mental health status. single-group, pretest-posttest design. n = 82 medically stable Type 2 Diabetes Mellitus patients. A capsule of 50,000 IU of Vit D2 (ergocalciferol) was administered once a week for 6 months	significant decrease in depression and anxiety improvement in mental health status	No need to have significant depressive symptoms to participate no randomization short duration no control group
Yalamanchili & Gallagher [46]		Vit D (25 OHD) (400–4800 IU/d)	Calcium (1000–1400 mg/Tag)	Female 57–90 years	1-year, randomized, double-blind, multidose, Placebo-controlled study. n = 274 elderly women with Vit D insufficiency	different doses of Vit D3 did not influence the depression score in Vit D insufficient older white and black women	Study not designed for depression. No data on socio-economic status – con-founding factor
Singh et al. [64]	Stress	Thiamin	Riboflavin (Vitamin B2)	Female, pregnant	n = 108 pregnant Latina teenager. Stress, depression and dietary intake was measured	social support was associated with a higher intake of thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin C, vitamin E, iron, and zinc	Sample size, recall bias

▶ **Table 2** Continued.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Khajehnasiri et al. [53]	stress	Omega-3 (2 × 1000 mg/d)	Vit C (2 × 250 mg/d)	Male (21–52 shift -workers)	randomized, double-blind, placebo-controlled trial, n = 136 men Measures: BDI & MDA (malondialdehyd) TAC (total antioxidant capacity) concentrations. n = 33 received omega-3 fatty acid soft gel (1000 mg twice daily) with vitamin C (250 mg twice daily) n = 31 received omega-3 fatty acid supplements and vitamin C placebo. n = 30 received omega-3 fatty acid supplement placebo and Vit C. n = 32 received omega-3 fatty acid supplement placebo and Vit C placebo	BDI score was reduced Significantly in all 4 groups. The greatest decrease was in the omega-3-fatty-acid alone supplement group. MDA level decreased significantly in groups with omega-3 fatty acids or vitamin C supplementation alone. omega-3 fatty acids alone and not in combination with vitamin C had an higher impact on depression and reduced MDA levels	Short duration, Self-report bias of alcohol and drug use (Iran) because of cultural issues
Frandsen et al. [47]		Vit D (70 µg/d)		Nurses	randomized, single-centre, double-blind, placebo-controlled trial, n = 34. Participants received a daily dose (during 3 months) of 70 µg Vit D or placebo. first outcome: the sum of the self-reported questionnaire Structured Interview Guide for the HAMD, Seasonal Affective Disorders (SIGH-SAD). The secondary outcome: WHO-5 of the healthcare professionals during the winter period	The sums of the SIGH–SAD at 12 weeks were not significantly different between the groups	exclusion criterion High PTH. drop-outs had lower 25(OH)D calculated sample size not reached
Khajehnasiri et al. [54]		Omega-3 (180 mg Eicosapentenac-id + 120 mg Docosahaxaenac-id) 2 × /d	Vit C (250 mg 2 × /d)	Shift workers Iran, Petrolindus-trie; (21–52)	Randomized, double blind, placebo-controlled and parallel-group clinical trial. n = 136. Four groups of omega 3 and/or Vit C supplementation and/or placebo	Sign. reduction in all groups. Supplementation of omega 3 and Vit C is associated with a reduction of depressive scores. O3 supp showed a better effect and high sensitivity C-reactive protein	
Parletta et al. [60]		Fishoil (2 Cap/d)	Mediteranian diet		Randomized controlled trial, n = 152. Group 1: food hampers and MedDiet cooking workshops for 3 months and fish oil supplements for 6 months, Group 2: attend social groups fortnightly for 3 months	Higher MedDiet score, consumed more vegetables, fruit, nuts, legumes, and vegetable diversity, less unhealthy snacks and red meat/chicken. Group1 had greater reduction in depression and improved mental health at 3 months.	single blinded. Self-reported, high dropout rate

▶ **Table 2** Continued.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Sarris et al. [65]		Folatic Acid, B6, B12	Omega-3		Review of adjunctive nutraceuticals for depression	Folic acid significant as adjunctive treatment in combination with fluoxetine (not significant with escitalopram or other tested antidepressants). Vit B12 significant as adjunctive treatment in combination with TCA/imipraimine or SSRI/fluoxetine. Vit B6 and 12 combined with folic acid not significant. EPA/DHA combined with any antidepressant or citalopram showed significant results, but not significant in combination with sertaline. EPA vs DHA: EPA shows more decrease in depressive symptoms than DHA. Ethyl-EPA: reduction of depressive symptoms in 3 trials, no sign. results in 1 double blind RCT	
Messamore et al. [55]	Bipolar disorder	PUFA	Eicosapentenacid		Review	Findings show: n-3 PUFA insufficiency is associated with pathophysiology and pathoetiology of mood Dysregulation. recommended: implementation of routine screening for and treatment of n-3-PUFA deficiency	
Mocking et al. [56]		PUFA	Omega-3		Review. Randomized placebo-controlled trials. Effects of omega-3 PUFA supplementation on depression. PubMED/EMBASE	overall beneficial effect of omega-3 PUFAs on depression in particular higher doses of EPA and in patients taking antidepressants. Supplementation is most beneficial	
Sarris et al. [57]	Bipolar disorder	Omega-3	N-acetyl cysteine		Review	positive results for adjunctive omega-3 for MDD and Bipolar Depression: (mainly EPA dominant formulations). N-acetylcysteine has shown effectiveness (in 1 RCT) in reducing depression in bipolar depression. Vit D showing beneficial effects in reducing depression.	
Trebatickáa et al. 2017	Cardiovascular disease	Omega-3			Review	changes in metabolism were induced changing dietary ratio of omega-6 to omega-3 fatty acids ; increased pro-inflammatory mediators/ modulations of different signaling pathways pathophysiological response related to both, cardiovascular diseases and depressive disorders.	

▶ **Table 2** Continued.

Authors (Year)	Second mental health condition	Supplement 1	Supplement 2	Probands	Design	Results	Limitations
Du et al. [58]	PTSD	PUFA	Cholesterin		Review. Nutrients: omega 3 fatty acids, antioxidants (vitamin C and zinc), members of the vitamin B family (Vitamin B12 , folic acid), magnesium and how they can protect against oxidative damage to mitochondria and lipids in the neuronal circuits associated with cognitive and affective behaviors	improving neurocognitive function, and therapeutic benefits for depression and suicidal behaviors. Regular consumption could be helpful to prevent mood disorders and suicidal behaviors in vulnerable individuals significantly support the therapeutic effect of antidepressants	
Parker et al. 2016		Vit D (25-hydroxy-Vit D)			Review: empirical papers published in recent years were identified	association between Vit D insufficiency and depression, and for Vit D supplementation and augmentation in those with clinical depression who are Vit D deficient	more randomized controlled longitudinal trials needed to clarify the role of Vit D in the pathogenesis of depression and its treatment
Stefanowski et al. [48]		Vit D3			Review: searching the Medline and PubMed	depressed individuals are at higher risk of Vit D3 deficiency factors related to lifestyle (food, not active, have low physical activity, spend more time indoors) predispose to the emergence of Vit D3 deficiency. Vit D3 supplementation in patients with depression may have antidepressant effect. Continuous supplementation may reduce the risk of recurrence	
Mulcahy et al. [37]	Schizophrenia	Vit D	Adults		Psychiatric illnesses often lead to an intake of medications that can inhibit the synthesis and absorption of Vit D. Recent literature supports that Vit D has implications in the CNS. No consistent results in human studies. Hard to define a cause and effect relationship	Risk of adding a supplement with questionable efficiency into a medication treatment. risk of adverse drug reactions and potential psychiatric exacerbation. Self-administration errors	
Rakofsky & Dunlop [34]					Review literature search for randomized, controlled clinical trials using nutritional supplements in the treatment of Bipolar Depression (PubMed and Ovid MEDLINE)	Inconsistent results for nutritional supplements (O3FAs, vitamin C, NAC, inositol or citicholine), no evidence for folic acid, choline, and O3FA-cytidine	

▶ **Table 3** The use of dietary supplements in anxiety disorder.

Authors (Year)	Second MH condition	Supplement	Probands	Parameter	Design	Results	Limitations
Wu et al. [66]			Adults, stroke	Vit D	n = 326, first acute ischemic stroke patients. n = 60 PSA, n = 166 non-PSA, n = 100 controls repeated measurement design, 2 stroke patient groups, 1 healthy group	26.55 % showed anxiety at 1 month. PSA (PSA = poststroke anxiety) and non-PSA patients had lower serum levels of Vit D than healthy subjects significant relationship between PSA and serum levels of Vit D -> low serum levels were interdependently associated with the development of PSA	Serum level of Vit D was tested only at admission. Some bias because of excluding criteria cognitive dysfunction and aphasia the duration of follow-up might be too short to distinguish ''true'' anxiety from ''reactive'' anxiety." Role of Vit D-binding protein in anxiety was not studied
Green et al. [68]			Adults	Omega-3 + PUFA	27 untreated, non-depressed patients with SAD (social anxiety disorder), 22 controls. SAD was assessed with the Liebowitz Social Anxiety Scale. Erythrocyte PUFA concentrations was measured by gas-liquid chromatography	Significant inverse correlations were obtained between levels of n-3 PUFAs and LSAS scores	Differences in the fatty acid composition between the 2 groups were found in the n-3 PUFA family and not in the n-6 PUFA family. Ratio of DHA to 22:5n-6 in erythrocytes was significantly lower in the patients. Sign. negative correlation between RBC DHA concentrations in the patients and SAD severity
de Oliveira et al. [69]		Vit C (500 mg/d)	Adults		double-blind, randomized, placebo-controlled trial; n = 42 (n = 21 vitamin c, n = 21 placebo)	Vitamin C reduced anxiety levels and in comparison to the controls → led to higher plasma Vit C concentration. Significant difference between Vit C and control group regarding the heart rates. Vit C led to decreased heart rate after the intervention. Vit C important therapeutic role on anxiety + possible use of antioxidants in reduction/ prevention of anxiety levels	
Gautam et al. [71]	Depression	Antioxidants; Vit A	Adults (20–60 years)		n = 100 (n = 40 GAD, n = 40 depressed, n = 20 healthy controls).	antioxidant supplement therapy useful adjuvant therapy for individuals with stress-induced psychiatric disorders	
de Koning et al. [67]			Adults (64–98)	Vit D	Results from the Longitudinal Aging Study Amsterdam (population-based cohort study); sample 1: n = 1259, 64–88 years; sample 2: n = 892, 60–98 years	individuals with 25(OH) D < 50 nmol/L showed more anxiety symptoms than individuals with 25(OH) D ≥ 50 nmol/L. No significant cross-sectional or longitudinal association between 25(OH)D levels and anxiety symptoms	possibility of selective non-response of the most vulnerable older persons excluding older and individuals with severe depressive symptoms small size of participants with clinically relevant anxiety symptoms (reduction of power). No control of potential confounders (sunlight exposure, Vit D intake)

▶ **Table 3** Continued.

Authors (Year)	Second MH condition	Supplement	Probands	Parameter	Design	Results	Limitations
Mazloom et al. [70]	Depression	Vit C (1000 mg/d), Vit E (400 IU/d)	Adults (DM II)		Randomized, single-blind, Placebo-controlled Trial. evaluation of the effects of Vit C and Vit E on depression, anxiety and stress levels (measured with Depression Anxiety Stress Scale 21-items) in DM II. Patients: n = 45; 3 groups: n = 14 Vit C, n = 14 Vit E, n = 13 placebo. duration: 6 weeks. Vit C group: 1000 mg daily for 6 weeks. Vit E group: 400 IU daily for 6 weeks. Placebo group: acetate cellulose 1000 mg daily for 6 weeks	significant decrease in anxiety levels in Vit C group	small sample size, short duration of treatment inadequate doses of vitamins no measurement of serum Vit C and E at baseline and follow-up
Yilmaz et al. 2016	Fibromyalgia	Vit D3 (50 000 IU/ week) calzium (1000 mg/d)		25-OH D3 < 25 ng/mL	n = 58 Chronic nonspecific widespread pain patients with Vit D deficiency	Vit D replacement treatment → improved musculoskeletal symptoms, level of depression and quality of life	no control group, short follow-up period, parathyroid hormone and urinary calcium not assessed
Su et al. 2018		Omega-3-PUFA			Review of 1203 participants, 55 % female, mean age 40.6 years	Additional treatment with PUFA could be successful in anxiety patients, but only in doses > 2000 mg/d. p = 0.01	
McCabe et al. 2015	Fibromyalgia	Vit B, Vit C, Zinc, Magnesium	Male (40–79);	Vit D	Longitudinal study (European Male ageing study) n = 2369. Pain was assessed at baseline and follow-up. Chronic widespread pain (CWP) was measured using the ACR criteria for fibromyalgia. Serum 25-hydroxyVit D (25-(OH) D) was assessed by radioimmunoassay	Low Vit D is associated with the new occurrence of CWP (this may be explained by adverse health factors like obesity and depression)	

20 patients receiving placebo, and there was no significant difference in outcomes; there was also no significant effect on inflammatory cytokines or CD8 + T cells [45]. A study of 274 females with low Vit D levels receiving different doses of Vit D and calcium showed no dose correlation [46]. A small survey with 34 nurses as probands also showed no effect of Vit D supplementation on depression [47]. Stefanowski et al. suggested that continuous supplementation may reduce the risk of recurrence of depression but saw only a possible effect in treatment [48].

Summarizing the described studies, there is no difference in relation to therapeutical effects when administrated Vit D [40–48].

Other supplements

The literature on other supplements was much poorer, mostly referring to PUFA. Smith et al. reported a 50 % reduction in MAM-D scores under supplementation with docosahexanacid (DHA) over 8 weeks [49]. Kiecolt-Glaser et al. [50] undertook a placebo-controlled survey with 68 medical students (34 vs. 34) over 12 weeks; the findings showed a significant reduction in anxiety (BAI) but no changes in depressive symptoms (CES-D) [50]. A decrease in inflammatory agents, such as IL-6 and TNF-α, could be observed. The same authors [51] reported that a diet with high n-6:n-3 PUFA ratios is associated in the elderly with an elevated risk of depression and inflammatory diseases. Only trends regarding to depression could be seen in 60 females aged 45–65 in a triple blind design study of PUFA supplementation in combination with citalopram [52]. A placebo-controlled study on shift workers (n = 136) demonstrated reduced BDI scores in all groups, including placebo [53, 54]. The PUFA group showed a stronger decline in inflammatory markers (C-reactive protein). Messarmore et al. [55] performed a review on PUFA in bipolar disorder and suggested a possible relationship with pathophysiology and pathoetiology [55]. Further reviews also displayed a positive effect on depression [56, 57]. A review of patients with depression and PTSD found improvements in neurocognitive functioning and benefits for depressive symptoms and suicidality [58]. Trebatikáa et al. found a surplus for patients with comorbid cardiovascular disease and depression [59]. As a natural source of PUFA, fish oil, combined with a Mediterranean diet, also had a positive effect on depression [60]. Administration of supplements like DHA, PUFA, and fish oil showed a positive effect therapeutical approach, inflammatory factors, pathophysiology, and pathoetiology of depression [49–60].

The effect of Vit C (1 g/day) on depression, in combination with citalopram, was not superior to the effect of citalopram and a placebo [61]. Payne et al. reported that depressive persons had a lower intake of food containing Vit C [62]. Ngyuen et al. found reduced consumption of all vitamins except for Vit D and retinol in a sample of 1634 Japanese individuals and elevated depressive symptoms primarily in female and overweight participants [63]. The reduced intake of B-group vitamins, Vit K and Vit C may be a possible link to this symptomatology. Singh et al. reported the positive effect of thiamine on depression [64]. Sarris (2016) found that folic acid only had a positive effect in combination with fluoxetin, not with other tested antidepressive drugs; the effect of Vit B 12 on depression was significant in combination with imipramine and fluoxetin, Vit B 6 or a combination of the mentioned ones showed no effect [65]. This suggests that the administration of supplements in combination with psychiatric medication lead to a positive effect on depression [62–64], but it has to kept in mind which combination and concentration can be inserted. [65].

The role of supplements in anxiety

The impact on anxiety is presented in ▶ **Table 3**.

The effects of Vit D on anxiety are also discussed very contradictorily. Wu et al. [66] reported the protective effects of higher Vit D levels in a cohort with anxiety and the history of stroke, whereas de Koning et al. [67] in another study could see no positive effect after adjustment for confounding variables. PUFA was reported to be useful [68] in anxiety, also the effect of Vit C [69–71].

Discussion

There are many indications of the complementary positive effects of Vit D and PUFA on depressive symptoms, anxiety, and pain, but there are few RCTs, and the recruitment of probands with mostly mild symptomatology and often relatively small number of probands recruited is a major limitation. The available reviews involve heterogeneous populations. Most authors recommend studies with more probands and narrower designs. Studies with more severely ill probands could only be carried out as an add-on to guideline therapies for ethical reasons. The supplements reviewed above are reported as harmless in most of the screened literature, in case that the authors are making a comment on this topic. Nevertheless, there is no clear objective and in case of overdose side effects and toxic symptoms could not generally be suspended, especially in case of the fat-soluble vitamins (A, E, D, K), which could accumulate in fatty tissue. However, in spite of the relatively low reported rate of such events, there are no remarkable reasons to suspend them generally as additions to standard therapy. The literature on supplements other than Vit D is scarce, so it is not possible to make recommendations. It has to be mentioned that most of the studies included were not designed to investigate the special therapeutical effect of supplements on psychiatric disorders, and for ethical reasons it is supposed to be critical to refuse evidence-based, guideline-suitable therapy to persons with severe illness for scientific reasons. Thus, for a final judgment of possible role of dietary supplements in depression and anxiety, further studies, especially designed to reveal such effects, are needed. Due to the fact that the topic of dietary supplement in psychiatry are not a special topic of research until now, and the psychiatric evidence of most of the screened literature is more a “side effect,” the validity of our study is imitated. As per findings of previous reviews, the current evidence base is limited by investigations with low power, a lack of standardized experimental design with widely varying outcome measures, and an inhomogeneous patient population, limiting the generalizability of results. Many studies are also not primarily designed to evaluate the topics relevant to this paper, and information is gathered as a side effect of other research topics. Thus, to enhance knowledge on the effects of dietary supplements in depression and anxiety, further investigations and surveys, especially designed on these topics, has to be carried out. In our opinion, such surveys will be very valuable due to the relative low rate of contraindications for the use of such substances and the low rate

of adverse effects, especially in comparison with standard pharmaceutical treatment.

Limitations

As a basic principle of a narrative review, the approach is vulnerable to limitations such as missed references, especially in comparison with a meta-analysis. We have tried our best to handle such limitations carefully. The aforementioned investigations do provide enough knowledge, however, to justify the efforts of a systematically and methodologically investigations with higher degree of evidence.

Contributors

BE and SK contributed to the literature search. KH wrote the first draft of the manuscript, and all authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors all declare no conflicts of interest.

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