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Dietary Supplementation for Symptom Alleviation of Major Depressive Disorder

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Abstract

Major depressive disorder, also known as clinical depression, is a mental disorder that is marked by a variety of debilitating symptoms, including feelings of worthlessness and suicidal thoughts or tendencies. MDD is also characterized by its inflammatory properties, and research has shown the presence of vitamin D receptors in the brain. Currently, antidepressants are the most commonly prescribed treatment for symptom alleviation. For these reasons, anti-inflammatory food sources or supplementations can be considered as alternative methods of reducing symptoms related to MDD. This study conducted a systematic review of relevant interventions and found a moderate-to-large effect of supplementation with omega-3 fatty acids and vitamin D for reducing symptoms related to MDD. These dietary supplements were well-tolerated and had fewer side effects than commonly prescribed antidepressants. Use of dietary supplements for symptom alleviation of MDD can also work to improve the overall health of the individual, however, more focused research is necessary to determine optimal dosages and time frames.

CHAPTER ONE

Background

The National Institute of Mental Health (NIMH) defines major depressive disorder, also referred to as major depression or clinical depression as “a mood disorder with severe symptoms that impair an individual’s thinking, feelings, and ability to handle daily activities” (NIMH, 2016). Major depression is a common and debilitating illness that affects over 300 million people worldwide (World Health Organization, 2017). In the United States, an estimated 18 million people, accounting for 8.1% of the total population above age 20, were diagnosed with major depression from 2013-2016 (Pratt & Brody, 2018). As of 2010, the economic burden of depression in the United States is reported to be over $200 billion, with about $90 billion attributed to direct costs and $10 billion attributed to costs related to suicide (Greenberg, Fournier, Sisitsky, Pike, Kessler, 2015).

Signs, Symptoms, and Diagnosis

There are many subsets of depression such as postpartum depression, bipolar depression, seasonal affective disorder, and major depression. An individual suffering from major depressive disorder experiences symptoms that occur more frequently and last for a longer period than a non-depressed individual. General symptoms include lack of energy, trouble thinking and concentrating, sleep disturbances, and frequent or recurrent suicidal thoughts or attempts (Mayo Clinic, 2014). Symptoms must be present every day of a two-week period, and can be noticed by the individual or an objective party, such as a clinician, friend, or family member (APA, 2014).

Diagnosis

According to the American Psychological Association (2014), the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is routinely used by mental health professionals to classify mental disorders. An individual must meet five or more of the nine predetermined criteria established in DSM-5, including: depressed mood and loss of interest or pleasure in the same two-week period, symptoms cause clinically significant impairment in social, occupational, or other key areas of function, the episode is not attributed to effects of a substance or another medical condition, and lifetime absence of manic or hypomanic episodes (APA, 2014). The full list of the DSM-5 predetermined criteria that are required for the diagnosis of major depressive disorders is presented in Appendix A.

When an individual is diagnosed with major depressive disorder, any one of several rating scales can be used to classify the severity of symptoms. They include The Hamilton Rating Scale for Depression (HRSD), the Beck Depression Inventory (BDI), and the Montgomery-Asberg Depression Rating Scale (MADRS). The HRSD is one of the most widely used and earliest measurement tools developed for the diagnosis of major depressive disorders (Sharp, 2015). Published by Max Hamilton in 1960, the HRSD is a clinician-rated questionnaire that evaluates the core symptoms of depression, and it has been stated that “the value of the questionnaire depends on the skill of the interviewer” (Sharp, 2015). The HRSD was designed to be administered by a health care professional in the form of a structured interview. The questionnaire covers categories including depressed mood, suicide, work and interests, gastrointestinal somatic symptoms, and weight loss (Hamilton, 1960).

The original questionnaire contained 17 items with four additional questions that can be used as a supplement to provide additional information. The points tallied from the four

supplemental questions are not included in the total score. Each question of the rating scale is scored on a scale between zero and four points. The classification and tally of the final scores vary based on which version of the questionnaire that was applied. Generally, a score of 0-7 is normal, 8-16 indicates mild depression, 17-23 indicates moderate depression, and a score greater than or equal to 24 indicates severe depression (Sharp, 2015).

The BDI is a 21-question self-reported measurement scale and is considered the "gold standard" for self-rated measurement scales (Cusin, Yang, Yeung, Fava, 2009). The purpose of the scale is to enable patients to describe their depressive symptoms at the time of completion of the questionnaire. This questionnaire was adapted to better align with DSM criteria by adding agitation, worthlessness, concentration difficulty and loss of energy to the questionnaire (Cusin, Yang, Yeung, Fava, 2009). All questions are scored on a scale between zero and three points, with higher scores indicating a higher severity of symptoms. Classification and tally of the final scores include the following: 0-13 indicates minimal depression, 14-19 indicates mild depression, 20-28 indicates moderate depression, and a score of 29-63 indicates severe depression (Beck, Steer, Ball, Ranieri, 2010).

The MADRS is a 10-item questionnaire administered by clinicians and was designed to be sensitive to the effects of antidepressant medications (Cusin, Yang, Yeung, Fava, 2009). The questions on the MADRS target the psychosocial aspects of major depressive disorders, as opposed to the physical symptoms. Each question is scored on a scale ranging from zero to six points. The classification and tally of the final scores is as follows: 7-19 indicates mild depression, 20-34 indicates moderate depression, and a score of 35-60 indicates severe depression (Cusin, Yang, Yeung, Fava, 2009). Table 1 provides a visual representation of score ranges for the three depression scales described above.

Table 1. Depression Rating Scale Scoring Classification

Depression Rating Scale	Score Ranges	Symptom Classification
HDRS	0-7	Normal
	8-16	Mild Depression
	17-23	Moderate Depression
	≥ 24	Severe Depression
BDI	0-14	Minimal
	14-19	Mild
	20-28	Moderate
	29-63	Severe
MADRS	7-19	Mild
	20-34	Moderate
	35-60	Severe

Treatment

Once an individual has been diagnosed with major depressive disorder, there are many treatment options including pharmaceuticals and psychotherapy that can be utilized. Data collected from 2011-2014 by the National Health and Nutrition Examination Survey (NHANES) showed that 12.7% of individuals 12 years and older reported taking antidepressant medication during the past month, and 25% of those who took antidepressants had done so for a duration of 10 or more years (Pratt, Brody & Gu, 2017).

In a healthy brain, neurons receive chemical messages from neurotransmitters; however, in the brain of an individual with major depressive disorder, neurotransmitters may not be released at all, or neuronal receptors may not recognize a specific neurotransmitter causing an excessive or inadequate response to the signal (Miller, 2009). Selective Serotonin Reuptake Inhibitors (SSRIs) work by blocking the reuptake of the neurotransmitter serotonin in the brain, making it more bioavailable (Mayo Clinic, 2016). The increased availability of serotonin helps to improve mood in individuals with major depression. SSRIs approved by the Food and Drug Administration include: citalopram, sertraline, escitalopram, fluoxetine, paroxetine, and vilazodone (Mayo

Clinic, 2016). Common side effects associated with these SSRIs include vomiting, muscle and joint pain, heavy menstrual periods, change in sexual drive, weight loss, anxiety, difficulty sleeping, and uncontrolled shaking, among others (United States National Library of Medicine, 2018). Although prescribed pharmaceuticals are the most common form of treatment for major depression, only 50-75% of patients experience symptom severity reduction with their first trial (Gertsik, Poland, Bresee, Rapaport, 2012). Additionally, individuals diagnosed with major depressive disorder have increased mortality by suicide, which was ranked the 10th leading cause of death in 2014 (CDC, 2015).

Role of Dietary Supplements in Depressive Disorders

Fats are classified by their chemical structure: saturated fats have no double-bonded carbons and unsaturated fats have one or many double-bonded carbons. Polyunsaturated fats have multiple double bonded carbons and are further classified based on the position of the double bond in the fatty acid chain. Dietary polyunsaturated fatty acids (PUFAs) are essential fatty acids that must be consumed via food sources since they are not synthesized in the human body (Grosso, Galvano, Marventano, Malaguarnera, et al., 2014).

Omega-6 (n-6) polyunsaturated fatty acids have the first double bond located on the sixth carbon in the fatty acid chain. N-6 PUFAs are synthesized from linoleic acid which can be converted to arachidonic acid (Grosso, et al., 2014). Linoleic acid is an essential fatty acid, meaning it must be consumed from food sources since it is not naturally made in the body (National Institute of Health, 2005). Omega-3 (n-3) fatty acids have the first double bond located on the third carbon in the fatty acid chain. N-3 PUFAs are synthesized from alpha-linolenic acid which then forms the long chain PUFAs eicosapentaenoic acid (EPA) and docosahexanoic acid

(DHA) (Grosso et al., 2014). Fish and fish oils, flaxseed and flaxseed oil, canola oil, soybeans and soybean oil, tofu, and walnuts are some of the various food sources (Ehrlich, 2014). Eicosanoids (signaling molecules) derived from arachidonic acid, an n-6 PUFA, promote inflammation while n-3 derived eicosanoids are anti-inflammatory. The suggested ratio of omega-3 to omega-6 is between 1:1 and 2:1; this ratio allows for anti-inflammatory n-3 derived eicosanoids to overtake the pro-inflammatory effects of n-6 derived eicosanoids (Grosso et al., 2014).

The typical Western diet, or standard American diet, is high in added sugars, saturated fats, salt, red meat and processed foods with low intake of whole grains, fruit, vegetables, and vegetable oils (Bloomfield, Kane, Wilt, Koeller, Greer, MacDonald, 2015). This dietary pattern has a disproportionate ratio of omega-6 to omega-3 (Papanikolaou, Brooks, et al., 2014), and it has been reported that countries with higher fish oil intake have lower prevalence of major depression (Nements, Stahl, Belmaker, 2002).

When the appropriate ratio (n-3:n-6) is consumed, n-3 replaces inflammation promoting n-6 in cell membranes throughout the body including blood vessels and neuronal cells. The n-3 fatty acids EPA and DHA have been shown to reduce inflammation and may also be important for brain health and development (Ehrlich, 2014). DHA is linked to neuronal membrane stability and the function of serotonergic and dopaminergic neurotransmission, two mood-related neurotransmitters, while EPA is important for balance immune and neuronal functioning (Martinez-Cengotitabengoa, Gonzales-Pinto, 2017).

Vitamin D is a fat-soluble vitamin and hormone. It is metabolized in the kidneys to form calcidiol and calcitriol; calcitriol (1,25 (OH) D) is the active form and the dietary supplement of focus for this review (Perez-Lopez, 2007). Vitamin D can be obtained via food sources such as

fatty fish (i.e., salmon, tuna, mackerel, etc.) and fish liver oil. Egg yolks, beef liver, cheese, and egg yolks also contain small amounts of Vitamin D. Other sources are sun exposure and dietary supplements. Fortified foods are the largest source of Vitamin D. Some research has shown the presence of Vitamin D receptors in areas of the brain known to be compromised by major depression, although the exact biological mechanisms of how brain regions are compromised are not completely understood (Parker, 2017). Changes in serum Vitamin D concentration can have an impact on various neurotransmitters such as serotonin, noradrenaline, and dopamine (Parker, 2017).

Major Depressive Disorder (MDD) is characterized by neuronal inflammation that affects signal transduction. Inflammation has been linked to worsening of symptoms in some individuals with major depressive disorder. The association of major depressive disorder and inflammation opens the door to the exploration of methods to reduce the severity of symptoms. Due to the inflammatory nature of the disease, anti-inflammatory food sources can be investigated as an alternative to antidepressant medications as a treatment option. (Cite at least one reference for this paragraph)

The present systematic literature review has two overarching goals, the first being to understand the efficacy of dietary interventions with supplementation for symptom alleviation of major depressive disorder. In order to accomplish this goal, the study has the following objectives:

- **Objective 1:** Conduct a systematic literature review of dietary supplementation interventions and their association with symptom alleviation of major depressive disorder.

- **Objective 2:** Examine the influence of the dietary supplements Vitamin D and Omega-3 polyunsaturated fatty acids (PUFAs) in reducing symptoms related to MDD.

The second goal of this systematic literature review is to determine the effectiveness of two separate dietary supplementation interventions, Vitamin D and Omega-3 PUFAs. In order to achieve this goal, the objectives are as follows

- **Objective 1:** Calculate the effect size of pooled studies to determine optimal dosage of Vitamin D for improvement of depressive symptomology.
- **Objective 2:** Calculate the effect size of pooled studies to determine optimal dosage and time frame of supplementation with the Omega-3 PUFAs EPA and DHA for improvement of depressive symptomology.

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CHAPTER TWO

Methods

The goal of this study is to conduct a systematic literature review to determine the efficacy of dietary supplements for symptom alleviation of major depressive disorder by examining two independent variables: (1) Omega-3 polyunsaturated fatty acids (n-3 PUFAs) supplementation and (2) Vitamin D supplementation. The dependent variable of focus is depressive symptoms as measured by various depression assessment scales including HDRS, BDI, and MADRS. Furthermore, the effectiveness of two separate dietary interventions, n-3 PUFAs and Vitamin D supplementations, will be analyzed to determine if one intervention is more beneficial than the other. Interventions will be deemed beneficial based on reduction of depressive symptoms as reported by a comparison of the scores from the three depression scale measurement tools (HRSD, BDI, and MADRS).

Randomized controlled trials—studies that randomly allocate participants to receive either an experimental treatment or placebo—conducted between 2002 and 2017 will be included in this systematic literature review. Systematic reviews (i.e., studies that summarize outcomes of relevant studies on a chosen research topic (Uman, 2011)) and meta-analyses (i.e., statistical analyses of large sets of study results with the aim of deriving conclusions on the research topic (Haidich, 2010)), will also be included in this systematic literature review. This review will include many peer-reviewed studies published over a long period of time which will ultimately provide for increased statistical power of results. A flowchart illustrating the process for selection of studies included in the literature review is shown in Figure 1.

Search Strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, a 17-item checklist used to create a standardized system of conducting systematic reviews and meta-analyses (Moher, Shameseer, Clarke, Ghersi, Liberati, Petticrew, Shekelle, Stewart, 2015). The literature search was completed using the databases PubMed, CINAHL, and Google Scholar. Search terms included the following combination of words: “major depression and omega-3 fatty acids,” “major depressive disorder and n-3,” “omega-3 and MDD,” “polyunsaturated fatty acids and major depression,” “MDD and omega-3,” “Vitamin D and MDD,” and “Vitamin D and major depressive disorder” to identify the desired and relevant studies. Randomized controlled trials, meta-analyses, and systematic reviews conducted from 2002 to 2017 were included. The selection process followed carefully defined search criteria for studies that were in compliance with the goals and objectives of this study.

Inclusion criteria

Randomized controlled trials involving human adults aged 18 and over were included in the analysis. RCTs were limited to the English language, regardless of the country of completion of the study. Participants must have been diagnosed with major depressive disorder without mania (an unusual and extreme elation or energized behavior) or psychosis, hallucinations or delusions attributed to a loss of contact with reality (National Institute of Mental Health, 2016).

Additionally, all studies included in the review must have incorporated Vitamin D or n-3 PUFAs supplementation for the primary intervention. Finally, studies were selected if the primary outcome measures were depression rating measurement scale scores reported using either HDRS, BDI, or MADRS. To reiterate, depression scale scores are representative of

depressive symptoms—a higher score indicates more severe depression and a lower score indicates decrease in symptom severity.

Exclusion Criteria

Studies were excluded if they did not include depression scale scores from the HDRS, BDI, or MADRS as primary outcome measures. Studies investigating depressive symptoms related to comorbid mood disorders such as schizophrenia, bipolar disorder, or anxiety were excluded. Finally, RCTs investigating depressive symptoms related to comorbid chronic diseases such as coronary heart disease, diabetes, or cancer were excluded from the analysis.

Statistical Analysis

Independent samples t-test values for mean decrease in depression scale scores between the placebo group and experimental group were extracted from published RCTs. P-values were provided to determine any statistical significance. The t-test values were then utilized in effect size calculations. Effect size is a statistical measure used to quantify the standard difference in means between two groups (Coe, 2002). Cohen's d will be calculated by subtracting the mean of the experimental group from the mean of the control group and dividing the difference by the combined standard deviation of the experimental and placebo groups (Coe, 2002).

Through some algebra using Cohen's d effect size values, the value of *r*, the correlation coefficient, can be derived. ($d \div \sqrt{d^2 + 4}$). Effect size of included RCTs will be reported to measure the magnitude of the effect of the intervention, if any, on participants in the experimental group compared to the participants in the control group. The correlation coefficient (r) will also be calculated from effect size to determine the strength of the relationship between the independent variables, dietary supplementation, and the dependent variable, depressive symptomology.

Results

Study Selection

Database searching yielded a total of 373 studies for review. After removing studies that were not relevant to the topic of focus, 50 studies were available for inclusion in the review. Thirty-seven (37) studies were identified through database searching and 13 studies were identified through citations from previous completed studies. Forty-one (41) studies were available for inclusion in full-text screening once duplicates were removed. Additional abstract screening resulted in elimination of 19 additional studies. Studies were removed for investigating depressive symptoms related to chronic disease (n=4), bipolar depression (n=2), depression with a comorbid mood disorder (n=2), lack of supplementation with PUFAs or Vitamin D (n=2), and mentally healthy patients (n=3). Furthermore, six studies were eliminated for not investigating major depressive disorder. At the conclusion of screening, 21 studies were available for inclusion in the systematic literature review, 14 RCTs and 7 meta-analyses.

Characteristics of Included Studies

Fourteen separate double-blind, randomized placebo-controlled trials were identified and included for analysis. Collectively the included studies represent over 1,000 participants. Data was extracted on sample size, dosage of dietary supplementation, type of dietary supplementation (EPA, DHA, or calcitriol), length of intervention, and depression scale used. Characteristics of included RCTs are depicted in Appendix B. Standardized mean differences made available in the included meta-analyses are reported in Appendix C.

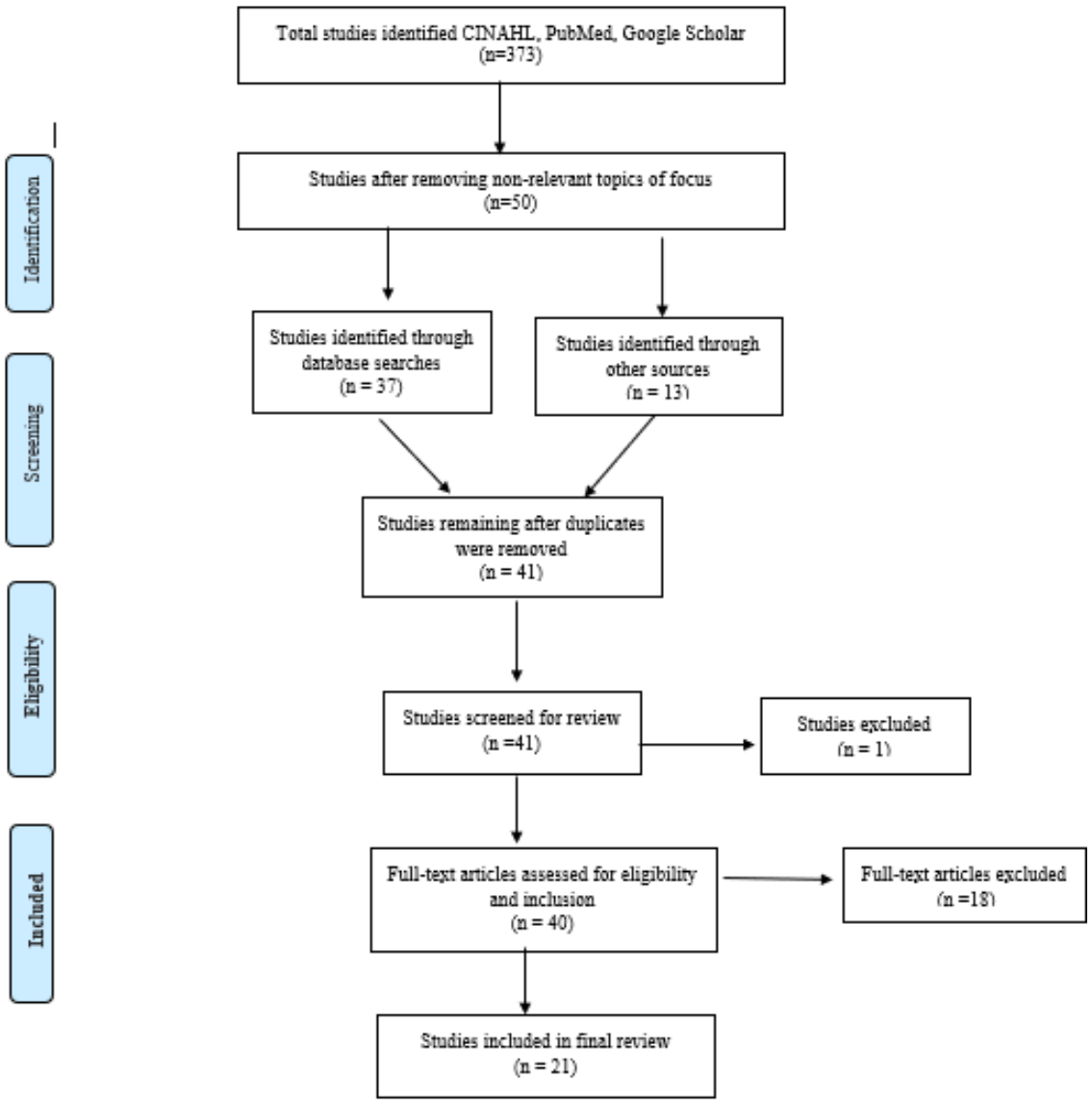

Figure 1. Flowchart of study selection (adapted from PRISMA protocol, Moher et al., 2015)

Data Analysis

Table 2 illustrates mean reduction in depressive scale scores reported as t-test values extracted from the published data. Change in scores were determined by subtracting mean scores at the trial's conclusion from mean scores at baseline in the placebo and experimental groups. The values are reported without units but represent overall decrease in depression scale score. Studies with statistically significant reductions are denoted with an asterisk (*). Three studies investigated augmentation of antidepressants with either EPA, DHA, or Vitamin D, however, only one study had sufficient data to complete calculations. Participants in the group receiving the antidepressant Fluoxetine in conjunction with Vitamin D supplementation saw a greater decrease in depression scale scores (17.7±7.0) when compared to participants receiving Fluoxetine alone (13.0±7.6). Of the remaining studies, seven saw a statistically significant decrease in depression scale score when comparing the placebo groups to the experimental groups receiving supplementation.

The effect sizes of the differences between placebo groups and experimental groups were calculated for the included RCTs (Table 3). Data for four RCTs was not included due to lack of appropriate data in the published studies. Seven of the included studies investigated PUFA supplementation with either e-EPA, EPA, DHA or a combination of both EPA and DHA. The effect sizes can be interpreted via the following classifications: 0.2-0.4 indicates a small effect, 0.5-0.7 indicates a medium effect, and 0.8 and above indicates a large effect. Four of the included RCTs showed the intervention provided a medium effect on reducing depressive symptoms when compared to placebo, four showed a large effect, and two showed the intervention provided a small effect on change in depressive symptoms. Highlighting studies that investigated more than one treatment option, one study showed treatment with EPA had a large

effect over placebo (1.58), while treatment with DHA had a small effect (0.17). The next study showed supplementation with 150,000 IU Vitamin D had a medium effect over placebo (0.76) while supplementation with 300,000 IU Vitamin D had a large effect (1.07). The final study that investigate more than one treatment option showed supplementation with DHA had a small effect over placebo (0.17) while supplementation with EPA had a large effect (1.07).

Table 2. Mean Decrease in Depression Scale Scores as Reported in Published Data

Author	Study group (placebo/experimental)	Mean Reduction	p-value
Nemets et al., 2002	Placebo	2.3 (9.2)	0.001*
	e-EPA	12.4 (6.8)	
Peet et al., 2002	Placebo	6.1	
	e-EPA		
	1g	9.9	0.02*
	2g	5.8	0.88
	4g	6.4	0.44
Marangell et al., 2003	Placebo	5.8 (8.6)	0.43
	DHA	8.1 (7.7)	
Khoraminya et al., 2012	Fluoxetine	13 (7.6)	0.004*
	Vitamin D + fluoxetine	17.7 (6.97)	
Sephermanesh et al., 2015	Placebo	3.3 (5.1)	0.06
	Vitamin D	8.0 (8.9)	
Rogers et al., 2008	Placebo	4 (9.1)	0.44
	EPA,DHA	3.3 (9.9)	
Mischoulon et al., 2009	Placebo	4.2 (7.9)	0.004*
	EPA	10.2 (8.6)	0.06
Mozaffari-Khosravi et al., 2012	Placebo	2.0 (0.6)	
	EPA	5.1 (0.5)	<0.001*
	DHA	2.1 (0.6)	
Jacka et al., 2016	Placebo	4.7 (1.6)	<0.001*
	Dietary Support	11.3 (1.5)	
Mozaffari-Khosravi et. Al., 2013	Placebo	2.1 (3.8)	
	150,000 IU	6.8 (7.9)	<0.001*
	300,000 IU	9.3 (8.7)	
Mischoulon et al., 2015	Placebo	9.49 (0.61)	0.794
	EPA	10.34 (0.62)	
	DHA	9.26 (0.62)	

Finally, effect size reported as standardized mean differences (SMD) are included as reported in the nine published meta-analyses (Table 4). Data is missing from one study, as SMD was not reported in the published meta-analyses. SMD values can be interpreted as so: SMD equal to zero indicates that there was no effect of the intervention over placebo, SMD < 0 indicates intervention with dietary supplementation was less effective than placebo and SMD > 0 indicates intervention with dietary supplementation was more effective than placebo.

Table 3. Effect Size and Correlation of Included RCTs

Author, Year	Supplementation	Dosage	Duration	Effect Size (d)	Correlation (r)
Nemets et al., 2002	e-EPA	2g/day	4 weeks	1.25*	0.53
Peet et al., 2002	e-EPA	1g, 2g, or 4g/day	12 weeks	---	---
Marangell et al., 2003	DHA	2g/day	6 weeks	0.28	0.14
Grenyer et al., 2007	EPA, DHA	0.6g, 2.2g	16 weeks	---	---
Rogers et al., 2008	EPA + DHA	1.5g/day	12 weeks	-0.07	-0.03
Jazayeri et al., 2008	EPA	1.g + 0.2g fluoxetine	8 weeks	---	---
Mischoulon et al., 2009	EPA	1g/day	8 weeks	0.73*	0.34
Gertsik et al., 2012	EPA, DHA	0.9g, 0.2g+ citalopram	9 weeks	---	---
Khoraminya et al., 2012	Vitamin D	1500 IU Vit D+0.02g fluoxetine	8 weeks	0.64*	0.31
Mozaffari-Khosravi et al., 2012	EPA DHA	1g/day 1g/day	12 weeks	5.61* 0.17	0.94 0.08
Mozaffari et al., 2013	Vitamin D	150,000 IU 300,000 IU	12 weeks	0.76* 1.07*	0.35 0.47
Sepehrmanesh et al., 2015	Vitamin D	50 IU/week	8 weeks	0.65*	0.31
Mischoulon et al., 2015	EPA DHA	1g/day 1g/day	8 weeks	1.38* 0.17	0.57 0.08
Jacka et al., 2017	EPA, DHA	---	12 weeks	4.26*	0.91

Additionally, effect size was measured as a standardized mean difference (SMD) in the nine included meta-analyses (Table 3). SMD was not reported in one of the included meta-analyses. Of the eight included studies, three showed the intervention had a moderate effect while the remaining five showed the intervention had a small effect.

Table 4. Reported Standardized Mean Differences from Included Meta-Analyses

Author, Year	Supplementation	Standardized Mean Difference
Sublette et al., 2011	EPA	0.558
Bloch et al., 2012	PUFAs	0.11
Martins, 2013	PUFAs	-0.291
Shaffer et al., 2014	Vitamin D	-0.60
Li et al., 2014	Vitamin D	-0.14
Spedding, 2014	Vitamin D	0.78
Appleton et al., 2016	PUFAs	-0.32
Mocking et al., 2016	PUFAs	0.398
Sarris 2017	Vitamin D, PUFAs	---

Discussion

Dosage for PUFAs (EPA and DHA) supplementation ranged from 1g to 4g daily, while dosage for Vitamin D supplementation ranged from 1,500 IU to 300,000 IU. Time frame of supplementation ranged from four weeks to 16 weeks in both PUFA and Vitamin D supplementation. Some studies investigated dietary supplementation adjunctive to prescription SSRIs fluoxetine, citalopram, and sertraline. Each of those studies displayed greater reduction in depressive symptomology in participants assigned to received combination therapy than those in monotherapy groups. One study utilized dietary support via personalized dietary advice with a dietitian and a recommended modified Mediterranean diet (Jacka, O'Neil, Opie, et al., 2017).

The Modified Mediterranean diet was low in sweets, fried food, fast food, processed meat and sugary drinks and high in whole grains, fruits, vegetables, legumes and protein. Individuals in the dietary support group saw a statistically significant decrease in MADRS scores in comparison to the placebo group, indicating that dietary modifications can also be deemed an efficacious treatment option.

Each study measured depressive symptoms using different rating scales, which makes it difficult to compare results. The effect size was calculated to produce a standardized value that represents the magnitude of the effect dietary supplementation had on reducing depressive symptoms compared to those who were not exposed to the intervention. The standardized effect size value also makes it possible to compare values across studies. Effect size was not reported on four studies, as the required data (mean and standard deviation) were not made available in the published studies. Seven out of the ten included RCTs had a statistically significant decrease in depression scale scores from the trial's end when compared to baseline scores. It can be inferred from these results that dietary supplementation is an efficacious treatment option for depressive symptom alleviation. Additionally, eight out of the ten included RCTs had a moderate-to-large effect size.

It is difficult to definitively state an optimal time frame and supplementation dosage due to the variations of participant demographics, range in depression severity and baseline dietary status. Based on the data, supplementation ranging from 8-12 weeks can be deemed a sufficient time frame to achieve a reduction in depressive symptoms. It can also be assumed by observing data that supplementation of 1g/day with EPA will result in sufficient decrease in symptoms. The available studies investigating Vitamin D all noticed a moderate to large effect of the intervention, which makes difficult to state an optimal dosage. The statistically significant

decreases in depression scale scores, and moderate to large effect sizes suggest dietary supplementations can be an advantageous treatment option when utilized as monotherapy or in combination with antidepressant medications.

Furthermore, very few adverse effects regarding dietary supplementation in the intervention groups were reported. Many of the reported adverse events were related to taste of supplement and gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. These adverse events are less bothersome than side effects associated with many common SSRIs. Limitations to this review include an unequal amount of studies that investigate supplementation with n-3 PUFAs compared to the amount of studies that investigate supplementation with Vitamin D. This inequality makes it difficult to make statistically valid claims surrounding which dietary supplementation is more effective. Another limitation is the study design of systematic review and meta-analyses. This study design was limited to any existing research surrounding n-3 PUFAs and Vitamin D supplementation.

Conclusion

Major depressive disorder is a debilitating mood disorder that affects over 18 million American adults. Common treatment with prescription SSRI has low adherence and high occurrence of unpleasant side effects such as nausea, vomiting, weight loss and trouble sleeping. Additionally, long-term use of antidepressants may lead to the brain developing a tolerance for a particular dosage, becoming less responsive to the drug and essentially rendering the drug useless (Harvard Health, 2014). Ways to combat this issue include taking a different antidepressant or increasing the dosage of the current antidepressant (Harvard Health, 2014).

The present systematic literature sought to investigate dietary supplementation as an alternative treatment option for alleviation of symptoms related to MDD. Nine meta-analyses and 14 RCTs were included for review and analysis. Based on statistical analyses, it can be concluded that dietary supplementation with both omega-3 PUFAs and Vitamin D had a moderate-to-large effect on decreasing depressive symptomology. Further, more specialized, research is necessary to determine most efficacious concentrations of EPA, DHA or Vitamin D for successful decrease in depressive symptomology.

Few adverse events related to bloating, fishy after taste, and gassiness were reported by participants in the experimental group. These are arguably more tolerable than the side effects associated with many common SSRIs. The low severity of adverse events may increase the likelihood of individuals adhering to their prescribed treatment regimen. Use of dietary supplements as a treatment option for MDD may also serve as a less expensive alternative to pharmaceuticals for individuals who may be uninsured or underinsured, thus increasing their access to mental health treatments. Future directions for further investigation of alternative treatments for MDD include incorporating regular physical activity into an individual's routine or modifying an individual's overall diet. Physical activity has been shown to ease depressive symptoms by releasing "feel-good endorphins" and serves as a distraction from negative thoughts that typically fuel depression (Mayo Clinic, 2017). From a public health standpoint, incorporating physical exercise, modifying the diet, as well as n-3 PUFAs or Vitamin D supplementation as a mental health treatment option will work to not only decrease depressive symptomology, but improve the overall health of the individual.

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APPENDICES

APPENDIX A: DSM-5 Criteria for MDD

DSM-5 Criteria for Major Depressive Disorder
A. Five or more of the following symptoms (at least one of depressed mood and loss of interest or pleasure) in the same 2-week period. Each represents change from previous functioning 1. Depressed mood (most of the day, nearly every day) indicated by subjective report or observation made by others 2. Diminished interest in pleasure in all or most activities 3. Significant weight loss or weight gain when not dieting, or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia nearly every day 5. Psychomotor retardation or agitation nearly every day 6. Loss of energy or fatigue most days 7. Excessive or inappropriate guilt, or feelings of worthlessness most days 8. Indecisiveness, or decreased ability to think or concentrate most days 9. Recurrent thoughts of death, suicidal ideation, suicide attempt, or specific plan for committing suicide
B. Symptoms cause clinically significant impairment in social, occupational, or other key areas of function
C. **Episode can not be linked to physiological effects of a substance or other medical condition.** ***Note:*** *Criteria A-C represent Major Depressive Episode; clinical judgement is required to distinguish if MDE is present as normal response to significant loss*
D. Is not explained by any psychotic disorders
E. **Lifetime absences of a manic or hypomanic episode** ***Note:*** *Does not apply if manic/hypomanic episodes are attributable to medical condition or substance-induced.*

APPENDIX B: *Characteristics of Included RCTs*

Depression Rating Scale	Author	Sample Size	Supplementation	Duration	Result
HDRS	Nemets et al., 2002	n=20	2g/day e-EPA	4 weeks	Clinically meaningful reduction
	Peet et al., 2002	N=70	1g e-EPA, 2g e-EPA, **or** 4g e-EPA	12 weeks	Treatment with 1g/day e-EPA effective
	Grenyer et al., 2007	N=83	2.2g/day DHA **and** 0.6g/day EPA	16 weeks	No significant difference between experimental and placebo groups
	Jazayeri et al., 2008	N=48	1g EPA + 0.02 g fluoxetine	8 weeks	EPA=+fluoxetine combo superior to monotherapy
	Mischoloun et al., 2009	N=57	1g/day EPA	8 weeks	No statistically significant difference in EPA vs placebo
	Mozaffari-Khosravi et al., 2012	N=81	1g/day EPA **or** 1g/day DHA	12 weeks	EPA more effective than DHA or placebo
	Gertsik et al., 2012	n=42	0.9g EPA, 0.2g DHA + citalopram	9 weeks	Combination therapy significantly greater improvement
	Khoraminya et al., 2012	N=42	1500 IU Vitamin D + 0.02g fluoxetine	8 weeks	Vit D+fluoxetine combo significantly superior
	Mischoulon et al. 2015	N=154	1g/day DHA **or** 1g/day EPA	8 weeks	No significant difference between three treatment groups
BDI	Rogers et al., 2008	N=190	1.5g/day EPA **and** DHA	12 weeks	Lack of therapeutic effect of PUFA supplementation
	Mozaffari et al., 2013	N=120	300,000 IU **and** 150,000 IU Vitamin D	12 weeks	Correction of Vit D deficiency improved depression state
	Sepehrmanesh et al., 2015	N=36	50,000 IU/week Vitamin D	8 weeks	Vit D supplementation had beneficial effects on BDI
MADRS	Marangell et al., 2003	N=35	2g/day DHA	6 weeks	No significant difference between DHA and placebo
	Jacka et al., 2017	N=67	Dietary Support-Mediterranean Diet	12 weeks	Dietary support may provide accessible, effective treatment

APPENDIX C: Characteristics of included meta-analyses

Author	Supplementation	Result
Sublette et al., 2011	EPA	EPA more effective
Bloch et al., 2012	n-3 PUFAs	Small, non-significant benefit
Martins et al., 2013	n-3 PUFAs	EPA more effective than DHA
Li et al., 2014	Vitamin D	No significant effect
Spedding, 2014	Vitamin D	Vit D supplementation somewhat beneficial
Shaffer et al., 2014	Vitamin D	No overall effect
Appleton et al., 2016	n-3 PUFAs	Small beneficial effect
Mocking et al., 2016	n-3 PUFAs	Overall beneficial effect
Sarris 2017	Vitamin D, PUFAs	Primarily positive effect