Canadian Psychiatric Association
Association des psychiatres du Canada

Systematic Review

The Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie
1-12

DOI: 10.1177/0706743720961734
TheCJP.ca | LaRCP.ca
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A Systematic Review of Nutraceuticals for the Treatment of Bipolar Disorder

Une revue systématique des nutraceutiques pour le traitement du trouble bipolaire

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Abstract

Background: Certain nutrient supplements (nutraceuticals) may target neurobiological pathways perturbed in bipolar disorder (BD) such as inflammation, oxidative stress, and mitochondrial dysfunction. Nutraceuticals thus may have a potential role as adjunctive treatments for BD.

Methods: A search of Embase via embase.com, PubMed via PubMed, Cumulated index to nursing and allied health literature (CINAHL) Complete via EBSCO, and Cochrane Central Register of Controlled Clinical Trials via cochranelibrary.com was conducted to identify published randomized controlled trials assessing the efficacy of nutraceuticals on mood symptomatology in adults with BD. Search terms for BD, nutraceuticals, and clinical trials (total search terms = 75) were used to search from inception to February 20, 2020. The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials was used to assess the risk of bias.

Results: A total of 1,712 studies were identified through the search. After rigorous screening, 22 studies were included in the review. There was large variability across the studies with 15 different nutraceutical agents assessed and as such insufficient homogeneity for a meta-analysis to be conducted (I^2 > 50%). Studies revealed promising, albeit conflicting, evidence for omega-3 fatty acids and N-acetylcysteine. Isolated positive results were reported for coenzyme Q10.

Conclusion: Given nutraceuticals are tolerable and accessible, they may be useful as potential adjunctive treatments for BD. Nutraceuticals targeting neuroinflammation or mitochondrial activity may have the most potential for the depressive phase. However, further studies are required to determine efficacy.

Abrégé

Contexte : Certains suppléments diététiques (les nutraceutiques) peuvent cibler des circuits neurobiologiques perturbés dans le trouble bipolaire comme l'inflammation, le stress oxydant et la dysfonction mitochondriale. Les nutraceutiques peuvent donc avoir un rôle potentiel comme traitements d'appoint du trouble bipolaire.

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Méthodes : Une recherche d'Embase a été menée dans embase.com, PubMed dans PubMed, CINAHL complète par EBSCO, et le registre Cochrane central des essais contrôlés par cochranelibrary.com, afin d'identifier les essais cliniques randomisés contrôlés publiés évaluant l'efficacité des nutraceutiques pour la symptomatologie de l'humeur chez les adultes souffrant du trouble bipolaire. Les termes de recherche du trouble bipolaire, nutraceutiques et essais cliniques (total des termes de recherche = 75) servaient à chercher du début jusqu'au 20 février 2020. L'outil de collaboration Cochrane qui évalue le risque de biais dans les essais randomisés a servi à évaluer le risque de biais.

Résultats : La recherche a produit un total de 1 712 études. Après un dépistage rigoureux, 22 études ont été incluses dans la revue. Il y avait une importante variabilité entre les études et 15 différents agents nutraceutiques ont été évalués et à ce titre, l'homogénéité était insuffisante pour mener une méta-analyse ($I^2 > 50\%$). Les études ont révélé des données probantes prometteuses, quoique conflictuelles, pour les acides gras omega-3 et la N-acétylcystéine. Des résultats positifs isolés ont été rapportés pour le coenzyme Q10.

Conclusion : Étant donné que les nutraceutiques sont tolérables et accessibles, ils peuvent être utiles à titre de traitement d'appoint potentiel du trouble bipolaire. Les nutraceutiques qui ciblent la neuro-inflammation ou l'activité mitochondriale peuvent avoir le plus de potentiel pour la phase dépressive. Toutefois, il faut d'autres études pour en déterminer l'efficacité.

Keywords
bipolar disorder, nutraceuticals, dietary supplement, depression, mania, psychiatry, mental health, neuroscience

Introduction

Treating bipolar disorder (BD) is difficult as standard treatments for BD have limited efficacy with a shortfall in recovery occurring for many people, thus reducing their quality of life. Most treatments are more effective at treating mania than depression,[1] and treatments for the depressive phase have limitations. For example, some antidepressants may cause a switch to the manic phase and be less effective than in the treatment of unipolar depression, or antipsychotic medications may cause metabolic syndrome.[1] As there is often a lack of full functional recovery following a mood episode, additional treatments for BD are needed to address this shortfall in recovery. One treatment avenue currently being explored is the adjunctive use of nutrient-based compounds. Nutraceuticals have been defined as standardized nutrients, or functional foods, with a pharmaceutical manufacturing grade, and can be used to potentially treat or prevent a disorder or disease.[2,3] These compounds can be viewed as the intersection between pharmaceuticals and nutrition.[4] Nutraceuticals can target biological processes including neurogenesis, inflammation, oxidative stress, and mitochondrial function, which are all known to be dysregulated in BD. For example, omega-3 fatty acids are known for their anti-inflammatory properties, vitamin D as an antioxidant and compounds such as coenzyme Q10 are involved in mitochondrial biogenesis. There are also amino acids such as N-acetylcysteine (NAC) which can show effects on these processes in BD. Nutraceuticals are readily available, affordable, and acceptable by the public, and therefore, they may be potential adjunctive treatments for BD.

Objectives

The use of adjunctive nutraceuticals in psychiatry is rapidly expanding, and there is increasing interest by clinicians and the general public. There has been more focus on the rigor around the preparation of nutraceuticals and the claims being made by companies. As such, it is timely to update and extend on previous reviews. Previous systematic reviews on the effects of nutraceuticals on BD symptomatology have been published (Sarris et al.,[5] Sylvia et al.,[6] and Fusar-Poli et al.[7]). Additionally, because of the inconsistent rigor in early nutraceutical trials, some previous reviews included open-label studies and did not require a primary mood–specific outcome. A more recent systematic review has recently been published that provides further support for the use of adjunctive nutraceuticals for BD.[7] Indeed, the generation of 2 systematic reviews in a similar time frame indicates that this field is of significant interest. The current review includes peer-reviewed inclusion criteria based on a published protocol.[8] Moreover, this systematic review included MESH terms, only studies investigating BD, and importantly, the trials containing validated primary mood outcomes. This strict approach was taken to ensure the inclusion of the best quality data available that specifically answered the research question and limiting the use of secondary outcomes. By contrast, the review by Fusar-Poli et al.[7] had more inclusive criteria and differences in search terms, allowing for schizoaffective diagnosis and studies that assessed mood outcomes without validated scales (e.g., time to next episode, time to discharge) which resulted in more studies included. The aim of the current systematic review is to explore the use of nutraceuticals as potential therapeutic agents in BD, using more rigorous criteria than in prior systematic reviews including randomized controlled trials (RCTs) and focusing on mood as the primary outcome. The aim of this systematic review will be to answer the research question: In patients with BD, how does the use of nutraceutical treatments compare with placebo in reducing mood symptoms?

Methods

Search Methods

A full protocol for the search has been peer reviewed and published elsewhere[8] and is registered on PROSPERO (CRD42019100745). Studies were first collated in EndNote Version X8 and then exported into Covidence[9] where all screening, extraction of data, and risk of bias were undertaken. Data were then analyzed using Review Manager (RevMan)Version 5.3[10] to produce risk of bias tables, and STATA statistical software Version 15[11] was used to assess homogeneity.

Databases. This systematic review was conducted in concordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Relevant literature has been identified via electronic searches of Embase (via embase.com), PubMed (via PubMed), CINAHL Complete (via EBSCO), and Cochrane Central Register of Controlled Clinical Trials (CENTRAL; via cochranelibrary.com). Databases were searched from their initial inception dates to February 5, 2019. Patient/Problem, Intervention, Comparison and Outcome (PICO) search framework was used to develop search terms relating to BD and nutraceuticals.

Key search terms. A total of 75 key search terms were used in the search. These included relevant BD terms ($n = 13$), nutraceutical and dietary supplement terms ($n = 56$), and terms for clinical trials ($n = 6$). For a comprehensive list of search terms and database limiters, please refer to the published protocol.[8]

Inclusion/Exclusion Criteria

Articles were screened for eligibility by 2 independent reviewers. For the initial title and abstract screen, authors MMA and WM independently assessed eligibility of all articles returned from the search. Authors MMA and BEK conducted the full-text screen, extraction of data, and assessment of bias. Throughout each stage, author OMD acted as adjudicator for any discrepancies. To be included in the review, manuscripts had to conform to the following inclusion/exclusion criteria.

Inclusion.

1. Intervention is a nutraceutical, complementary medicine, or dietary nutrient supplement
2. Diagnosis of BD according to any version of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) or *International Classification of Diseases* criteria
3. Double-blind, RCT
4. Any length study intervention permissible
5. Any sample permissible
6. Adjunctive or monotherapy studies
7. Comparator: placebo or positive control (i.e., any therapeutically active intervention)
8. Isolated or combination nutraceuticals (all dosage levels permissible)
9. Depression and mania severity symptoms were scored using validated scales, that is, Montgomery Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), Hospital Anxiety and Depression Scale, Bipolar Depression rating scale, Beck Depression Inventory or Quick Inventory of Depressive Symptomatology (QIDS), Patient Health Questionnaire-9. Mania must have been assessed using any of the following standardized scales: Young Mania Rating Scale (YMRS), The Bech–Rafaelsen Mania Rating Scale, the mania subscale of the Schedule for Affective Disorders and Schizophrenia, the Altman Self-Rating Mania Scale, and the Biegel Mania Rating Scale
10. Adult population (18 years old and over, with no upper age limit)
11. Published, peer reviewed
12. Testing effects of the medication on the reduction of depressive or manic symptoms
13. Inpatients or outpatients
14. English-language publications

Exclusion criteria.

1. Observational studies, open-label trials, or prophylaxis studies
2. Unpublished data, case reports, gray literature, protocol papers, or conference presentations.
3. Children (<18 years)

Of note, studies that had a mixed sample of unipolar and bipolar depression (and where results were pooled) were excluded from the review as they did not fit the "primary analysis" criterion laid out in the protocol.[8]

There have been a few minor changes from the published protocol. First, the inclusion of the Biegel Mania Rating Scale, which was not listed in accepted mania scales for inclusion. It was decided to include this scale as it is validated and more appropriate for short-term studies (i.e., in the tryptophan depletion studies where changes need to be seen within hours). Second, other iterations of the QIDS including Inventory of Depressive Symptomatology and clinician and self-rated versions of each were also included but not specifically stated in the original protocol.

Statistical Analysis

Overall heterogeneity of the studies was analyzed by measuring I^2 using the Metan[13] program on STATA Data Analysis and Statistical Software 15.[11] The overall heterogeneity was analyzed for studies that reported means, standard deviations, and sample sizes in the paper (17 of the total 22 studies), and overall heterogeneity was found to be considerable ($I^2 = 82.5\%$). As per the protocol, a meta-analysis would be performed if there were more than 2 studies of the same agent with sufficient homogeneity ($I^2 < 50\%$). There was only 1 agent that fulfilled the more than 2 studies criterion (NAC); however, the heterogeneity was considerable

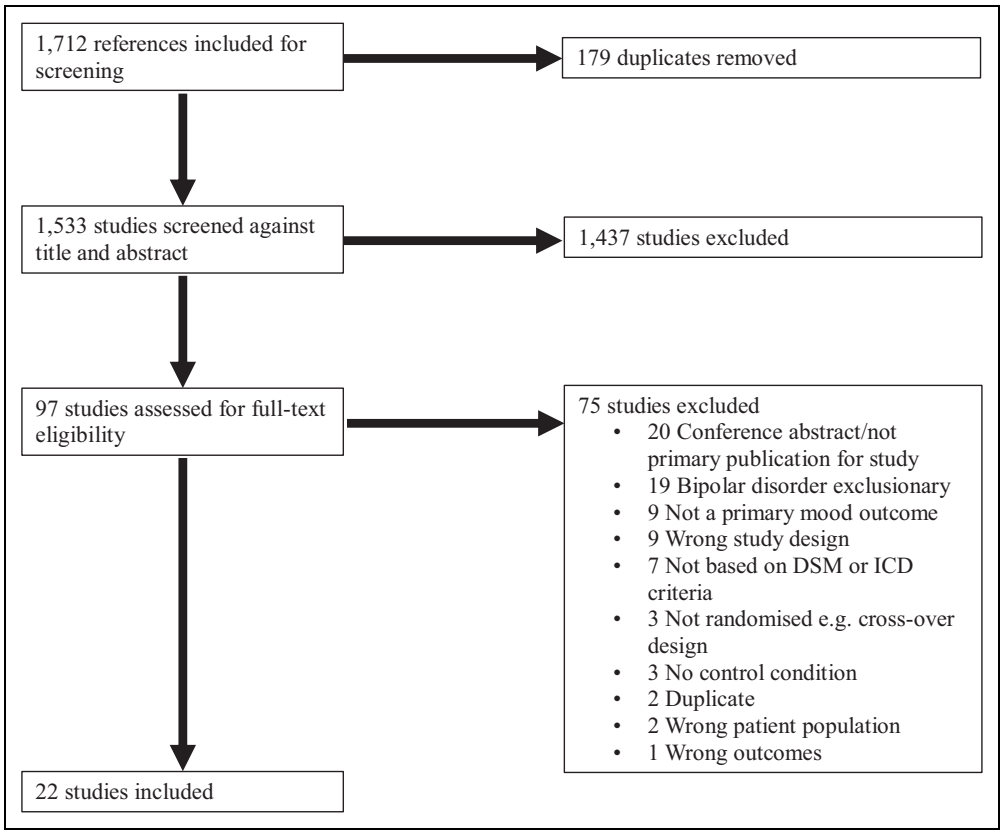

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for eligibility of studies in systematic review.

(78.2%) and there were inconsistent study lengths. Therefore, no meta-analysis was conducted for the NAC studies or any other agent. Each agent was separated into classes (e.g., amino acids, omega-3 fatty acids), and these were also checked for heterogeneity, but all returned $I^2 > 50\%$. Of note, the omega-3 fatty acids class was not explored further as no new studies, which meet our inclusion and exclusion criteria, have been published since the systematic review by Sarris et al.[5] (also a contributing author) where the data were reviewed and a meta-analysis was unable to be performed.

Results

Initial Search Yield

Author MMA performed the initial database search from their initial inception dates to February 5, 2019. The search was conducted under the guidance of a research librarian. A total of 1,581 references were identified, of which 179 were removed due to duplication, leaving 1,418 articles screened. Of these, 96 had full texts reviewed for eligibility, and subsequently, 68 articles were removed. Due to delays, a subsequent search was conducted to find any additional articles from February 5, 2019, to February 21, 2020. The updated search returned 131 new articles, of which 16 were duplicates, 114 were excluded at title and abstract screen, and 1 new article was added to the systematic review. A total of 22 articles met the criteria and were included in the systematic review. A PRISMA flowchart in Figure 1 describes the breakdown of eligibility steps. Attempts were made to contact corresponding authors for incomplete data sets and information. A summary of nutraceutical agents in BD studies identified by the initial search can be found in Supplementary File 1.

Assessment of Bias

Risk of bias was assessed via the Cochrane Collaboration's tool for assessing the risk of bias.[14] A summary of bias scores for each study can be found in Figure 2. It is important to note that all studies were scored as high for the "other bias" criterion as an indication of sampling and recruitment biases inherent in clinical trials. For example, studies did not include women who were pregnant or breastfeeding, and some studies only included participants already receiving treatment that excludes the generalization to individuals who are not already in care. Thus, the other bias limitations are common to all compounds, and we cannot assume indications of their performance in other recruited groups can be automatically applied.

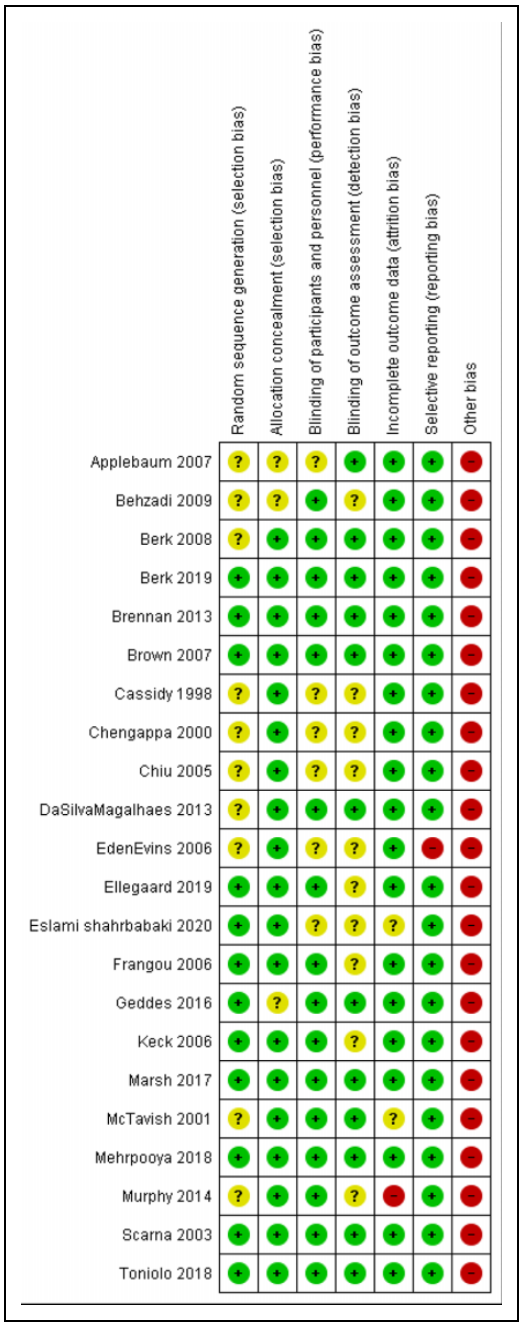

Figure 2. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

Description of Studies

An overview of all studies included in the review is shown in Table 1. Of the 22 studies included in the review, the primary outcome was the improvement in the scores of depression in 12 studies, mania in 7 studies, and both depression and mania in 3 studies. The average sample size of the studies was 56 and ranged from 8 to 186. The length of studies ranged from 5 hours to 24 weeks with 12 weeks being the most common length ($n = 5$). The studies were conducted in Australia, Brazil, Denmark, Iran, Israel, Taiwan, United Kingdom, and United States of America. All studies used the *DSM* to diagnose BD, with all but 2 used the *DSM-IV* version, and the remaining used *DSM-III* or *DSM-5* criteria.

Since the publication of the systematic reviews by Sarris et al.[5] and Sylvia et al.,[6] 9 studies have been added to the field. These were studies of acetyl-L-carnitine and α-lipoic acid in combination,[15] coenzyme Q10,[16] creatine monohydrate,[17] S-adenosyl-L-methione (SAMe),[18] folic acid,[19] vitamin D,[20] 2 studies of NAC,[21,22] and 1 three-arm study of NAC and a combination of nutraceuticals including NAC.[23] Since the publication of Fusar-Poli,[7] 1 new study has been published which explored probiotics for the treatment of BD.[24] The current systematic review also reviewed 3 agents that were not addressed in the previous reviews (SAMe,[18] citicoline,[25] and a probiotic combination[24]).

Amino acids. Studies explored the effects of amino acids with varying results. Brennan et al.[15] ($n = 40$) found no statistical difference between a combination of acetyl-L-carnitine (1,000 to 3,000 mg daily) and α-lipoic acid (600 to 1,800 mg daily) versus placebo for the treatment of bipolar depression over 12 weeks (mean difference = −1.4 [−6.2 to 3.4], $P = 0.58$).

There were 3 RCTs investigating the effects of NAC. Berk et al. (2008; $n = 75$)[26] first assessed NAC (2 g/day) versus placebo in a BD sample where participants could be experiencing any phase of the disorder at baseline (e.g., depressed, hypomanic, manic, euthymic). In this 24-week RCT, NAC was superior to placebo at reducing depression symptoms on the MADRS (Least squares [LS] mean difference [95% CI]: −3.08 [−5.99 to −0.17], $P = 0.039$). Magalhães et al.[21] ($n = 15$) conducted a subgroup analysis from this RCT, which included only participants in a manic or hypomanic phase at their baseline visit. While there was a significant improvement in YMRS scores for participants receiving NAC, this was not significantly superior to placebo. In contrast, Ellegaard et al.[22] ($n = 80$) found no significant difference between 20 weeks of NAC (3 g/day) and placebo at reducing depression symptoms measured on the MADRS in a bipolar depression sample. Berk and colleagues next embarked on a replication of their 2008 study. Berk et al. (2019; $n = 181$)[23] was a 3-arm study of 16-week treatment with placebo versus NAC (2 g/day) versus NAC plus a combination of additional nutraceuticals (including acetyl L-carnitine 1,000 mg, coenzyme Q10 200 mg, α-lipoic acid 150 mg, magnesium [orotate chelation] 64 mg) and other relevant cofactors. Neither NAC nor the combination treatment was superior to placebo at 16 weeks at reducing depression (MADRS). However, the combination was significantly superior to placebo at reducing MADRS scores at Week 20, at the end of the 4-week washout phase ($M_{diff} = -5.2$, $SE_{diff} = 2.4$), $t(111.5) = -2.19$, $P = 0.031$). All studies reported relatively low risk of bias. The variety of treatment times for these NAC studies may account for some of the variance in results. The trial with the longest follow-up

Table 1. A Description of Studies Included in Review.

Author	Intervention	Dose	Duration	Country	Sample Size: Active Arm (*n*)	Sample Size: Comparator Arm (*n*)	Age: Overall Mean (*SD*)	Diagnosis	Primary Outcome Measure	Findings
Amino acid										
Brennan (2013)	Acetyl-L-carnitine and α-lipoic acid	1,000 to 3,000 mg daily and 600 to 1,800 mg daily, respectively	12 weeks	United States	20	20	45.5 (11.1)	*DSM*-IV BDI or II, MADRS > 20	MADRS	No significant differences in mood outcomes
Berk (2008)	NAC	2 g	24 weeks	Australia	38	37	45.6 (12.5)	*DSM-IV*, BD I or II	MADRS	Significant improvement in depression
Magalhães (2013)	NAC	2 g	24 weeks	Australia	8	7	44 (range = 38)	*DSM-IV*, BD I or II	YMRS	Significant improvement in mania in NAC group but no significant between-group differences
Ellegaard (2019)	NAC	3 g	20 weeks	Denmark	40	40	43.4 (10.1)	*DSM-IV* BDI or II, MADRS > 18	MADRS	No significant differences between 2 groups for depression
Berk (2019)	NAC, mitochondrial cocktail	2 g	16 weeks	Australia	59 and 61, respectively	61	45.5 (12.3)	*DSM-IV* BDI, II or NOS, MADRS ≥ 20	MADRS	No significant between-group differences at Week 16, significant at Week 20 for cocktail only
Omega-3 fatty acids										
Frangou (2006)	EPA	1g, 2 g	12 weeks	UK	24 and 25, respectively	26	46 (9.95)	*DSM-IV* BDI or II, HAM-D ≥ 10	HAM-D	Significant improvement in depression for both EPA groups, compared to placebo
Keck (2006)	EPA	6 g	4 months	United States	59	57	45.25 (12)	*DSM-IV* BDI, II or NOS	YMRS/IDSC	No significant differences in mood outcomes
Chiu (2005)	Omega-3 fatty acids	(EPA 440 mg, DHA 240 mg)	3 weeks	Taiwan	7	7	N/A	*DSM-IV* BDI, YMRS ≥ 20	YMRS	No significant differences between 2 groups (mania)
Vitamins										
Behzadi (2009)	Folic acid	3 mg	3 weeks	Iran	44	44	35.0 (8.4)	*DSM-IV*, current mania	YMRS	Significant improvement in mania
Geddes (2016)	Folic acid	500 μg	12 weeks	UK	92	94	36 (19.4)	*DSM-IV* BDI or II, QIDS-SR16 ≥ 11	QIDS-SR16	Not superior to placebo, possibly reduces the effects of lamotrigine
Marsh (2017)	Vitamin D	5,000 IU	12 weeks	United States	16	17	44.2 (13.1)	*DSM-IV* BDI, II or NOS, MADRS ≥ 7	MADRS	No differences between groups

(continued)

Table 1. (continued)

Author	Intervention	Dose	Duration	Country	Sample Size: Active Arm (*n*)	Sample Size: Comparator Arm (*n*)	Age: Overall Mean (*SD*)	Diagnosis	Primary Outcome Measure	Findings
Other nutrients										
Mehrpooya (2018)	Coenzyme Q10	200 mg	8 weeks	Iran	45	44	38.5 (10.8)	*DSM-IV*, MADRS > 15	MADRS	Significant improvement in depression
Brown (2007)	Citicoline	500 to 1,500 mg	12 weeks	United States	23	21	41.4 (7.1)	*DSM-IV* BD or schizoaffective BD type	YMRS/IDS-SR	No significant differences in mood outcomes
Toniolo (2018)	Creatine monohydrate	6 g	6 weeks	Brazil	16	11	43.8 (9.3)	*DSM-IV* BDI or II, MADRS $\geq$ 20	MADRS	No differences between groups for ITT, significant responders
Murphy (2014)	SAMe	1,600 mg	4 weeks	United States	9	8	N/A	*DSM-IV* BDI or II, MADRS $\geq$ 15	MADRS	No differences between groups
Chengappa (2000)	Inositol	6 to 12 g	6 weeks	United States	12	12	43 (10.5)	*DSM-IV* BDI or II, HAM-D $\geq$ 15	HAM-D 17	No significant change in HAM-D, "trend" in MADRS
Evins (2006)	Inositol	5.7 to 19 g	6 weeks	United States	9	8	45.8 (12.2)	*DSM-IV* BDI or II, HAM-D $\geq$ 15	HAM-D 17	No significant difference in depression
Amino acid depletion										
Cassidy (1998)	Tryptophan depletion	93.5 g	5 hours	United States	4	4	52.5 (31 to 66)	*DSM-III-R*, manic episode	YMRS	No significant change in mood
Applebaum (2007)	Tryptophan depletion	102.1 g	7 days	Israel	9	8	42.1 (7.8)	*DSM-IV*, manic episode	YMRS	Significant improvement in mania
McTavish (2001)	Tyrosine depletion	90 g	6 hours	UK	10	10	37.2 (3.5)	*DSM-IV* BDI, current manic episode	YMRS/Biegel Manic State Rating Scale	Significant improvement in mania
Scarna (2003)	Branched-chain amino acid drink	60 g	7 days	UK	13	12	41.3 (12.4)	*DSM-IV* BDI, YMRS > 20	YMRS/Biegel Manic State Rating Scale	Significant improvement in mania
Probiotics										
Eslami Shahrbabaki (2020)	Probiotics	1 capsule daily	8 weeks	Iran	19	19	38.9 (9.83)	*DSM-5*	YMRS HAM-D 24	Significant reduction in depression and mania for both treatment groups. No significant differences between groups

Note. BD = bipolar disorder; BDI = Beck Depression Inventory; DHA = docosahexaenoic acid; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; EPA = ethyl-eicosapentaenoic acid; HAM-D = Hamilton Depression Rating Scale; IDS-C = Inventory of Depressive Symptomatology - clinician; IDS-SR = Inventory of Depressive Symptomatology - self-rated; ITT = Intention to treat MADRS = Montgomery Åsberg Depression Rating Scale; NAC = N-acetylcysteine; NOS = not otherwise specified; QIDS-SR16 = Quick Inventory of Depressive Symptomatology - Self Report 16 item; SAMe = S-adenosyl-L-methione; YMRS = Young Mania Rating Scale.

period (6 months) was positive, while the shorter trials were negative.

Omega-3 fatty acids. Omega-3 has been explored for potential effects on depression,[27] mania,[28] and rapid cycling.[29] Frangou et al.[27] ($n = 75$) compared 12 weeks of ethyl-eicosapentaenoic acid (EPA) at 1 g and 2 g daily doses to placebo for efficacy of reducing depression in BD. Both EPA doses demonstrated a significantly greater reduction in HAM-D scores compared to placebo ($P = 0.03$); however, there was no difference between the EPA groups. Keck et al.[29] ($n = 116$) split participants into groups of either bipolar depression or rapid cycling (based on *DSM-IV*) who were then randomized to 4 months treatment with either EPA 6 g or placebo. There were no significant differences between each treatment arm for depression or mania outcomes. Chiu et al.[28] ($n = 14$) assessed a combination of omega-3 fatty acids (EPA 440 mg, docosahexaenoic acid 240 mg), in addition to valproate 20 mg/kg/day as a treatment for manic inpatients and found the treatment was not significantly superior to placebo after 3 weeks in reducing symptoms of mania (YMRS). This study may have been limited as it was relatively short (only 3 weeks) and has been assessed to have a relatively high risk of bias.

Vitamins. Folic acid has been trialed as an adjunctive agent to treat mania[30] and depression[19] in BD. Behzadi et al.[30] ($n = 88$) found sodium valproate plus folic acid (3 mg/day) compared to sodium valproate plus placebo showed a significantly greater improvement in manic symptoms of participants in their 3-week trial ($P = 0.005$). However, Geddes et al.[19] ($n = 186$) found no statistically significant benefit of adding folic acid (500 μg/day) to the combination of quetiapine (50 to 300 mg/day) and lamotrigine (100 to 200 mg/day) to treat depression in BD (QIDS-SR) over 12 weeks. The study was a 2 × 2 factorial design for 12 weeks. A lack of benefit in depression may be due to the use of folic acid rather than methylfolate (which is not subjected to the T677C polymorphism affecting its metabolism[31]).

Marsh et al.[20] ($n = 33$) found no significant between-group differences in their 12-week trial of vitamin D (5,000 IU) versus placebo for bipolar depression. Participants in this study were included if they had low serum vitamin D levels prior to baseline, and only 31.3% of participants among those receiving vitamin D had adequate levels at the end of the trial, and thus, longer treatment time or higher dose may be required.

Other nutrients. A variety of other nutrients have been explored to treat all phases of BD. Coenzyme Q10 (200 mg/day) was found to be superior to placebo in reducing depression symptoms in an 8-week study by Mehrpooya et al.,[16] $F(2, 134) = 18.57$, $P < 0.001$, $n = 89$. Coenzyme Q10 was chosen as it is part of the mitochondrial electron transfer chain. Of note, this nutrient was also included in the combination treatment of Berk et al 2019[23] at the same dose.

In Brown et al.'s[25] ($n = 44$) study of participants with BD and who were in early recovery of cocaine abuse, citicoline (500 mg to 1,500 mg/day) was not superior to placebo at reducing depression or mania symptoms after 12 weeks. However, this does represent a restricted population. Toniolo et al.[17] ($n = 27$) conducted a 6-week trial of adjunctive creatine monohydrate (6 g/day) versus placebo for the efficacy of reducing bipolar depression. In their completer's analysis, there were no significant between-group differences for reducing MADRS depression scores. However, significantly more participants receiving creatine monohydrate achieved remission (MADRS $\leq$ 12 at Week 6) compared to participants receiving placebo in both the completer's analysis ($n = 27$, creatine 66.7% vs. placebo 18.2, $P = 0.036$, odds ratio [OR] = 9.0) and in the a priori intention to treat model ($n = 35$; creatine 52.9% vs. placebo 11.1%, $P = 0.012$, $OR = 9.0$). Murphy et al.[18] ($n = 17$) conducted a 6-week study comparing the effects of SAMe versus placebo for treatment-refractory bipolar depression. Due to the possibility of manic switch, SAMe was administered in participants on mood stabilizers at a therapeutic dose for 1 month prior to study enrolment. An intermittent dosing schedule was also used whereby participants received active SAMe for only 3 days per week, and doses were increased at each visit if there had been no response, ranging from 400 to 1,600 mg/day. There were no between-group differences for reduction in depression scores across the 4-week study.

Two studies administering inositol were included in this review. In the first study by Chengappa et al.[32] ($n = 24$), participants received inositol 6 to 12 g/day adjunctive to valproate, carbamazepine, or lithium treatment for 6 weeks. The inositol (or placebo) was administered 3 times a day as powder mixed in water. There were no significant between-group differences for change in depression scores for either the HAM-D or the MADRS. In a similar study, Evins et al.[33] ($n = 17$) trialed inositol versus placebo for 6 weeks, adjunctive to treatment as usual. In this study, inositol was administered in 950 mg capsules ranging from 5.7 to 19 g/day. There were no significant between-group differences for reduction in HAM-D scores. However, in the a priori analysis of responders (>50% reduction in HAM-D), there was a trend of improvement in the inositol group ($P = 0.053$). While there was no significant efficacy of inositol for depression, there was a relatively high risk of bias for both studies.

Amino acid depletion studies. There were 4 studies that used rapid amino acid depletion as a potential treatment for acute mania, 2 tryptophan depletion,[34,35] and 2 tyrosine depletion studies.[36,37] In a population of recently manic inpatients being treated with lithium, Cassidy et al.[34] ($n = 8$) trialed a drink consisting of amino acids (some in capsule form), without tryptophan compared to a control drink that contained one-quarter of the concentration of amino acids. The authors found no significant differences in YMRS scores for either tryptophan depletion or control group 5 hours after treatment. Applebaum et al.[35] ($n = 17$) trialed a similar

tryptophan-free amino acid drink or similar tasting drink without amino acids as a control condition. In this study, all participants received sodium valproate (starting dose: 1,000 mg/day) and consumed the study drink every morning for 7 days. Participants receiving the tryptophan depletion drink had a significantly larger reduction in their mania rating (YMRS) compared to the control condition across the 7 days, $F(3, 45) = 6.2$, $P = 0.001$. The difference in results of these 2 studies may be owing to the single treatment in Cassidy et al. indicating inadequate length.

McTavish et al.[36] ($n = 20$) found tyrosine depletion had rapid antimanic effects. In this study, inpatients experiencing a current manic episode were randomized to receive a single dose drink of amino acids with tyrosine (the control arm) or without tyrosine (the tyrosine depletion arm). Participants receiving the tyrosine-free drink showed significantly greater improvement in their manic symptoms over the 6-hour study compared to the control condition ($F = 4.5$, $P < 0.05$). Scarna et al.[37] ($n = 25$) found significant improvement in depression symptoms measured by the YMRS when comparing a branched-chain amino acid drink (a combination of valine, isoleucine, and leucine), chosen to deplete tyrosine, to a matched placebo. The branched-chain amino acid drink or placebo was administered every morning for 7 days, and comparisons were made at 6 hours postconsumption, Day 8, and Day 15. The branched-chain amino acid drink was significantly superior to placebo at reducing mania symptoms at 6 hours postconsumption ($F = 2.84$, $P = 0.02$) and Day 15 ($F = 10.16$, $P = 0.01$).

Probiotics. Eslami Shahrbabaki et al.[24] ($n = 38$) explored the efficacy of a combination of probiotics in a sample of hospitalized patients diagnosed with bipolar I. Participants were included in the study if they were not taking any medications at the beginning of the trial; however, once starting on the study, they were allowed to receive lithium up to 900 mg, sodium valproate up to 1,200 mg per day, or risperidone (unspecified dose). Participants were randomized to receive 8 weeks of either placebo ($n = 18$) or a probiotic capsule containing Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus bulgarigus, Streptococcus thermophiles, Bifidobacterium longum, Bifidobacterium breve, and Lactobacillus rhamnosus ($n = 18$). Results showed a significant reduction in mania (YMRS) and depression (HAM-D) scores for both the placebo and probiotics groups across the 8 weeks. However, there were no significant between-group differences, meaning the probiotics group was not superior to placebo at reducing BD symptoms. There was no comment in the paper of diet consumed by participants before and during the study which may influence the efficacy of a probiotic treatment.

Discussion

The systematic review explored the effects of nutraceuticals for treating BD in RCTs that investigated the effects of nutraceuticals for treating BD. The current review extends previous knowledge by including additional (10) studies that have been published since the review by Sarris et al.[5] It also highlights that despite the current interest by clinicians and consumers, and the push toward ensuring improved rigor through RCTs, there has been little traction at the research and industry coalface to improve the evidence regarding adjunctive nutraceuticals.

Regarding bipolar depression, a study of coenzyme Q10 was positive, albeit from only a single study. Studies of omega-3 fatty acids and NAC reported both positive and negative results for treating bipolar depression. For α-lipoic acid, citicoline, creatine, inositol, SAMe, folic acid, and vitamin D, only single negative studies have been reported.

In regard to the treatment of mania, positive results have been reported for 1 folic acid and 1 small NAC study. Treatment with tyrosine-depleting amino acids found positive results in 2 studies. Studies of tryptophan depletion were conflicting with both positive and negative results. Finally, 1 study of omega-3 fatty acids for the treatment of mania returned negative results.

The heterogeneity across the included studies was large, with a variety of agents, varying dosing regimens, and a wide range of study durations (from 5 hours to 24 weeks). Given the theory of mitochondrial dysfunction[38,39] contributing to the pathophysiology of BD, it is interesting that the nutraceuticals from this review include many with a mitochondrial target. Although Coenzyme Q10 and NAC have both demonstrated potential efficacy for treating bipolar depression, replication studies are required. Of interest, varying treatment duration may play a role in the lack of efficacy in the replication studies for NAC. The original significant study was of 24-week duration, and separation between the groups was not seen until at least Week 20 and a greater separation at Week 24.[26] The replication studies of shorter durations did not find this separation of groups at earlier time points.[22,23] There are parallels in the schizophrenia literature, with positive studies of NAC generally being between 6 and 12 months of duration.[40,41] Furthermore, the combination of both coenzyme Q10 and NAC in the study of Berk et al.[23] study may be synergistic in terms of mitochondrial biogenesis and should be researched further as a combination therapy in longer studies. However, as the significant separation of groups in study of Berk et al.[23] was after the 4-week washout period, not the primary endpoint, this theory should be cautiously interpreted.

Additional studies, which demonstrated significant results, were tyrosine depletion and folic acid for the treatment of mania. The depletion of tyrosine serves as a proof of concept that catecholamines are involved in the etiology of mania (as a precursor of dopamine[42]). Folic acid was chosen to correct possible deficiencies and therefore may be more appropriate when stratified by individual needs and also being more effective when given in the methylfolate form. There were conflicting results for tryptophan depletion in rapid mania treatment, though duration of studies may have

influenced these results. Conflicting results were also found for EPA whereby doses of 1 g and 2 g were efficacious but not 6 g for the treatment of depression (representing a potential U-shaped response curve). EPA possibly targets lipid peroxidation or neuroinflammation to treat bipolar depression; however, further research is required.

This systematic review is limited by the wide variety of agents included. These agents are also known to act on different pathways in the pathophysiology of BD. The differences in symptoms for the depressive and manic phases make it difficult to assess the utility of agents for the disorder as a whole. However, this review does highlight some areas for future replication studies to explore, in particular coenzyme Q10, NAC, and EPA. The significant discrepancies in clinical trial designs across the studies included in this review preclude direct comparison or the use of a meta-analysis. This raises a potential need for harmonization and standardization of clinical trials for nutraceuticals, including the use of standard rating instruments, dosing, and visit schedules (e.g., a minimum of 24 weeks for treatment of bipolar or psychotic disorders).

A strength of this systematic review was the strict criteria for inclusion, with restrictions such as excluding open-label studies, and only including primary validated mood scales. These restrictions add to the integrity of the review. The protocol for this review has been peer reviewed and published, further adding to the scientific integrity of the review. Presented here is a comprehensive review and update of nutraceuticals as adjunctive treatments for BD, which adds to the evidence base for treating physicians who wish to supplement conventional treatments. This systematic review has highlighted concerns for study lengths by demonstrating that studies of NAC at shorter lengths showed reduced efficacy. As nutraceuticals are easily accessible, affordable, and have a relatively low-side-effect profile, they may be appealing to patients and physicians alike when administered adjunct to conventional treatments.

Clinical Considerations

Based on the results of the current systematic review, omega-3 fatty acids, NAC, and coenzyme Q10 could potentially be used by clinicians as adjunctive interventions to aid the treatment of bipolar depression in individuals who may not have benefited from first-line therapies. However, due to the lack of robustness of the available evidence, clinical judgment and close monitoring of patients are imperative, as further studies are still required to support these interventions as first-line adjunctive therapies. This clinical caveat applies even more so to the management of more severe BD symptoms, and in particular for mania, as the aforementioned nutraceuticals do not have supportive evidence for this latter application. Indeed, due to the potential of some nutraceuticals upregulating mitochondrial activity, caution is needed in a manic phase. If clinicians are considering prescribing nutraceuticals, a careful history is needed to establish, if possible, the patient's current affective state and pattern of mood changes, in addition to other clinical features. It is important to also assess whether adjunctive nutraceutical prescription may be of benefit (especially in the context of any comorbidity and the additional consideration of any potential drug interactions).

Conclusion

The use of adjunctive nutraceuticals, principally those targeting mitochondrial biogenesis pathways and inflammation, may be useful in treating the depressive phase of BD, although the level of evidence remains preliminary. Further research with consistent long-term studies at adequate doses is required.

Authors' Note

The sponsors and funding bodies have played no role in collection, analysis, interpretation of results, or writing of the article.

Acknowledgment

The authors wish to thank Blair Kelly for library support in creation of the search strategy and guidance when conducting the search.

Author Contributions

MMA developed the research question and search strategy; performed the initial database search; independently screened all articles for inclusion at title, abstract, and full-text phases; independently assessed risk of bias and data extraction of all included studies in review; conducted all statistical tests; drafted the initial article and contributed to edits; and approved final version. BEK independently assessed all full texts for inclusion and exclusion criteria, independently assessed risk of bias and data extraction of all included studies in review, revised the search strategy and methodology, and edited and approved the article. WM independently assessed all title and abstracts for inclusion/exclusion criteria and edited and approved the article. OD, MB, CHN, and MH conceptualized the research question, revised the search strategy and methodology, and edited and approved the article. JS and LJW revised the search strategy and methodology and edited and approved the article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MMA has received grant/research support from Deakin University, Australasian Society for Bipolar Depressive Disorders, Lundbeck, Australian Rotary Health, Ian Parker Bipolar Research Fund, and Cooperative Research Centre for Mental Health. MB has received grant support from NIH, Simons Autism Foundation, Cancer Council of Victoria, CRC for Mental Health, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, and Servier. MB also has received grant/research support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2

milk company, Meat and Livestock Board, Woolworths, Avant, and the Harry Windsor Foundation; has been a speaker for Astra Zeneca, Lundbeck, Merck, and Pfizer; and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer, and Servier—all unrelated to this work. MH has received grant support from ISSCR, Ramsay Health Foundation, Lyndra, Praxis, Servier, US DOD, and Bionomics; has been a speaker for Janssen-Cilag, Lundbeck, and Servier; and has been a consultant for AstraZeneca, Eli Lilly, Grunbiotics, Janssen-Cilag, Lundbeck, and, Servier. BEK has received grant/research support from the Australian Government Research Training Program Scholarship, Australian Rotary Health Ian Scott PhD Scholarship, and the International Society for the Study of Personality Disorders. JS has received either presentation honoraria, travel support, clinical trial grants, book royalties, or independent consultancy payments from Australian Natural Therapeutics Group Integria Healthcare & MediHerb, Pfizer, Scius Health, Key Pharmaceuticals, Taki Mai, Bioceuticals & Blackmores, Soho-Flordis, Healthworld, HealthEd, HealthMasters, Elsevier, Chaminade University, International Society for Affective Disorders, Complementary Medicines Australia, Terry White Chemists, ANS, Society for Medicinal Plant and Natural Product Research, UBiome, Omega-3 Centre, the National Health and Medical Research Council, and CR Roper Fellowship. OMD is a R. D. Wright Biomedical NHMRC Career Development Fellow (APP 1145634) and has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC, and ASBDD/Servier. She has also received in-kind support from BioMedica Nutraceuticals, NutritionCare, and Bioceuticals.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: MMA would like to acknowledge the support of Australian Rotary Health/Ian Parker Bipolar Research Fund PhD scholarship and the ASBDD/Lundbeck PhD neuroscience scholarship. MB is supported by a NHMRC Senior Principal Research Fellowship (1059660 and 1156072). BEK is supported by an Australian Government Research Training Program Scholarship, and an Ian Scott Mental Health PhD Scholarship, Australian Rotary Health. LJW is supported by a NHMRC Career Development Fellowship (APP1064272) and a NHMRC Investigator grant (1174060). JS is supported by an NHMRC Clinical Research Fellowship (APP1125000). OMD is supported by a R. D. Wright Biomedical NHRMC Research Fellowship (APP1145634).

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Supplemental Material

Supplemental material for this article is available online.

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