Topic Brief: Dietary Supplements for Mental Health and Substance Abuse

Date: 7/14/2022
Nomination Number: 0979

Purpose: This document summarizes the information addressing a nomination submitted on May 7, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The nominator is interested in a systematic review of dietary supplements for mental health to be used as general information for patients and healthcare providers.

Findings: We found one meta-review that covered most of the scope of the topic. It did not include participants with substance abuse disorder, and we found very few primary studies of substance abuse patients.

Background

Mental health includes areas of emotional, psychological, and social well-being. More than 50 percent of people will be diagnosed with a mental illness or disorder in their life, and one in 25 Americans experience serious mental illness, such as schizophrenia, bipolar disorder, or major depression.[1]

Psychotherapies and pharmacotherapies are the recommended first-line treatments for mental disorders, although their effectiveness may be limited.[2] Dietary supplements are sometimes used to augment first-line treatments, but they are not regulated by the Federal Drug Administration as are pharmaceuticals and they are not typically prescribed.[3] The evidence for the benefits of dietary supplements on mental health or other health conditions is not clear. Despite this, the general population commonly uses supplements. Between 2017 and 2018, about 58 percent of adults over the age of 20 said they used any dietary supplement within the past 30 days.[4]

Scope

1. What is the effectiveness, comparative effectiveness, and harms, of different dietary supplements (as adjunct treatment to usual pharmacological treatment) on:
    a) Alcohol use disorder
    b) Opioid use disorder
    c) Schizophrenia and other psychotic disorders
    d) Major depressive disorder
    e) Bipolar disorders

Table 1. Questions and PICOs (population, intervention, comparator, outcome)

Question	a. Effectiveness and harms of dietary supplements on alcohol use disorder	b. Effectiveness and harms of dietary supplements on mental health opioid use disorder	c. Effectiveness and harms of dietary supplements on schizophrenia and other psychotic disorders	d. Effectiveness and harms of dietary supplements on major depressive disorder	e. Effectiveness and harms of dietary supplements on bipolar disorder
Population	Adults 18-64 years with alcohol use disorder, in remission Consider patient characteristics such as age, gender, race/ethnicity, and symptom severity	Adults 18-64 years with opioid use disorder, in remission Consider patient characteristics such as age, gender, race/ethnicity, and symptom severity	Adults 18 to 64 years with schizophrenia or other psychotic disorders Consider patient characteristics such as age, gender, race/ethnicity, and symptom severity	Adults 18 to 64 years with major depressive disorder Consider patient characteristics such as age, gender, race/ethnicity, and symptom severity	Adults 18 to 64 years with bipolar disorder Consider patient characteristics such as age, gender, race/ethnicity, and symptom severity
Interventions	Any dietary supplements (i.e., vitamins, herbs) as adjuncts to pharmacological treatment	Any dietary supplements (i.e., vitamins, herbs) as adjuncts to pharmacological treatment	Any dietary supplements (i.e., vitamins, herbs) as adjuncts to pharmacological treatment	Any dietary supplements (i.e., vitamins, herbs) as adjuncts to pharmacological treatment	Any dietary supplements (i.e., vitamins, herbs) as adjuncts to pharmacological treatment
Comparators	No supplements/ Placebo; other supplement	No supplements /placebo; other supplement	No supplements/ placebo; other supplement	No supplements/ placebo; other supplement	No supplements/ placebo; other supplement
Outcomes	Changes in symptoms (e.g., ratings on mental health/psychological functioning scales), quality of life, consumption outcomes, harms	Changes in symptoms (e.g., ratings on mental health/psychological functioning scales), quality of life, opioid use, harms	Changes in symptoms (e.g., ratings on mental health/psychological functioning scales), quality of life, harms	Changes in symptoms (e.g., ratings on mental health/psychological functioning scales), quality of life, harms	Changes in symptoms (e.g., ratings on mental health/psychological functioning scales), quality of life, harms

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found one meta-review of a variety of dietary supplements for a variety of mental illnesses that addressed most of the scope, and too few and varied primary studies for the remainder of the scope.

The meta-review on the efficacy and safety of nutrient supplements on the treatment of mental disorders included patients with common and severe forms of mental disorders, as well as those at ultra-high risk or clinical high risk of developing mental disorders, and all nutrient supplements (i.e., vitamins, minerals, macronutrients, fatty acids, or amino acids) used as either adjunctive treatment or monotherapy. Investigators reported some indication of efficacy for some supplements, most robustly for polyunsaturated fatty acids for depression, and good safety profiles for all supplements.[5]

The meta-review addressed all mental disorders of interest except substance abuse disorders. We reviewed a sample of primary studies found only two qualifying studies on substance abuse disorder, one examining inulin-prebiotic fiber in alcohol use disorder[6] and the other examining probiotics in opioid use disorder.[7]

Table 2. Literature identified for each Question

Question	Systematic reviews (3/2019-6/2022)	Primary studies (6/2017-6/2022)
Question 1: Effectiveness and harms of dietary supplements on mental health	Total: 1[5] • Cochrane: 0 • AHRQ: 0 • Other: 1[5] Covers mental health conditions other than substance abuse disorders	Total: 2[6, 7] • RCT: 2[6, 7] Clinicaltrials.gov • Recruiting: 0

Abbreviations: AHRQ=Association for Healthcare Quality and Research; RCT=randomized controlled trial.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

The nominators are requesting a systematic review on adjunctive dietary supplements for various mental health conditions to be used to generally inform patients and providers. An existing meta-review from 2019 addresses the primary and adjunctive treatment of most mental health conditions of interest.[5] It does not include substance abuse disorders and we found very few and varied studies addressing the adjunctive use of supplements for substance use disorders.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

1. About Mental Health. Centers for Disease Control and Prevention. doi: https://www.cdc.gov/mentalhealth/learn/index.htm.
2. Leichsenring F, Steinert C, Rabung S, et al. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry. 2022 Feb;21(1):133-45. doi: https://doi.org/10.1002/wps.20941. PMID: 35015359.
3. Wu K, Messamore, E. Reimagining roles of dietary supplements in psychiatric care. AMA J Ethics. 2022:E437-42. doi: https://doi.org/10.1001/amajethics.2022.437.
4. Dietary supplement use among adults: United States, 2017-2018. Centers for Disease Control and Prevention. doi: https://www.cdc.gov/nchs/products/databriefs/db399.htm.
5. Firth J, Teasdale SB, Allott K, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials.

World Psychiatry. 2019 Oct;18(3):308-24. doi: https://doi.org/10.1002/wps.20672. PMID: 31496103.
6. Amadieu C, Coste V, Neyrinck AM, et al. Restoring an adequate dietary fiber intake by inulin supplementation: a pilot study showing an impact on gut microbiota and sociability in alcohol use disorder patients. Gut Microbes. 2022 Jan-Dec;14(1):2007042. doi: https://doi.org/10.1080/19490976.2021.2007042. PMID: 34923905.
7. Molavi N, Rasouli-Azad M, Mirzaei H, et al. The Effects of Probiotic Supplementation on Opioid-Related Disorder in Patients under Methadone Maintenance Treatment Programs. Int J Clin Pract. 2022;2022:1206914. doi: https://doi.org/10.1155/2022/1206914. PMID: 35685534.
8. Reducing the economic burden of unmet mental health needs. The White House. doi: https://www.whitehouse.gov/cea/written-materials/2022/05/31/reducing-the-economic-burden-of-unmet-mental-health-needs/#:~:text=The%20Federal%20Government%20covers%20some,from%20the%20U.S.%20Medicaid%20program.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years June 19, 2022 - June 22, 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Joanna Briggs Institute http://joannabriggs.org/
- PsycINFO https://www.apa.org/pubs/databases/psycinfo/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years June 22, 2019 - June 22, 2022. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for each question for inclusion. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE ALL <1946 to June 22, 2022>

Date searched: June 23, 2022
1 alcohol-related disorders/ or alcoholism/ or (alcoholism or (alcohol* adj3 disorder*)).ti,kf. (87886)
2 exp Opioid-Related Disorders/ or (opiate$1 or opioid or opium or heroin).ti,kf. (76626)
3 exp "schizophrenia spectrum and other psychotic disorders"/ or (schizophreni* or psychosis or psychoses or psychotic).ti,kf. (181351)
4 Depressive Disorder, Major/ or "major depressive".ti,kf. (39797)
5 Bipolar Disorder/ or "bipolar disorder*".ti,kf. (47701)
6 or/1-5 (406299)
7 exp Vitamins/ or ("folate acid" or vitamin$1).ti,kf. (372195)
8 exp Dietary Supplements/ or ("docosahexaenoic acid" or "eicosapentaenoic acid" or "fish oil" or magnesium or microbio* or "N-acetyl cysteine" or "N-acetylcysteine " or nutraceutical$1 or nutrient$1 or nutrition* or "omega-3" or phytoceutical$1 or prebiotic* or probiotic* or psychobiotic$1 or selenium or supplement* or zinc).ti,kf. (526358)
9 or/7-8 (856825)
10 and/6,9 (5725)
11 limit 10 to english language (4860)
12 11 not ((Animals/ not Humans/) or ("animal model" or canine or cat$1 or dog$1 or feline or mice or monkey$1 or mouse or ovine or pig$1 or porcine or primate$1 or rat$1 or rattus or rodentia or sheep).ti.) (4316)
13 limit 12 to yr="2019 -Current" (903)
14 (meta-analysis or systematic review).pt. or (metaanal* or meta-anal* or ((evidence or scoping or systematic or umbrella) adj3 (review or synthesis))).ti. (355844)
15 and/13-14 (94)
16 limit 12 to yr="2017 -Current" (1282)
17 ("randomized controlled trial" or "controlled clinical trial").pt. or (trial* or control* or placebo* or random*).ti. (1356728)
18 and/16-17 (219)
19 exp cohort studies/ or exp epidemiologic studies/ or (cohort or comparative or evaluation or follow-up or longitudinal).ti,kf. (3695642)
20 and/16,19 (242)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials (May 2022)
Date searched: June 23, 2022
1 alcohol-related disorders/ or alcoholism/ or (alcoholism or (alcohol* adj3 disorder*)).ti,kf. (5188)
2 Opioid-Related Disorders/ or (opiate$1 or opioid or opium or heroin).ti,kf. (7585)
3 "schizophrenia spectrum and other psychotic disorders"/ or (schizophreni* or psychosis or psychoses or psychotic).ti,kf. (15920)
4 Depressive Disorder, Major/ or "major depressive".ti,kf. (7691)
5 Bipolar Disorder/ or "bipolar disorder*".ti,kf. (4106)
6 or/1-5 (39569)
7 Vitamins/ or ("folate acid" or vitamin$1).ti,kf. (18785)
8 Dietary Supplements/ or ("docosahexaenoic acid" or "eicosapentaenoic acid" or "fish oil" or magnesium or microbio* or "N-acetyl cysteine" or "N-acetylcysteine " or nutraceutical$1 or nutrient$1 or nutrition* or "omega-3" or phytoceutical$1 or prebiotic* or probiotic* or psychobiotic$1 or selenium or supplement* or zinc).ti,kf. (66675)
9 or/7-8 (77742)
10 and/6,9 (730)
11 limit 10 to yr="2017 -Current" (29)
12 limit 11 to english language (281)

Ovid APA PsycInfo <1806 to June Week 2 2022>

Date searched: June 23, 2022
1 alcohol-use disorders/ or (alcohol* adj3 disorder*).ti. (4298)
2 exp "opioid use disorder"/ or (opiate$1 or opioid or opium or heroin or morphine).ti. (23184)
3 exp schizophrenia/ or exp psychosis/ or (schizophreni* or psychosis or psychoses or psychotic).ti. (133666)
4 Major Depression/ or (major adj3 depress*).ti. 140252)
5 exp Bipolar Disorder/ or "bipolar disorder*".ti. (33382)
6 or/1-5 (314537)
7 Vitamins/ or ("folate acid" or vitamin$1).ti. (3943)
8 dietary supplements/ or ascorbic acid/ or exp choline/ or folic acid/ or nicotinamide/ or nicotinic acid/ or vitamin therapy/ or ("docosahexaenoic acid" or "eicosapentaenoic acid" or "fish oil" or magnesium or microbio* or "N-acetyl cysteine" or "N-acetylcysteine " or nutraceutical$1 or nutrient$1 or nutrition* or "omega-3" or phytoceutical$1 or prebiotic* or probiotic* or psychobiotic$1 or selenium or supplement* or zinc).ti. (18201)
9 or/7-8 (21069)
10 and/6,9 (2124)
11 limit 10 to english language (2027)
12 11 not ("animal model" or canine or cat$1 or dog$1 or feline or mice or monkey$1 or mouse or ovine or pig$1 or porcine or primate$1 or rat$1 or rattus or rodentia or sheep).ti. (1875)
13 limit 12 to yr="2019 -Current" (418)
14 limit 13 to ("0830 systematic review" or "1200 meta analysis") (37)
15 13 and (metaanal* or meta-anal* or ((evidence or scoping or systematic or umbrella) adj3 (review or synthesis))).ti. (38)
16 or/14-15 (43)
17 limit 12 to yr="2017 -Current" (621)
18 limit 17 to "0300 clinical trial" (86)
19 17 and (trial* or control* or placebo* or random*).ti. (89)
20 or/18-19 (122)
21 limit 17 to ("0430 followup study" or "0450 longitudinal study" or "0451 prospective study") (55)
22 17 and (cohort or comparative or evaluation or follow-up or longitudinal or prospective).ti. (32)
23 or/21-22 (69)

ClinicalTrials.gov
Date searched: June 23, 2022
(docosahexaenoic OR eicosapentaenoic OR EXPAND[Concept] "fish oil" OR magnesium OR microbiome OR N-acetyl cysteine OR N-acetylcysteine OR nutraceutical OR nutrient OR nutrition OR omega-3 OR phytoceutical OR prebiotic OR probiotic OR psychobiotic OR selenium OR supplement OR vitamin OR zinc) AND AREA[StudyType] EXPAND[Term] COVER[FullMatch] ("Interventional" OR "observational") AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Recruiting" OR "Not yet recruiting" OR "Active, not recruiting" OR "Enrolling by invitation") AND AREA[ConditionSearch] ((alcohol OR opioid OR opiate OR heroin OR opium OR morphine) AND disorder OR EXPAND[Concept] "major depression" OR bipolar OR psychosis OR psychotic) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[06/24/2019, 06/24/2022] (412)

Epistemonikos
Date searched: June 24, 2022
title:(((alcohol OR opioid OR opiate OR heroin OR opium OR morphine) AND disorder) OR (major AND (depression OR depressive)) OR bipolar OR schizophrenia OR psychotic OR psychosis OR psychoses)) AND title:((docosahexaenoic OR eicosapentaenoic OR "fish oil" OR magnesium OR microbiome OR N-acetyl cysteine OR N-acetylcysteine OR nutraceutical OR nutrient OR nutrition OR omega-3 OR phytoceutical OR prebiotic OR probiotic OR psychobiotic OR selenium OR supplement OR vitamin OR zinc)) (88)

ClinicalTrials.gov

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the US?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	More than 50% of people will be diagnosed with a mental illness or disorder in their life, and 1 in 25 Americans experience serious mental illness, such as schizophrenia, bipolar disorder, or major depression.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. About $280 billion was spent on mental health services in 2020.[8]
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. About $280 billion was spent on mental health services in 2020.[8]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	An existing meta-review from 2019[5] addresses the primary and adjunctive treatment of the majority of mental health conditions of interest, thus addressing the majority of the scope, but does not include substance abuse disorders.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Guidelines for treating mental health disorders with adjunctive supplements do not exist.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	The FDA does not regulate supplements in the same was as pharmaceuticals. Clinicians may be wary of prescribing treatments that lack authoritative regulation.[3]
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: We found one study in opioid use disorder [7] and one study in alcohol use disorder [6] and each study used different supplement types. A new systematic review would be limited.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; FDA=Federal Drug Administration; US=United States.