**Dietary and Supplementation Interventions for Depression and Anxiety in Chronic Fatigue Syndrome: a Literature Review**

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**Abstract**

**Background:** Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) is characterized by persistent and unexplained fatigue. Dietary interventions and supplementation can be used to target symptoms of CFS/ME, in particular mood symptoms of the illness. This review presents some of the dietary and supplementation interventions which have been used to treat depression and anxiety in CFS/ME.   
**Main results:** Sixteen studies are included in this review. Interventions are divided based on whether they are nutrition or non-nutritious in nature. Eicosapentaenoic acid, ubiquinol-10, and L-carnitine supplementation can lead to improvement in depression. Porcine serum polypeptide, NADH and probiotics interventions note some beneficial effects on anxiety. Chocolate rich in cocoa polyphenol appears to improve both depression and anxiety.   
**Conclusions:** Despite some promising results, lack of replication, small sample sizes, short trial times and the variety of mood scales used limit interpretation of results. As of now, no given dietary or supplementation intervention can be recommended for treatment of anxiety and depression for individuals with CFS/ME. Further research accounting for the aforementioned limitations is needed.

**Layman’s summary**

Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) is an illness which affects about 1% of the population, and about 60-70% of people with CFS/ME are women. The main symptom of CFS/ME is a fatigue which does not improve with sleep. There are different levels of illness severity, with some people with CFS/ME living relatively normal lives while others are permanently bed-bound. Other common symptoms of CFS/ME include muscle pain, insomnia and other sleep problems, digestive issues, headaches, sensitivity to light and sound, a sore throat, memory and concentration issues, and mood-related symptoms, such as depression and anxiety.

The cause of CFS/ME is not known. In fact, there might be multiple possible causes, including viral infections, hormonal imbalances, or somatization, which is when a mental and/or emotional load causes physical symptoms. Most likely, CFS/ME is caused by an interaction of different environmental, societal, and genetic factors. Because these factors have not been identified yet, designing a treatment plan for people with CFS/ME can be challenging. Currently, the most common and most effective treatment for CFS/ME is cognitive behavioral therapy (CBT). For most patients, CBT will successfully improve most symptoms, and in some cases it can lead to complete remission. However, not everyone is receptive to CBT. Access to CBT may also be restricted or limited in some countries. Because of this, it is important to look into other possible treatments for CFS/ME.

Complete remission of symptoms is very rare. Often times, a more realistic goal for treatment is improvement of Quality of Life (QoL), so that individuals with CFS/ME can live relatively normal lives. There are multiple ways to improve QoL, and one of them is to target the mood symptoms of CFS/ME, in particular depression and anxiety. Multiple therapeutic approaches have been attempted to achieve this. One way is to change the diets of people with CFS/ME. A connection between the gut, diet and mood has already been established in healthy people, and it is possible that this connection can be used in individuals with CFS/ME to improve depression and anxiety.

To this day, many different types of diet interventions have been used to try and treat mood symptoms of CFS/ME. Some of these interventions are nutritious interventions, meaning the supplements used hold some type of nutritional value. This is the case for vitamins and minerals, for example. Other common nutritious supplements among healthy people include ginger, ginseng, and garlic. Dietary interventions can also be non-nutritious, meaning they do not have a nutritional value. Those are somewhat less common, and include supplements such as melatonin, probiotics, and NADH. The aim of this project is to provide an overview of the different dietary interventions which have been used to try and improve depression and anxiety in people with CFS/ME.

**Introduction**

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is an illness primarily characterized by persistent and unexplained fatigue, which does not improve with rest and sleep. Most recent estimates place the worldwide prevalence of CFS/ME at around 1%, with females being 1.5 to 2 times more affected than males (1). In addition to fatigue, individuals with CFS/ME will often experience many other symptoms such as headaches, muscle pain, gastrointestinal disturbances, sore throat, painful and swollen lymph nodes, and neuropsychological disturbances such as sleep, memory, concentration, and mood impairments (2). The most common mood-related symptoms are anxiety and depression, with about 24 to 27% of people with CFS/ME being affected by an anxiety disorder and 17 to 20% being affected by a mood disorder such as depression (3,4).

The causes of CFS/ME are still unknown, and the illness is suspected to occur from the interactions between biological, psychological and social components, although this theory is still heavily debated (5). Some current theories paint CFS/ME as having immunological roots, being caused either by a viral infection (6) or arising as an autoimmune disease with unknown triggers (6,7). Another possible cause would be a neuroendocrinological disturbance, particularly in the HPA axis (6). As the cause has not yet been identified, treatments are usually designed to ease symptoms. Psychological and social factors are believed to come into play in terms of managing the illness, receptivity to treatment and self-perception. Many approaches are currently in use, including exercise, medication, cognitive behavioral therapy (CBT), and dietary interventions (8), with CBT currently being the most commonly used treatment for CFS/ME. Therapeutic success of these approaches appears to be greatly dependent on individual characteristics, further highlighting the heterogeneous nature of CFS/ME.

Quality of life (QoL) is noticeably low for those affected by CFS/ME (9). As there are currently no permanent treatment for CFS/ME, improvement of QoL is often chosen as the main treatment aim, rather than complete recovery. Mental health is one of the major components of QoL, therefore, improving the mental health of patients with CFS/ME by targeting anxiety and depression should improve QoL. To achieve this, traditional approaches such as CBT have been attempted, and although results are promising, the effect is not as strong as desired, and receptivity to CBT varies greatly (10). In addition, the success of CBT in treating anxiety specifically in patients with CFS/ME is somewhat limited.

Dietary interventions and supplementation have been of increasing interest in the last decade. The main target of these interventions is the primary symptom of CFS/ME, fatigue (11). However, dietary interventions have also been shown to be able to regulate other symptoms, such as sleep disturbances, cognitive impairments, and mood disturbances (11,12). The connection between dietary habits and mood has already been established in healthy individuals (13), however whether or not this connection can be exploited to alleviate complains of depression and anxiety in people with CFS/ME is not yet known. This literature review aims to provide an overview of dietary interventions and supplementation which have been used to improve depression and anxiety symptoms in patients with CFS/ME. As many different dietary treatments have been tested, a distinction has been made between nutritional approaches, which include adding or removing foods from one’s diet, and non-nutritional approaches, which as the term suggests, are supplements with no nutritional value, such as melatonin.

**Diets and Nutritional complements**

The databases used for literature research were PubMed, SCOPUS, JSTOR, ScienceDirect, and PsycNet. The keywords used were “chronic fatigue syndrome” or “chronic fatigue” with either “depression”, “anxiety”, “mood” or “psychological”, and either “dietary”, “diet”, “nutrition”, “nutritional”, or “supplement”. Animal studies were excluded. For practical purposes, all of the studies included in this review were conducted on adults between 18 and 65 years old. The majority of dietary interventions consisted of adding a single supplement to the patients’ diets, rather than a complete diet change. The majority of these supplements were non-nutritional in nature. Description of the included studies can be found in Table 1. This section is concerned with nutritional complements, including ginseng, essential fatty-acids, chocolate, and the low-sugar low-yeast diet.

**Ginseng**

Ginseng is a type of root native to East-Asia and is considered a type of traditional medicine in multiple East-Asian countries. In particular, the Korean and Chinese ginseng are believed to have strong healing properties (14). Of the multiple species of ginseng, two have been tested to improve depression and anxiety symptoms of CFS/ME: Korean red ginseng and Siberian ginseng.

The first study by Sung et al (15) was a randomized control trial of 50 patients with chronic fatigue (CF), in which participants would either ingest Korean red ginseng powder or a placebo daily. The broad diagnosis of CF includes both CFS and idiopathic CF. The trial lasted 6 weeks and another follow-up was conducted 4 weeks later. Depression was among the secondary outcomes of this trial and was measured using the Beck Depression Inventory (BDI). Significant improvements in depression levels were observed from both the Korean red ginseng and the placebo, but no significant difference was found between the intervention and control groups.

The second study was a randomized control trial conducted by Hartz et al (16). This study included 61 patients over the age of 21 with CF and both depression and anxiety were assessed as secondary outcomes using the Mood and Anxiety Symptom Questionnaire (MASQ). The intervention consisted of Siberian ginseng extract consumed daily, while the control group received a placebo. The trial lasted for 8 weeks. There were no improvements in depression or anxiety in either the intervention or control groups.

**Essential fatty-acids**

Individuals with CFS/ME have been observed to have altered essential fatty acids (EFA) ratios, which has been the basis for testing EFA supplementation for treating both fatigue and other symptoms of CFS/ME (17). One study by Warren et al (18) assessed the effect of evening primrose oil and concentrated fish oil supplementation on depression in 50 patients with CFS/ME when compared with sunflower oil supplementation, which acted as a placebo. The evening primrose and concentrated fish oil combination allows for the supplementation of four different EFAs at once. Depression was assessed using the BDI. Improvements in depression levels were observed in both groups, but no significant difference was found between the intervention and control groups.

One of the four EFAs used by Warren et al (18) was Eicosapentaenoic acid (EPA). This EFA was also the primary intervention of a case-report by Puri and Holmes (19) of a 25-year old woman with CFS/ME. They observed a vast improvement in depressive symptoms after a 16-week program during which the patient consumed twice the recommended amount of EPA daily. The Montgomery and Asberg Depression Rating Scale (MADRS) was used to measure depression. At time of publication, the patient had decided to continue with the supplementation.

**Other food supplements: Chocolate, BioBran and Porcine serum polypeptide**

A study by McDermott et al (20) assessed the benefits of supplementing with BioBran, a food supplement derived from rice bran. The study was an RCT following 64 patients over 8 weeks, where the Hospital Anxiety and Depression Scale (HADS) was used to assess both depression and anxiety. At the end of the trial, no improvements were found for either depression or anxiety.

Another study by Sathyapalan et al (21) assessed the effect of cocoa polyphenol rich chocolate intake on depression and anxiety in CFS/ME. The study was designed as a randomized cross-over study, followed 9 participants with CFS/ME and lasted a total of 16 weeks. Depression and anxiety were assessed using HADS. The placebo was chocolate with low cocoa polyphenol. Depression and anxiety improved during the high cocoa polyphenol intervention and deteriorated during the low cocoa polyphenol treatment.

Lastly, one pilot study following 43 patients with CFS/ME or fibromyalgia evaluated the benefits of supplementing with a porcine serum polypeptide extract (22). The majority of participants met the diagnostic criteria for both CFS/ME and fibromyalgia, and only 3 participants met the criteria for fibromyalgia but not CFS/ME. The porcine serum used in this study is sometimes used for treatment of malnutrition and previous studies had observed that individuals with fibromyalgia appeared to benefit from it to some extent (22). A Visual Analog Scale (VAS) was used for all outcomes, including anxiety. This study found anxiety had significantly improved at the end of the 5 week trial.

**Diet: Low-sugar low-yeast**

Only one study reported the effect of a complete diet change on the depression and anxiety in CFS/ME (23). This study followed 29 participants with CFS/ME over 24 weeks after randomization to the low-sugar low-yeast (LSLY) diet group (intervention) or the healthy diet group (control). The intervention was based on the possibility of a connection between overgrowth of the Candida albicans fungus in the gut and CFS/ME (24). The LSLY diet, which theoretically would combat the Candida overgrowth, is particularly restrictive and notoriously difficult to follow. It excludes sugar, refined carbs, yeast, alcohol, and caffeine (including tea), and limits consumption of fruits and dairy. The healthy diet was based on general health recommendations, including consuming more fibers, fruits, and vegetables, reducing fat and sugar consumption, and eating fish twice a week. Compliance to the LSLY diet was low, with only 24% completing the 24 weeks. Both anxiety and depression were assessed during this trial using the HADS, but no improvements were found in either the LSLY group or the healthy eating group.

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| **Table 1: Characteristics of selected studies** | | | | | | | |
| **Reference** | **Study design** | **Study duration** | **Sample size** | **Treatment** | **Control** | **Mood symptom** | **Significance** |
| Sung et al (15) | RCT | 6 weeks | 50 | Korean ginseng | Placebo | Depression | NS |
| Hartz et al (16) | RCT | 8 weeks | 29 | Siberian ginseng | Placebo | Depression | NS |
| Warren et al (18) | Case-control | 12 weeks | 75 | Primrose and fish oil | Sunflower oil | Depression | NS |
| Puri and Holmes (19) | Case-report | 16 weeks | NA | EPA | NA | Depression | Significant |
| McDermott et al (20) | RCT | 8 weeks | 64 | BioBran | Placebo | Depression and anxiety | NS |
| Sathyapalan et al (21) | Cross-over RCT | 8 weeks each arm | 9 | Cocoa polyphenol rich chocolate | Chocolate low in polyphenol | Depression and anxiety | Significant for both |
| Teitelbaum et al (22) | Cohort | 5 weeks | 43 | Porcine serum polypeptide | NA | Anxiety | Significant |
| Hobday et al (23) | RCT | 24 weeks | 29 | LSLY diet | Healthy diet | Depression and anxiety | NS |
| Fukuda et al (25) | Open-label study | 8 weeks | 20 | Ubiquinol-10 | NA | Depression | Significant |
| RCT | 12 weeks | 31 | Ubiquinol-10 | Placebo | Depression | Significant |
| Alegre et al (26) | RCT | 12 weeks | 77 | NADH | Placebo | Anxiety | Significant |
| Plioplys and Plioplys (27) | Cross-over RCT | 8 weeks each arm | 28 | L-carnitine | Amantadine | Depression | Significant |
| Menon et al (28) | Open-label study | 16 weeks | 10 | CoQ10, Alpha lipoic acid, NAC, acetyl L-carnitine, magnesium, calcium ascorbate dehydrate, cholecalciferol, a-tocopherol, retinyl palmitate, vitamin B cofactors | NA | Depression | NS |
| Rao et al (29) | RCT | 8 weeks | 35 | Lactobacillus casei powder | Placebo | Depression and anxiety | NS for depression, significant for anxiety |
| Venturini et al (30) | Pilot study | 8 weeks | 9 | Enterelle, Bifiselle, Ramnoselle, Citogenex, Rotanelle | NA | Depression | NS |
| Castro-Marrero et al (31) | RCT | 16 weeks | 50 | Melatonin and zinc | Placebo | Depression and anxiety | NS |
| Williams et al (32) | Cross-over RCT | 12 weeks each arm | 30 | Melatonin, phototherapy | Placebo | Depression and anxiety | NS |

RCT: Randomized-controlled trial. NA: Not applicable. NS: Not significant.

**Non-Nutritional complements**

A number of non-nutritional complements have been used to treat depression and anxiety in CFS/ME. Among these, mitochondria-boosting supplements have become quite popular (28). Probiotics and melatonin have also been of interest.

**Mitochondria-boosting supplements**

Mitochondria are the cell component responsible for converting nutrient into energy to supply to the rest of the body. As CFS/ME is characterized by a lack of energy, a popular theory is that the mitochondria of people with CFS/ME are not able to perform correctly, leaving the person with no energy to spare (33). Following this theory, it is hypothesized that boosting the mitochondrial processes through supplements would result in less fatigue, and possibly improve other CFS/ME symptoms.

Fukuda et al (25) conducted an open-label study followed by an RCT on the benefits of Ubiquinol-10 on CFS/ME symptoms. Ubiquinol-10 is the reduced product of coenzyme 10 (CoQ10), which is an essential component of mitochondrial functioning. The first study lasted 8 weeks and included 20 patients with CFS/ME over the age of 20, while the RCT had 31 participants and lasted 12 weeks. Depression was measured using the Center for Epidemiologic Studies Depression Scale (CES-D). In both cases, significant improvements in depression were observed, while fatigue did not improve.

Another important component necessary for mitochondrial processes is NADH. An RCT conducted by Alegre et al (26) with 77 participants over 3 months found that NADH supplementation significantly improved anxiety, but no improvement was found in other CFS/ME symptoms, including fatigue.

Carnitine is an essential mitochondrial component. A cross-over study aimed to assess the potential treatment effect of L-carnitine supplementation on multiple CFS/ME symptoms, including fatigue and depression, which was measured using the BDI (27). Each study arm lasted 2 months, and 20 participants completed the trial. When not on L-carnitine, participants were treated with amantadine, an anti-viral agent (34). Amantadine was not well tolerated, with close to half of the original sample stopping amantadine supplementation early as it was worsening their symptoms. Those who did complete the amantadine treatment did not see any improvements in any of their symptoms. On the other hand, L-carnitine was well tolerated and significantly improved depression.

An extended approach was attempted by Menon et al (28). In their pilot study, 10 participants were given a mix of mitochondrial boosting supplements, including CoQ10, L-carnitine, vitamin B cofactors, alpha lipoic acid, and magnesium. Depression was assessed using the MADRS. After a duration of 16 weeks, there were no significant changes in depression, although fatigue levels did significantly decrease.

**Probiotics**

The gut-brain axis is one of the many avenues being explored in CFS/ME research. Imbalances in the gut microbiome could be responsible for multiple symptoms of CFS/ME, both physical and psychological (35). Based on this theory, two studies evaluated the effect of probiotics on mood symptoms of CFS/ME. Rao et al (29) conducted an RCT over 8 weeks in 35 participants with CFS/ME, using Lactobacillus casei powder as the intervention. Participants were evaluated for both depression and anxiety using the BDI and Beck Anxiety Inventory (BAI) respectively. At the end of the trial, significant improvement of anxiety was found in the intervention group, however no changes in depression were observed. The second study was an observational pilot study over 8 weeks in 9 patients (30). The probiotic supplement was changed every week for the first 4 weeks of the intervention, followed by another 4 weeks using a probiotic mix. The BDI was used to assess depression. A decrease in depression was observed as the trial went on, but this change did not reach significance.

**Melatonin**

As the most characteristic symptom of CFS/ME is fatigue, it has been suggested that disruption in the circadian rhythm could be responsible for this illness (36). In particular, many individuals with CFS/ME report difficulties falling and staying asleep. A common supplement to treat and reset circadian rhythms is melatonin, a hormone which is naturally released to initiate a sleep cycle (37). Melatonin supplements have also been tested to treat CFS/ME symptoms, including depression and anxiety.

Castro-Marrero et al (31) conducted an RCT in which 50 participants with CFS/ME were given a melatonin and zinc complement or a placebo for 16 weeks. Fatigue and other CFS/ME symptoms were measured at the 16 weeks mark as well as after a 4-week follow-up. A slow and gradual improvement in fatigue was found, but no changes were observed for anxiety or depression as measured by the HADS.

The second study evaluating the effect of melatonin on CFS/ME lasted a total of 60 weeks (32). During this period, 30 participants with CFS/ME were split into two groups and went through five 12-week periods consisting of placebo (twice), phototherapy, a washout period, and melatonin treatment. The order of these periods was different between the two groups, and participants were tested for both depression and anxiety levels using the HADS. Ultimately, no changes were found for any of the CFS/ME symptoms that were measured.

**Discussion**

Dietary interventions and supplementation use are fairly popular choices among people with CFS/ME, with or without the guidance of a doctor, as over the counter supplements make for an easily accessible self-medication option. Furthermore, many individuals with CFS/ME have reported benefitting from such dietary interventions (38). The aim of this literature review was to report some of the dietary interventions and supplementations which have been tested to improve symptoms of anxiety and depression in patients with CFS/ME.

**Summary of interventions**

Of the two ginseng interventions, neither reported any improvements in anxiety or depression. Depression was the only mood outcome for both of the EFAs studies, and while the case-report by Puri and Holmes did note significant improvements, the trial by Warren et al did not. The chocolate intervention by Sathyapalan et al (21) saw significant improvements for both depression and anxiety. The porcine serum intervention also appeared to reduce anxiety in patients with CFS/ME. The BioBran supplementation (20), which assessed both depression and anxiety, saw no improvements in mood at the end of the trial. Lastly, the LSLY diet did not appear to benefit participants in any way and was particularly difficult to adhere to.

A number of non-nutritional interventions were tested as well. Separately, ubiquinol-10 and L-carnitine both significantly improved depression symptoms in CFS/ME participants. However, when used together along with other mitochondrial-boosting supplements, this beneficial effect on depression was no longer observed. NADH supplementation was found to successfully reduce anxiety levels. Of two studies assessing the effect of probiotic supplementation on the mood of CFS/ME participants, neither study reported any improvement in depression, but one did find significant improvement in the anxiety. Another two studies measured differences in depression and anxiety levels in participants after treatment with melatonin, but neither noted improvements in mood.

**Study limitations**

Several limitations were found across the studies included in this review, making interpretation of the results less straightforward. One of the common limitations was small sample size. Excluding the case-report by Puri and Holmes (19), 7 of the 16 studies reported had a sample size of 30 or under. This could be explained by the relatively low prevalence of CFS/ME, or by that the fact that individuals with particularly severe CFS/ME were not able to participate.

Another possible limitation is the study length. Short trial times and lack of follow-up could mask an intervention’s true effect. Although there are no official guidelines for duration of dietary interventions (39,40), it has been suggested that a study duration of about 12 weeks would be best when measuring changes in depression and anxiety following a dietary intervention in otherwise healthy patients (41). A shorter trial might end before an intervention can fully take effect, or might only present an initial improvement and not report a return to baseline that would occur after a longer period (40,41). Follow-up of 1 to 3 months is recommended to assess a return to baseline effect as well (39,41). Half of the studies in this review were 8-week long or less, and only two studies had a 4-week follow-up.

None of the treatments were replicated. Whereas multiple studies assessed the benefits of mitochondrial boosting supplements, each of these studies used a different supplement for intervention. The same was observed for the use of probiotics supplementation. Some of the interventions consisted of supplements which are not common or readily available, which could be a reason they have not been replicated despite apparent improvements. This could be the case for the chocolate intervention (21), which used a specific chocolate formula not otherwise manufactured, and the porcine serum ((22), which is not commonly used by hospitals. Lack of replication makes the interpretation of the results more difficult.

Inclusion criteria varied greatly, with one study focusing on patients with CFS/ME and comorbid fibromyalgia (22), and two studies ran their interventions in participants with CF but not necessarily CFS/ME (15,16). Different scales were used to assess depression and anxiety as well. Most studies used the BDI for depression or the HADS for both depression and anxiety, but other scales included the MADRS, MASQ, BAI, VAS, and CES-D. These scales may vary in terms of validity and reliability (42). All these differences make comparison between study results more challenging.

**Recommendations**

There are two main things to consider when choosing a dietary intervention for a patient, regardless of diagnosis. The first is whether or not the intervention is likely to improve the patient’s symptoms. The second is whether or not the intervention is well tolerated and sustainable (43). Tolerability is mainly related to harmful side effects; an intervention is considered well tolerated when it triggers little to no undesirable side effects. Sustainability refers to the feasibility of an intervention in the long term. An intervention might be unsustainable if it is too restrictive or not pragmatic.

There are two interventions in this study that cannot be recommended on the basis of tolerability and sustainability. The first is amantadine supplementation, which exacerbated CFS/ME symptoms of half of the participants. The second is the LSLY diet, which was too restrictive to adhere to. These interventions are most likely not viable options for most individuals with CFS/ME.

Significant improvement in depression or anxiety should be interpreted carefully as well. As previously mentioned, about half the studies had less than 30 participants. More importantly, the majority of studies did not report a power calculation for sample size. Performing and reporting a power calculation would provide more support to the results. Additionally, 8 of 16 studies ran for a duration of less than the recommended 12 weeks, and 14 out of 16 did not have a follow-up. These studies should be replicated with a longer trial run and a follow-up time for better evaluation of intervention effect.

Three of the study recruited participants other than individuals with CFS/ME only. Both studies assessing ginseng effect were conducted in individuals with CF, but not necessarily CFS/ME. The porcine serum intervention was conducted in participants with CFS/ME and comorbid fibromyalgia. Replication of these studies with a strict inclusion of participants with CFS/ME only is needed for a more accurate representation of these interventions’ effects.

Other differences in participant selection could explain why some interventions were found successful by one group and not by another. Ubiquinol-10 and L-carnitine were reported to improve depressive symptoms when given separately, yet when given together in addition to other mitochondria-boosting supplements, they were no longer effective. It is possible that confounding hid the true effect of these supplements. Stratification of participants based on relevant characteristics, such as baseline dietary habits, severity of the main CFS/ME symptoms, and severity of baseline anxiety and depression could reduce confounding. Standardization of scales for measuring depression and anxiety might remove some additional confounding.

EPA supplementation shows to be effective at improving depression during a case-report, but was not effective when combined with other EFAs during a trial. This could be because the case-report intervention consisted of supplementing with twice the recommended daily EPA intake, while the trial used doses under the recommended daily intake for all of the EFAs. It could be that EFA supplementation is only effective when much larger doses are prescribed. It would be beneficial to carry out an RCT using the same EPA dosage as the case-control to give more insight on the potential use of EPA and EFA supplementation.

Probiotics appear to be effective at reducing anxiety, but not depression. This should be further explored. The same can be said about NADH supplementation. Both of these interventions were successful, but were only conducted once and need to be replicated before it is possible to draw any conclusions.

Finally, the only intervention which was successful in improving both anxiety and depression in CFS/ME participant was the chocolate high in cocoa polyphenol. It is also among the most well tolerated and sustainable interventions reported in this review. However, this study suffered from a lot of limitations, including a small sample size of 9 participants and no follow-up time. Replication of this trial with a larger sample size, a longer trial time and follow up is required to better evaluate the actual benefits of chocolate supplementation.

**Conclusions**

The benefits of dietary interventions have already been demonstrated for multiple chronic conditions, including diabetes type 2, cardiovascular disease, and chronic inflammation (44). It is then possible that people with CFS/ME could also benefit from such interventions. The aim of this review was to report the different dietary interventions and supplementations which have been tested to improve symptoms of anxiety and depression in patients with CFS/ME. As of now, there is not enough evidence to support implementation of dietary changes for individuals with CFS/ME.

There are some recurring limitations among the studies included in this review. Small sample size, shorter trial times, no follow-ups, inconsistent patient selection, inconsistent results across studies, use of many different scales to measure anxiety and depression, and lack of study replication are all issues that make it inappropriate to draw any definite conclusions.

Overall, dietary interventions for mood-related symptoms in CFS/ME show some promise, but there is still a dire need for further research before any formal recommendation can be made.

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