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The Effect of Vitamin D, B12, and Folic Acid Supplements in Relieving Major Depressive Symptoms, General Anxiety Disorder among Adults and Adolescents - A Systemic Article Review

Authors

Dr Abdeljawad Salim Ayesh Salem[1], Iyad Awad Yousef Tanash[2], Shakil Ahmad[3]

[1]Consultant Family Medicine, South Wakra Health Center, Department of Primary Healthcare (PHCC), Ministry of Public Health (MOPH), Al wakra city. Qatar

[2]Specialist Family Medicine, South Wakra Health Center, Department of Primary Healthcare (PHCC), Ministry of Public Health(MOPH), Al wakra city. Qatar

[3]Manager of Data and Performance Management, Department of Primary Health Care (PHCC), Ministry of Public Health (MOPH), Doha, Qatar

Abstract

Subjective

- *Depression and anxiety disordersare a heterogeneous disorders and are thought to develop as a result of complex interactions between genetic and environmental Factors.(1)*
- *Vitamin D deficiency is the most common cause of Osteomalacia among adults and adolescents with its associated classical symptoms such as bones pain, muscle weakness which may affect productivity, daily activates, school and work absence and mood.*
- *Vitamin B12 deficiency causes complex hematological and neurological signs and symptoms as easy fatigability, lethargy, pallor, ictrous, paresthesia, difficulty of balance or loss of proprioception and neuropsychiatric symptoms may be presented in severe cases.*
- *Vitamin B9 deficiency is a rare condition causes complex hematological signs and symptoms as easy fatigability, lethargy, pallor, ictrous, symptoms may be presented in severe cases.*

Aim of the study: *To review articles studying the relationship between Vitamin D deficiency and/ or vitamin B12 deficiency, and/or B9 deficiency levels and supplements in relieving major depression (MDD) and general anxiety disorder (GAD) symptoms.*

Methods: *Performed between January 2023 and August 2023, the main inclusion criteria were randomized controlled trials (RCTs), with patients ≥ 12 years old, both sexes, fulfilling target diagnoses of major depressive disorder (MDD), generalized anxiety disorder (GAD), or mild to severe depressive and anxiety symptoms. In addition, the RCTs were included if the scales to assess the severity of the symptoms were standardized rating scales in psychiatric. Trials that reported diagnoses of schizophrenia, perinatal depression, bipolar depression, sleep disorders, eating disorders, cancer, and multiple sclerosis in association with any of the mentioned diagnoses were excluded.*

Discussion: *Upon the 19 article (RCTs)studies reviewed and included, 8 articles were studying the significant relationship between vitamin B12 and B9 supplementation alone on the relieving of symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), 3 articles were studying the significant relationship between vitamin B12, vitamin B9, vitamin D supplementation on the relieving of symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD) and 8 articles were studying the significant relationship between vitamin D supplementation alone on the relieving of symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD)*

Result: *According to the above mentioned 19 RCTs: included in this review articles the results showed that there is a significant relationship between vitamin D supplements on relieving on some symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), also there is a significant relationship between both vitamin B12 and D supplements on relieving some symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD) but there is no significant relationship between vitamin B12 and B9 alone.*
Keywords: *Major Depressive Disorder (MDD), General Anxiety Diorder(GAD),Vitamin D ,Vitamin B12, Vitamin B12 and Folic acid.*

Introduction

Depression and General Anxiety Disorder (GAD) are extremely common mood disorder with up to 30% of primary care patients having depression, while GAD is the most prevalent psychiatric disorder, about 7% of women and 4% of men attending to primary health services will meet the criteria for GAD over a lifetime. (2)

The COVD 19 Pandemic undoubtably increased the risk of depression and GAD. One meta-analysis of studies of community -based prevalence of depression found a seven folds increase in depression in some heavily impacted unities in Europe and Asia.(2)

Depression is the leading cause of disability worldwide and induces substantial individual and societal burden. In addition, health-related quality of life (HRQOL) can be compromised by both mental disorders and reduced physical functions.(3)

Depression and low HQROL increase the risk of institulization and mortality. Especially in elderly adults, management of depression is often suboptimal, for instance due to the side effects of antidepressant medications with other drugs. Such complexities emphasize the need for simple and safe interventions for both prevention and treatment of Depression.(3)

According to the Global Burden of disease (GBD-2019) results, around285, 642 million people were diagnosed with Depression Disorder and 301,390 million with anxiety disorder worldwide until 2019.(3)

Vitamin D deficiency Incidence is increasing throughout the world because of diminished exposure to sunlight Caused by urbanization with the use of automobiles and public transportation, living at high latitudes, winter season, institutionalization, sunscreen use. About 36% of adults in the United States are deficient in Vitamin D. Other risk factors include: the following: pregnant women, age over 65 years, obesity, dark colored skin persons, malnutrition,and intestine malabsorption.(2)

Vitamin B12 deficiency, Since Vitamin B12 is presented in foods of animal origin and dietary foodso vitamin B12 is extremelyrare, but it is seen. Vitamin B12 belong to the family of Cobalamins and serves as a cofactor for two important of homocysteine to reactions in humans as methylcarbylamine, it is a cofactor for methionine synthesis in the conversion methionine, and as adenosyl cobalamin for the conversion of methyl malonyl coenzyme A (COA) to succinyl CoA.(2)

Vitamin B12 deficiency causes complex hematological and neurological signs and symptoms as easy fatigability, lethargy, pallor, ictrous, paresthesia, difficulty of balance or loss of proprioception and neuropsychiatric symptoms may be presented in severe cases.(2)

Materials and Methods

Information sources and study design

The PRISMA 2020 guideline was followed to report this systematic review. The search was conducted in the Access, Cambridge Core, Cochrane Library, PubMed, and Science Direct electronic databases between January 2023 and August 2023. We considered randomized controlled trials (RCTs) published in English in the last ten years, screened in filter tools in all databases. A maximum of 8% of the references are from earlier periods, as it is necessary to cite the classic literature in this area. The Medical Subject Headings (MeSH) employed in the mentioned databases were: ‘folic acid’ OR ‘vitamin B12’ OR ‘vitamin D’; combined with

'generalized anxiety disorders' OR 'major depressive disorder' OR 'treatment-resistant depressive disorder'. Besides, we also used the following search terms: 'homocysteine and depressive disorder', 'methyl folate and depression', 'nutritional psychiatry and depressive disorder', 'B12 and depressive disorders', 'vitamin D and depressive disorders', and 'vitamin D and anxiety disorders', only in PubMed and Science Direct databases, screening RCTs on filters and advanced search.[3]

The peer-reviewed studies presenting results of RCTs, available within PubMed or Web of Science databases until September 2021 and published in English, were intended to be included. Systematic literature searching was conducted within two stages for studies published until October 2019 (before COVID-19) and from October 2019 to October 2022 (after announcing the first COVID-19 case). For the studies included within the second stage, additional searching of the COVID-19 incidence information in the studied group was conducted. The procedure applied was based on a previously adapted one for the assessment of vitamin D on mental health in adolescent and adults, including populations with diabetes, multiple sclerosis, as well as inflammatory bowel diseases and irritable bowel syndrome.[2]

Eligibility Assessment and Inclusion/Exclusion Procedure: Table 1. The patient, intervention/exposure, comparator, outcome, and study design (PICOS) criteria. The studies assessing the influence of supplementation of vitamin D and/or vitamin B12 and B9 on MDD and GAD within RCTs were intended to be included, based on the following inclusion criteria:

1. Study conducted in adults and adolescents (≥12 years old).
2. Study presenting oral vitamin D and/or vitamin B12 and B9 supplementation of known dose.
3. Studied population of patients with MDD and GAD.
4. A study described it as RCT.
5. Study published as an article in a peer-reviewed journal.
6. MDD and GAD monitored within the study using a valid mental health outcome measure.

The exclusions were conducted based on the following exclusion criteria:

1. The population age less than 12 years old.
2. Study presenting the influence of multiple nutrients combined.
3. Animal model study.
4. Study not published in English.
5. Study conducted in subjects with concurrent eating disorders.
6. Study conducted in subjects with concurrent intellectual disabilities.
7. Study conducted in subjects with any concurrent physical disease or disability.
8. Study conducted in pregnant women.

Table 1. The patient, intervention/exposure, comparator, outcome, and study design (PICOS) criteria.

PICOS Criterion	Inclusion	Exclusion
Population	Adult and adolescent patient wit MDD and GAD	Pregnant women, patients with any concurrent physical disease or disability, patients with concurrent eating disorders, patients with concurrent intellectual disabilities
Intervention/exposure	Vitamin D and/or B12 and B9 supplementation of known dose	Multiple nutrients supplementation
Comparison	Compared with control group	No compression with control without Vitamin D and/or B12 and B9 supplementation of known dose
Outcome	Depression and anxiety monitored	No valid mental health outcome measure applied
Study design	Randomized Controlled Trials (RCTs) published as articles in peer-reviewed journals	Studies not published in English, animal model studies

Subsequently, we read the remaining articles and excluded those failing to comply with the study topics by including patients more 12 years old or RCTs with non-standardized rating scales in psychiatric, or other than those selected in the inclusion criteria of this review, to assess the severity of depressive and anxiety symptoms. The eligible scales were Hamilton Depression Rating Scale (HAM-D/HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology/ Clinician Rating (QIDS-SR), Beck Depression Scale (BDI), Beck Depression Scale-II (BDI-II), Depression, Anxiety, and Stress Scale (DASS-21), Generalized Anxiety Disorder- 7 Scale (GAD7), and Geriatric Depression Scale-15 (GDS-15). Those with control groups with neither placebo nor current pharmacological treatment, or depressive symptoms diagnosed in a minority of the sample (less than 10%) were also excluded after reading.

Data Collection

The overview of data extraction in the selected studies is publication information first author); study design and sample profile (sample size, age, sex); diagnosis (MDD, GAD, depressive outcomes); intervention protocol (vitamin intervention as monotherapy or as an adjuvant to pharmacological treatment, AND control group under pharmacological treatment and/or with vitamin-placebo); presence of deficiency or low serum vitamin concentration at baseline; study duration (in weeks); outcomes (changes in blood biomarkers concentration, changes in rating scales scores for assessment of anxiety and/or depression symptoms); p-value (to report statistical significance).

Discussion

Diagnosing of MDD and GAD depending on DSM-IV criteria in most of the reviewed articles

Depression is defined as a mood disorder causing a persistent feeling of sadness and loss of interest, while the depressive disorders are classified as follows: disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dys- thymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition. The diagnosis of depression is based on assessment of nine depressive symptoms (sleeping disturbance, reduction in interest/pleasure, guilt feelings/thoughts of worthlessness, energy changes/fatigue, impairment of concentration/attention, ap- petite/weight changes, psychomotor disturbances, suicidal thoughts, and depressed mood), while in order to diagnose depression, five of them must be present-including depressed mood or interest/pleasure reduction. The etiology of depression includes stressful experiences which may trigger depression in vulnerable patients, while individual susceptibility results from biological and psychosocial characteristics and circumstances combined.

The detailed electronic search strategy applied for the systematic review within PubMed or Web of Science databases is presented in Supplementary Table S1. After searching databases for potentially eligible studies, duplicated records were removed, if found both within PubMed and Web of Science databases. Afterwards, potentially eligible studies were identified, while using inclusion and exclusion criteria. In order to identify ligible studies, the procedure was conducted within three stages: based on titles, based on abstracts, and based on full texts. Identification based on titles and based on abstracts were conducted using data available within PubMed and Web of Science databases. Only for the studies defined as potentially eligible, after a procedure based on title and based on abstract, the full texts were assessed. In order to obtain the full text of the study, electronic databases and libraries were searched, and if not available, the corresponding authors were asked for them. The identification within all stages was conducted by two researchers independently, but in case of disagreement, the third researcher was asked for an opinion.

Data Extraction Procedure and Study Assessment Procedure After including eligible studies, they were analyzed in order to extract necessary datato describe the study and the influence of vitamin D supplementation on depression. The following data were extracted:

1. the general description of the study and studied population (including authors andyear of the study; country/detailed location; studied population; period of the study);
2. the description of the studied population (including number of participants; female/ male proportions; age; inclusion and exclusion criteria);
3. the description of the supplementation of vitamin D (including dosage regimen; intervention duration) and of the assessment of depression status (including psycho- logical measure);
4. the observations and conclusions (based on those formulated by authors of the study).

If possible, all the data were obtained from a published study (or other publications referred within the study). If any information was missing, the corresponding authors were contacted. The data extraction was conducted by two researchers independently, but if any disagreement appeared, the third researcher was asked for an opinion.

The quality of the studies included was assessed based on the risk of bias defined for the studies. The revised Cochrane risk-of-bias tool for randomized trials was used with the RoB 2 tool. Each study was assessed within the following five domains of the risk of bias: arising from the randomization process, due to deviations from the intended interventions, due to missing outcome data, in measurement of the outcome, in selection of the reported result; and afterwards, it was assessed for the overall risk of bias.

Results

Search results

We identified 215 studies after removing duplicate trials (n = 189). The articles that constituted the results of this review are at the end of the flow chart. A total of 19 RCTs met the inclusion criteria. Then were categorized into three groups: vitamin B12 and B9 therapy group (Table 2), vitamin D therapy group (Table 3) and vitamin D and both vitamins B12 and B9 groups(Table 4).

In a total of 1121 subjects, patients ranged from 12 to 76 years of age. The diagnoses included in this study are 306 subjects with MDD alone or MDD and psychiatric comorbidities other than those cited in the exclusion criteria; 29 subjects with treatment-resistant major depressive disorder (R-MDD), 5 subjects with GAD; 156 subjects with mild to severe depressive symptoms, and 87 subjects with depressive outcomes. The strength and limitation of the findings are acknowledged in the discussion section.

Category 1: Vitamin B12 and B9 group

- Eight RCTs using B vitamins therapy in patients with R- MDD (n = 1), MDD (n = 4), or moderate to severe Quick depression (n = 3) were identified and evaluated. Three placebo-controlled Beck RCTs demonstrated that supplementation of folic acid, B12, or the metabolized active forms L-methylfollate and methylcobalamin, significantly increased the ale-15 serum concentration of serum folate or red cell folateand serum B12
- A cross-sectional (RCTs) study carry the title: The Effect of Two Years vitamin B12 and folic acid supplementation on Depressive symptoms and Quality of life in older with elevated Homocysteine concentration (the authors Elisa J. de Koning EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands, et.al Published: 23 November 2016 published in MDPI journal)

Methods and materials of this study: Double-bind, placebo-controlled intervention trial investigating the effect of two-years daily vitamin B12 (

500mcg) and folic acid (400mcg) supplementation versus placebo in relieving depreesive symptoms among old adult population sample. Participants were recruited from three different regions in Netherlands: Wageningen, Amsterda, and Rotterdam. Participants werr included if the had elevated Hcy concentrations (12-50mcmol/L). Exclusion criteria included cancer diagnosis withi the last 5 yeats (except for non-melanoma skin cancer).Serum Creatinin >150 mcmol/L. Current or rcent receiving intramuscular Vitamin B12 injection (<4 months).Use of high dose of folic acid(>300 mcg daily) (<4months).participation in other interventional studies.

	Crude Model		Model 1 [a]		Model 2 (Fully Adjusted) [b]	
	RR (95% CI)	*p*	RR (95% CI)	*p*	RR(95% CI)	*p*
GDS-15	1.03 (1.00, 1.07)	0.04	1.02 (0.99, 1.06)	0.26	1.00 (0.96, 1.03)	0.85
SF-12 PCS	1.04 (1.02, 1.05)	<0.001	1.02 (1.00, 1.04)	0.04	1.01 (0.99, 1.03)	0.51
SF-12 MCS	1.02 (1.00, 1.04)	0.06	1.02 (1.00, 1.03)	0.13	1.01 (0.99, 1.03)	0.33
EQ-5D Index	1.03 (1.01, 1.05)	<0.001	1.02 (1.00, 1.04)	0.02	1.02 (1.00, 1.04)	0.11
EQ-5D VAS	1.04 (1.02, 1.05)	<0.001	1.03 (1.01, 1.04)	0.01	1.02 (1.00, 1.04)	0.15

Table 3. Effect of the treatment on depressive symptoms, analyzed with logistic regression (total sample) and ANCOVA (subsample with symptoms) (intention-to-treat).

	Baseline	Two-Year Follow-up	Model 1 [a]			Model 2 (Fully Adjusted) [b]		
Logistic regression (total sample, *N* = 2588)	*N* with GDS-15 ≥ 5 (%)	*N* with GDS-15 ≥ 5 (%)	OR [c] (95% CI)	*p*		OR [c] (95% CI)	*p*	
			1.1 (0.8, 1.5)	0.56		1.1 (0.8, 1.5)	0.45	
B-vitamins	101 (7.0)	112 (8.6)						
Placebo	99 (6.8)	111 (8.5)						
ANCOVA (subsample GDS-15 ≥ 5, *N* = 161)	Median GDS-15 score (IQR)	Median GDS-15 score (IQR)	Mean change (95% CI)	*F*	*p*	Mean change (95% CI)	*F*	*p*
				0.57	0.45		0.36	0.55
B-vitamins	6 (5–8)	5 (3–7)	1.4 (0.7, 2.2)			1.5 (0.7, 2.2)		
Placebo	6 (5–8)	4 (3–6)	1.8 (1.1, 2.5)			1.8 (1.1, 2.5)		

	Intervention (*N* = 1461)	Placebo (*N* = 1458)	*p*
Descriptive variables:			
Women	736 (50)	724 (50)	0.70
Age (years)	73 (69–78)	73 (69–78)	0.38
Education (years)	9 (6–15)	9 (6–15)	0.59
Study location:			0.91
WU (Wageningen)	426 (29)	431 (30)	
Erasmus MC (Rotterdam)	649 (44)	636 (44)	
VUmc (Amsterdam)	386 (26)	391 (27)	
Smoking			0.97
Current	139 (10)	142 (10)	
Former	828 (57)	821 (56)	
Never	494 (34)	495 (34)	
Alcohol use:			0.31
Light	994 (68)	972 (67)	
Moderate	417 (29)	422 (29)	
Excessive/very excessive	50 (3)	62 (4)	
Body mass index, kg/m^2	26.7 (24.6–29.2)	26.6 (24.6–29.4)	0.65
Physical activity (kcal/day)	546 (335–823)	556 (347–831)	0.32
MMSE (score 0–30)	28 (27–29)	28 (27–29)	0.10
Depressive symptoms/quality of life measures:			
GDS-15	1 (0–2)	1 (0–2)	0.45
SF12 MCS	57.1 (52.3–59.8)	56.6 (51.6–59.8)	0.29
SF12 PCS	51.3 (43.8–54.2)	50.8 (42.4–54.4)	0.32
EQ-5D Index	0.86 (0.81–1.00)	0.86 (0.81–1.00)	0.84
EQ-5D VAS	80 (75–90)	80 (75–90)	0.50
Biochemical analyses:			
Serum folate (nmol/L)	18.8 (14.9–24.7)	18.9 (14.8–24.5)	0.53
Serum vitamin B_{12} (pmol/L)	267 (213–341)	266 (204–343)	0.27
Serum holoTC (pmol/L)	65 (48–86)	63 (45–84)	0.03
Serum MMA (µmol/L)	0.22 (0.18–0.30)	0.23 (0.18–0.31)	0.26
Plasma Hcy (µmol/L)	14.3 (13.0–16.5)	14.5 (13.0–16.7)	0.46
Serum creatinine (mmol/L)	82.0 (71.0–94.0)	82.0 (71.0–94.0)	0.59

Table 1. Randomized clinical trials on the effect of intervention with B vitamins on individuals with depressive disorder.

Author	Study and Sample	Diagnosis	Intervention Protocol	Deficiency or low B vit. levels**	Study Duration	Results	p
Papakostas et al. [62]	RCT 1 Start: 148 subjects End: 119 subjects RCT 2 *(Sequence of RCT 1)* Start: 75 subjects End: 61 subjects Both sexes Age: 18–65 years	R-MDD	RCT 1 IG (n = 36): 7.5 mg/day L-methylfolate + antidepressant SSRIs CG (n = 112): placebo + antidepressant SSRIs RCT 2 IG (n = 47): 15 mg/day L-methylfolate + antidepressant SSRIs CG (n = 28): placebo + antidepressant SSRIs	***	RCT 1: 4 weeks RCT 2: 4 weeks	RCT 2 IG: ↓ HAM-D and QIDS-SR score	<0.05
Syed et al. [63]	RCT Start/end: 73 subjects Both sexes Age: 24–51 years	Depressivesymptoms (HAM-D ≥ 16)	IG (n = 34): 1,000 mcg/week B12 intramuscular injectable for 6 week + antidepressant SSRIs or TCA CG (n = 39): antidepressant SSRIs or TCA	Yes (Low normal B12 190–300 pg/ml)	12 weeks	IG: ↓ HAM-D	<0.01
Almeida et al. [64]	RCT Double-blind Placebo-controlled Start: 153 subjects End: 128 subjects Both sexes Age: 50–85 years	MDD	IG (n = 62): 2 mg/day folic acid, 25 mg/day vitamin B6, 0.5 mg/day B1 + 10–40 mg/day Citalopram CG (n = 66): placebo + 10–40 mg Citalopram	No	52 weeks	IG: ↑ [red cell folate,serum B12] and ↓[serum Hcy]; ↓ MADRS score	<0.05; >0.05
Bedson et al. [65]	RCT Double-blind Placebo-controlled Start: 475 subjects End: 440 subjects Both sexes Age: 19–81 years	Moderate or severe depression (BDI-II ≥ 19)	IG (n = 223): 5 mg/day folic acid + antidepressant SSRIs or TCA CG (n = 217): placebo + antidepressant SSRIs or TCA	No	12 weeks	IG: ↑ [serum folate, red cellfolate]; ↓ [Hcy]; ↓ BDI-II score and ↓ MADRS	< 0.001 < 0.05; > 0.05
Ghaleiha et al. [66]	RCT Double-blind Placebo-controlled Start/end: 51 subjects Both sexes Age: 18–50 years	MDD or severe depression (HDRS >24)	IG (n = 25): 300 mg/day thiamine + 20 mg/day fluoxetine CC (n = 26): 300 mg/day placebo + 20 mg/day Fluoxetine	No	12 weeks	IG: ↓ HDRS score from the 6th week and maintenance until the 12th week.	<0.05
***Mech and Farah** [24]	RCT Double-blind Placebo-controlled Start: 330 subjects End: 282 subjects Both sexes Age: 18–67 years	MDD (alone or withattention deficit; hyperactivity and GAD – and positive for MTHFR C677 T or A1298C polymorphism)	IG (n = 159): 25 µg/day B1, 25 µg/day B2, 25 µg/day B6; 10.5 mg/day B9, 50 µg/day B12; 25 µg/day NADH; 500 µg/day TMG; 1.5 mg/day AminoFerr®, 24 mg/day vit.C-Mg; 1 mg/day vit.C-Zn; 1 mg/day LTAMS, and 20 mg/day FS-ω3 CG (n = 123): placebo gelatin capsule	***	8 weeks	IG: ↓ [serum Hcy]; ↓ MADRS scorewith 42% in complete MDD remission	<0.001 <0.05
Kakar, Jehangir and Khattak [67]	RCT Placebo-controlled Start/end: 260 subjects Both sexes Age: 18–60 years	MDD and HAM-D score >14 (moderate to severedepression)	IG (n = 130): 15 mg/day L-methylfolate + antidepressant SSRIs CG (n = 130): placebo + antidepressant SSRIs	***	24 weeks	IG: ↓ HAM-D	<0.05

Ref.	Authors, Year	Country/Detailed Location	Studied Population	Period of the Study
[29]	Khoraminya et al., 2013	Iran/Tehran	Patients with major depressive disorder from the Roozbeh Psychiatry Hospital, Tehran University of Medical Sciences, Tehran	From November 2010 to December 2011
[30]	Marsh et al., 2017	United States of America (USA)/Massachusetts	Patients with bipolar depression and vitamin D deficiency from central Massachusetts, USA	From June 2013 to April 2015
[31]	Hansen et al., 2019	Denmark/Esbjerg, Odense and Svendborg	Patients with depressive episode from the mood disorder clinic in the Region of Southern Denmark	From November 2010 to June 2014
[32]	Alavi et al., 2019	Iran	Older patients with moderate to severe depression from three psychiatric clinics	From March 2016 to February 2017
[33]	Kaviani et al., 2020	Iran/Tehran	Patients with mild to moderate depression referred to the outpatient clinics of Baharloo Hospital	From May 2018 to June 2019
[34]	Amini te al., 2020	Iran/Ahvaz	Female patients with postpartum depression from the outpatient clinic of Ahvaz Jundishapur University of Medical Sciences	From June to November 2017
[35]	Alghamdi et al., 2020	Saudi Arabia/Jeddah	Patients with major depressive disorder from the psychiatry clinic at the King Abdulaziz University Hospital	Not specified (3 months)
[36]	Zhu et al., 2020	China/Anhui	Patients with depression, anxiety and low 25(OH)D levels recruited through advertisements from Anhui Mental Health Center	From November 2015 to September 2019

Category 2: Vitamin D group

- Eight RCTs investigating Vitamin D therapy in patients with MDD (n = 3), GAD (n = 1), or mild to severe depressive symptoms (n=4) were identified. All studies reported the presence of deficiency (< 20 ng/ml) or inadequate serum vitamin D levels (20 > 30 ng/ml) in the sample at baseline (Table 2). The 25-hydroxyvitamin D (25(OH)D) is the primary circulating metabolite of vitamin D and was the routine laboratory biomarker for monitoring organic status in all studies included in vitamin D clusters.

The RCTs demonstrate that vitamin D supplementation significantly increased serum 25(OH)D concentration, and individuals with a proven serum 25(OH)D deficiency/inadequate concentration benefited from supplementation to correct hypovitaminosis.

Category 3: Vitamin B12, B9 and Vitamin D group

- three RCTs investigating Vitamin D , B12 and B9 therapy in patients with MDD (n = 2), GAD (n = 1), A cross-sectional study (RCT)carry the title :The relationship between Vitamin B12 and Vitamin D levels and subjective cognitive complaints in patients with first episode major depression(the authors Selen Isik Ulusoy et-al;Baskent University, Faculty of Medicine, Konya Research Hospital, Department of Psychiatry, Konya – Turkey; Accepted: December 10, 2020)
- According to the above mentioned from the 20 RCTs included in this review article the results showed that there is a significant relationship between vitamin D supplements on relieving on some symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), also there is a significant relationship between both vitamin B12 and D supplements on relieving some symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD) but there is no significant relationship between vitamin B12 and B9.

Conclusion

According to the results of the above mentioned reviewed studies vitamin D has the most significant and effective rule in relieving some major depressive disorders symptoms especially the cognitive function in Adolescent n, depressed mood, easy fatigability and lethargy either in its usual daily doses (1000-2000 unit per day) or weekly dose(50000unit once a week) for adults and adolescent ($\geq$ 12 years old)of age and adults, also adding vitamin B12 supplements in its either daily dose (500-1000 mcg daily added with vitamin B12 has a significant improvement in adolescent who are suffering from some cognitive functions disabilities and poor school performance as mentioned in a reviewed study above) but there is no significant relationship between giving patient folic acid alone vitamin B12 alone or bothin relieving of depressive or GAD symptoms. The recommendation is to look for any serum vitamin D or vitamin B12 deficiencies among patient who attending to your clinic suffering from MDD or GAD symptoms and treating them effectively.

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