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Nutraceuticals and nutritional supplements for the treatment of bipolar disorder: protocol for a systematic review

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ABSTRACT

Introduction First line pharmacological treatments for bipolar disorder (BD) can leave shortfalls in recovery leading to patients seeking alternative and adjunctive treatments such as nutraceuticals. This protocol for a systematic review and proposed meta-analysis aims to answer the research question: in patients with BD, how does use of nutraceutical treatments compare with placebo in reducing depressive and mania symptoms?

Methods and analysis Clinical trials will be identified through database searches using PubMed via PubMed, EMBASE via embase.com, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via cochranelibrary.com and CINAHL Complete via EBSCO. Search terms for BD and specific nutraceuticals (75 total search terms) will be used. Double-blind, randomised, controlled, clinical trials of adults with BD will be included in the review. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.

Ethics and dissemination This review will only look at published data (already reviewed for ethical compliance); therefore, ethical approval is not required. We aim to publish the systematic review in a peer-reviewed journal and present at conferences.

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Strengths and limitations of this study

- This review will update and extend previously completed systematic reviews of the effects of nutraceuticals in bipolar disorder (BD).
- This review will employ rigorous screening and assessment of studies to be included allowing for only good quality, peer reviewed publications.
- A strength of this review is the range of potential nutraceutical agents to be assessed.
- A limitation of the review will be the inherent differences in manic and depressive phases means it will be difficult to compare agents across BD as a whole.
- There is likely to be high heterogeneity for the nutraceutical agents and measures for symptomology across the studies limiting the comparisons for a meta-analysis.

INTRODUCTION

Bipolar disorder

Bipolar disorder (BD) is a biphasic disorder characterised by manic and depressive episodes.[1] Common pathways to pathology include dysregulation of monoamines, increased oxidative stress, perturbed inflammatory processes and mitochondrial disturbances.[2] The depressive phase of the disorder is more common than mania (3:1) and can be harder to treat.[3] Most first-line treatments for BD are more effective at treating the manic phase, including mood stabilisers (eg, lithium) and second-generation antipsychotics (eg, lurasidone or quetiapine).[4] Antidepressants, especially tricyclic antidepressants and selective serotonin-norepinephrine reuptake inhibitors, can cause some people with BD to switch to a manic phase, therefore antidepressants are not recommended as monotherapy.[5–7] Other common side effects of currently available treatments for BD can include extrapyramidal symptoms such a tremors, akathisia[8] and weight gain.[8 9] Thus, polypharmacy is more common practice than monotherapy.[4] Due to tolerability issues and shortfalls in recovery, additional treatment options are often sought.

Nutraceuticals have been defined as functional foods that treat or prevent a disease or disorder[10] and in particular are nutrients that have been standardised and of pharmaceutical grade.[11] Originally described as a combination between nutrition and pharmaceuticals,[12] nutraceuticals are a growing field of medications. The Therapeutic Goods Association of Australia regulate complementary medicines defined as therapeutic goods containing one or more of the following active ingredients: amino acid, mineral, vitamin or provitamin, choline salt,

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lipid (including an essential fatty acid or phospholipid), a sugar, polysaccharide or carbohydrate, mucopolysaccharide, plant or herbal material, an essential oil, charcoal, micro-organism, non-human animal material, or homeopathic preparation.[13] Dietary supplements have been defined by the Food and Drug Administration in the Dietary Supplement and Health Education Act as an orally administered dietary ingredient that could contain minerals, vitamins, enzymes, amino acids or herbs.[14] Approximately 30% of individuals with BD have reported taking nutraceuticals, although the authors highlighted that under-reporting of nutraceuticals is common due to the perceived idea they are often considered relatively benign. Because of this perception of nutraceuticals, treating physicians may not be notified of the patient's nutraceutical use.[15]

The term Nutraceutical encompasses a broad range of agents, which may have differing effects within the body on the pathophysiology of some disorders. Some nutraceuticals have bioactive properties that can target the putative pathophysiology of BD. For example, omega-3 is known for its high anti-inflammatory properties, L-theanine for its antioxidant properties and the amino acid N-acetylcysteine is known for both its anti-inflammatory, antioxidative and mitochondrial properties. We will present an overview of nutraceuticals broadly and then explore subgroups, based on those reported in the previous systematic review to allow comparisons with the previous literature (eg, fatty acids). For the purposes of this review, lithium will not be included despite coming under the definition of minerals. Lithium will not be included as it has been extensively researched previously[16] and will fall outside of the scope of this review. Two previous systematic reviews have been conducted in this field (Sarris *et al*[17] and Sylvia *et al*[18]). However, given the expansion of the field and progress in the understanding of the underlying biological processes, this systematic review will form a comprehensive and much needed update of the current literature.

Objectives

The objectives of this systematic review are to identify and evaluate published clinical trials of nutraceuticals as treatments for BD. The systematic review will include both mania and depressive phases of the disorder. However, as the depressive phase of the disorder is the most frequent and disabling phase and therefore been more widely studied, it is likely to return the most results. If there is sufficient data within two studies or more and homogeneity established, a meta-analysis will be conducted to assess the effect of nutraceuticals compared with placebo. If the studies demonstrate considerable heterogeneity then subanalyses will be performed. The aim of this review will be to answer the research question: In patients with BD, how does use of nutraceutical treatments compare with placebo in reducing symptoms of depression and mania?

METHODS

Search methods

This systematic review protocol has been prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Protocols guidelines.[19]

Relevant literature will be identified via electronic searches using PubMed via PubMed, EMBASE via embase.com, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via cochranelibrary.com and CINAHL Complete via EBSCO. Searches will be conducted from inception to the date of search. In addition to the database searches, reference lists of other systematic reviews and retrieved trials will also be reviewed for studies to be included in the screening process.

Search strategy

PICO (Patient, Intervention, Comparison/Control, Outcome) search framework was used to develop search terms relating to BD and nutraceuticals. Key search terms will be used as follows, by searching 'all fields'. Relevant formatting for each database will be used. The following Medical Subject Headings (MeSH) and Emtree terms will be used ('bipolar disorder' OR 'bipolar and related disorders' OR 'cyclothymic disorder' OR 'bipolar I disorder' OR 'bipolar II disorder') AND (prebiotics OR probiotics OR 'nutritional supplement' OR 'nutrition supplement' OR 'nutrition therapy' OR 'nutritional support' OR minerals OR mineral OR 'dietary supplement' OR 'complementary therapies' OR 'alternative medicine' OR 'medicine, traditional' OR 'traditional medicine' OR 'amino acids' OR acetylcysteine OR 'fatty acids' OR 'fatty acid' OR 'eicosapentaenoic acid' OR 'fatty acid, omega-3' OR 'Fatty acid, omega-6' OR 'folic acid' OR antioxidants OR 'fatty acid, essential' OR tryptophan OR creatine OR chromium OR inositol OR choline OR zinc OR ubiquinone OR curcumin OR 'thioctic acid' OR acetylcarnitine OR s-adenosylmethionine OR melatonin OR taurine) AND ('clinical trial' OR 'randomized controlled trial' OR 'controlled clinical trial'). In addition, other common, non-MeSH key terms will be included in the coinciding sections of the search: ('bipolar affective disorder' OR 'bipolar depression' OR 'bipolar mania' OR mania OR hypomania OR cyclothymia OR BPAD OR BD) AND (Nutraceutical OR 'functional food' OR nutrient* OR supplement OR 'nutrient-based therapy' OR complementary OR vitamin* OR 'amino acid' OR n-acetylcysteine OR methylfolate OR PUFA OR cannabinoids OR omega* OR folate OR magnesium OR tryptophan OR 'essential fatty acids' OR tonic OR 'coenzyme q10' OR 'alpha-lipoic acid') AND (RCT OR trial OR 'randomised controlled trial'). The full search strategy for each database can be found in online supplementary file 1.

Inclusion/exclusion criteria

Types of studies

For this review, only peer-reviewed, published, double-blind, randomised, controlled trials will be included. Studies may either include adjunctive agents or monotherapy and will be compared with either a placebo or other intervention.

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Only studies testing the effects of the medication on the reduction of depressive or mania symptoms of BD will be included. Therefore, prophylaxis studies and studies will be excluded. Case reports, observational studies, open-label trials, cross-sectional design studies, grey literature, protocol papers and conference presentations will also be excluded.

Types of participants

We will review studies including adults with a diagnosis of BD I, II, NOS based on Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. In-patient and out-patient participants will all be included.

Subgroup analyses will be performed to determine the effects of the study medication specifically on the active depressive phase of BD. For the relevant studies, current depression must be assessed using the following standardised scales: Montgomery Åsberg Depression Rating Scale (MADRS),[20] Hamilton Depression Rating Scale (HAM-D),[21] Hospital Anxiety and Depression Scale (HADS),[22] Bipolar Depression rating scale (BDRS),[23] Beck Depression Inventory[24] or Quick Inventory of Depressive Symptomatology, Patient Health Questionnaire-9.[25] Mania must be assessed using the following standardised scales: Young Mania Rating Scale (YMRS),[26] The Bech-Fafaelsen Mania Rating Scale,[27] the mania subscale of the Schedule for Affective Disorders and Schizophrenia[28 29] and the Altman Self-Rating Mania Scale.[30] Appropriate cut-off scores will be used for relevant severity of disorder in each study, as determined by or established for each scale. For example, if a study was interested in at least moderate level of depression and utilising the MADRS, a cut-off score of 20 or above would be appropriate given 0–6 is considered recovered, 7–19 mild depression, 20–34 moderate depression and 35–60 severe depression.[31]

Types of interventions

To be included in the review, interventions must come under the definition of nutraceuticals, complementary medicines or dietary supplements (see the Introduction section for definitions) and must aim to improve depressive or manic symptoms. Following the initial search, a table of agents which are included and excluded through the systematic review process will be provided. Comparator arms of the studies may be placebo or another intervention (eg, another medication).

Outcome measures

Primary outcome measure will be an assessment of depression or mania symptomology (eg, standardised mean differences in scores on MADRS, BDRS, YMRS and so on). In the case of multiple outcome measures in the study, only the primary outcome will be included in the systematic review and potential meta-analysis. Any secondary outcomes will not be included as they are likely to be underpowered.

Patient and public involvement

Participants and the public were not involved in the design of the review. As the review will use only previously published research, consent was not required from participants and dissemination to participants will not be required. The authors are working towards better outcomes for participants with BD and factors that influence those outcomes were considered when designing this review.

DATA ANALYSIS

Data management

Covidence,[32] an online database tool, will be used to manage references and search results during the screening and reviewing process. The program allows for handling of duplicate records and detailed tracking of inclusion/exclusion of references allowing for easy extraction into PRISMA flow diagrams.

Identification of eligible studies

The initial search will be conducted by one lead reviewing author to identify relevant articles. Articles will be screened for inclusion/exclusion based on title and abstract; then by reviewing the full text. A second independent reviewing author will independently screen the titles and abstracts. If there are any discrepancies, an experienced third author will act as adjudicator to decide on inclusion into full-text review. After screening, relevant full-text articles will be independently reviewed for bias and content by two independent reviewing authors. If there are discrepancies or disagreements between the two reviewing authors and a consensus cannot be reached, a third independent reviewing author will adjudicate.

Assessment of included articles

Extracted data will include study design, details of intervention(s), details of comparator arm (ie, placebo or intervention), outcome measures, characteristics of samples and risk of bias. The extracted data will follow Consolidated Standards of Reporting Trials (CONSORT) guidelines.[33] STATA Data Analysis and Statistical Software V.15,[34] will be used to analyse data and data synthesis. Treatment effects will be measured by standardised mean differences with 95% CI to allow for differences in interpretation of scores across the scales. In this model, sample sizes and standard deviations will be used to give weightings to each study. If there are no clear summaries of all data to fulfil the CONSORT guidelines and risk of bias then in the first instance authors will be contacted in an attempt to fill in gaps. If contacting the author is not possible then the studies will not be included due to insufficient data.

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[35] will be used to assess bias of all included trials. The criteria for bias included scores of 'low risk of bias', 'high risk of bias' and 'unknown risk of bias' in the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. In the event of missing data in the published study, published protocols will also be used to assess bias, such as publication bias. Publication bias will be assessed via funnel plots. Attempts

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will be made to contact corresponding authors for missing data in the published studies. In accordance with the Cochrane Handbook 5.1[36] suggestions, I^2 will be used to assess for heterogeneity of the trials. If I^2 is >50% then the studies will be considered to have a substantial heterogeneity and will be included in the summarising sections of the systematic review, but the proposed meta-analysis will not be conducted. Quality of evidence of the studies will be assessed and summarised using the Grades of Recommendation, Assessment, Development Evaluation approach.[37] If a meta-analysis is possible, a random-effects model will be used. Results will be reported as standardised mean differences with 95% CI.

Subgroup analysis

The following subgroup analyses will be performed if there is significant heterogeneity across the studies (if I^2 >50%). Subgroup analyses will include different phases of BD and different groups of nutraceuticals.

1. Effect of treatment on depressive symptoms.
2. Effect of treatment on mania symptoms.
3. Depressive phase compared with euthymia.
4. Any phase of BD upon entry into study and depression or mania scores at treatment phase completion.
5. Treatment outcomes of vitamins.
6. Treatment outcomes of fatty acid supplements (eg, omega-3).
7. Treatment outcomes of minerals (eg, zinc, magnesium).
8. Treatment outcomes of amino acids.
9. Treatment outcomes of individual agents.
10. Combination treatments (eg, multivitamins and minerals) versus single treatments.

Sensitivity analysis

Sensitivity analyses will be conducted to take into consideration the following methodological differences (1) differences in diagnostic tool (DSM vs ICD), (2) difference in BD subgroups, (3) different measures of symptoms (eg, MADRS vs HADs) and (4) length of study. For each sensitivity analysis data will be analysed separately and results will be compared with the initial all-inclusive analysis to ensure similar results. In addition, studies will be analysed for differences in gender, age, location and dose of nutraceutical studied, if there are differing doses. If data for the sensitivity analysis is missing in the studies, authors will be contacted in the first instance. If more details cannot be obtained, the study will not be included in the analysis and this will be noted in the results.

Presentation and reporting of results

The review will adhere to PRISMA guidelines and data will be reported using a PRISMA flow diagram.[38] The PRISMA flow diagram will depict numbers excluded at each stage of screening (identification, screening, eligibility and reasons for exclusion) to show the number of studies included and excluded in the review.

Ethics and dissemination

This review will only use published data that has received ethical approval, therefore specific ethical approval for this review is not required. We aim to publish the systematic review in a peer-reviewed journal and the results may be presented at a scientific conference.

CONCLUSION

This rigorous review will evaluate the current literature on the use of nutraceuticals as treatments for BD. This review may be used by clinicians to assist with treatment choices for their patients with BD. Ultimately, this review aims to evaluate additional treatment options for BD and if positive, with the view to reduce the burden of the disorder.

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