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ORIGINAL INVESTIGATION

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Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce

Jerome Sarris[a,b,c], Arun Ravindran[d], Lakshmi N. Yatham[e], Wolfgang Marx[f], Julia J. Rucklidge[g], Roger S. McIntyre[h], Shahin Akhondzadeh[i], Francesco Benedetti[j,k], Constanza Caneo[l], Holger Cramer[m], Lachlan Cribb[b], Michael de Manincor[a], Olivia Dean[f,n], Andrea Camaz Deslandes[o], Marlene P. Freeman[p], Bangalore Gangadhar[q], Brian H. Harvey[r], Siegfried Kasper[s], James Lake[a,t], Adrian Lopresti[u], Lin Lu[v], Najwa-Joelle Metri[a], David Mischoulon[w], Chee H. Ng[b], Daisuke Nishi[x,1], Roja Rahimi[y], Soraya Seedat[z], Justin Sinclair[a], Kuan-Pin Su[aa,ab], Zhang-Jin Zhang[ac,ad] and Michael Berk[c,f,ae]

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ABSTRACT

Objectives: The therapeutic use of nutrient-based 'nutraceuticals' and plant-based 'phytoceuticals' for the treatment of mental disorders is common; however, despite recent research progress, there have not been any updated global clinical guidelines since 2015. To address this, the World Federation of Societies of Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Disorders (CANMAT) convened an international taskforce involving 31 leading academics and clinicians from 15 countries, between 2019 and 2021. These guidelines are aimed at providing a definitive evidence-informed approach to assist clinicians in making decisions around the use of such agents for major psychiatric disorders. We also provide detail on safety and tolerability, and clinical advice regarding prescription (e.g. indications, dosage), in addition to consideration for use in specialised populations.

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Nutrients; herbal medicines; schizophrenia; ADHD; affective disorders

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Methods: The methodology was based on the WFSBP guidelines development process. Evidence was assessed based on the WFSBP grading of evidence (and was modified to focus on Grade A level evidence – meta-analysis or two or more RCTs – due to the breadth of data available across all nutraceuticals and phytoceuticals across major psychiatric disorders). The taskforce assessed both the 'level of evidence' (LoE) (i.e. meta-analyses or RCTs) and the assessment of the direction of the evidence, to determine whether the intervention was 'Recommended' (+++), 'Provisionally Recommended' (++), 'Weakly Recommended' (+), 'Not Currently Recommended' (+/−), or 'Not Recommended' (−) for a particular condition. Due to the number of clinical trials now available in the field, we firstly examined the data from our two meta-reviews of meta-analyses (nutraceuticals conducted in 2019, and phytoceuticals in 2020). We then performed a search of additional relevant RCTs and reported on both these data as the primary drivers supporting our clinical recommendations. Lower levels of evidence, including isolated RCTs, open label studies, case studies, preclinical research, and interventions with only traditional or anecdotal use, were not assessed.
Results: Amongst nutraceuticals with Grade A evidence, positive directionality and varying levels of support (*recommended, provisionally recommended,* or *weakly recommended)* was found for adjunctive omega-3 fatty acids (+++), vitamin D (+), adjunctive probiotics (++), adjunctive zinc (++), methylfolate (+), and adjunctive s-adenosyl methionine (SAMe) (+) in the treatment of unipolar depression. Monotherapy omega-3 (+/−), folic acid (−), vitamin C (−), tryptophan (+/−), creatine (+/−), inositol (−), magnesium (−), and n-acetyl cysteine (NAC) (+/−) and SAMe (+/−) were not supported for this use. In bipolar disorder, omega-3 had weak support for bipolar depression (+), while NAC was not currently recommended (+/−). NAC was weakly recommended (+) in the treatment of OCD-related disorders; however, no other nutraceutical had sufficient evidence in any anxiety-related disorder. Vitamin D (+), NAC (++), methylfolate (++) were recommended to varying degrees in the treatment of the negative symptoms in schizophrenia, while omega-3 fatty acids were not, although evidence suggests a role for prevention of transition to psychosis in high-risk youth, with potential pre-existing fatty acid deficiency. Micronutrients (+) and vitamin D (+) were weakly supported in the treatment of ADHD, while omega-3 (+/−) and omega-9 fatty acids (−), acetyl L carnitine (−), and zinc (+/−) were not supported. Phytoceuticals with supporting Grade A evidence and positive directionality included St John's wort (+++), saffron (++), curcumin (++), and lavender (+) in the treatment of unipolar depression, while rhodiola use was not supported for use in mood disorders. Ashwagandha (++), galphimia (+), and lavender (++) were modestly supported in the treatment of anxiety disorders, while kava (−) and chamomile (+/−) were not recommended for generalised anxiety disorder. Ginkgo was weakly supported in the adjunctive treatment of negative symptoms of schizophrenia (+), but not supported in the treatment of ADHD (+/−). With respect to safety and tolerability, all interventions were deemed to have varying acceptable levels of safety and tolerability for low-risk over-the-counter use in most circumstances. Quality and standardisation of phytoceuticals was also raised by the taskforce as a key limiting issue for firmer confidence in these agents. Finally, the taskforce noted that such use of nutraceuticals or phytoceuticals be primarily recommended (where supportive evidence exists) adjunctively within a standard medical/health professional care model, especially in cases of more severe mental illness. Some meta-analyses reviewed contained data from heterogenous studies involving poor methodology. Isolated RCTs and other data such as open label or case series were not included, and it is recognised that an absence of data does not imply lack of efficacy.
Conclusions: Based on the current data and clinician input, a range of nutraceuticals and phytoceuticals were given either a supportive recommendation or a provisional recommendation across a range of various psychiatric disorders. However several had only a weak endorsement for potential use; for a few it was not possible to reach a clear recommendation direction, largely due to mixed study findings; while some other agents showed no obvious therapeutic benefit and were clearly not recommended for use. It is the intention of these guidelines to inform psychiatric/medical, and health professional practice globally.

Introduction

These joint World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines were first conceptualised in 2019 and further developed in 2020 and 2021 by an expert taskforce committee convened for the area of 'Integrative and Complementary Medicine'. The primary purpose was to formulate up to date evidence-informed and clinically relevant guidelines to direct the appropriate prescription of nutrient-based 'nutraceuticals' or plant-based 'phytoceuticals' as monotherapy or adjunctive therapy for the treatment of a range of psychiatric disorders. This work extends from the CANMAT 2009 and 2016 guidelines by Ravindran et al. (2009, 2016).

This therapeutic approach broadly fits under the umbrella of Traditional, Complementary, and

Integrative Medicine (TCIM) as defined by the World Health Organisation (2020). The specific therapeutic application of natural products which are produced via pharmaceutical good manufacturing practice (GMP), standardised and optimised, and in some cases purified (e.g. curcumin) or slightly modified (e.g. n-acetyl cysteine) can be further broken into the terms 'nutraceuticals' (Sarris et al. 2016) and 'phytoceuticals' (Grandhi et al. 2007). Below is a list of the common nomenclature within the broader field:

- *Integrative Medicine:* Overarching field which seeks to combine approaches of both modern medical interventions (e.g. pharmaceuticals, surgery, allied health therapies, scientific diagnostics) with traditional medical systems and evidence-informed complementary interventions (e.g. nutrient or plant-based medicines, lifestyle medicine, mind-body techniques such as acupuncture, yoga, tai chi, or meditation
- *Complementary Medicine:* May refer to natural supplements as a broad category or the entire field (1) Biologically based systems e.g. phytoceuticals, nutraceuticals or dietary modification; (2) Manipulative and body-based systems e.g. massage or acupuncture; (3) Mind-body-medicine e.g. yoga or tai chi; (4) Traditional medical systems e.g. naturopathy or traditional Chinese medicine; (5) Energy therapy e.g. Reiki or qi gong. If non-mainstream practice is used together with conventional medicine, it can be considered as 'Complementary' medicine.
- *Alternative Medicine:* If a non-mainstream practice is used in place of conventional medicine, it can be considered as 'Alternative' medicine.
- *Nutraceutical:* Nutrient-based natural products which are produced via pharmaceutical GMP, standardised and optimised
- *Phytoceutical:* Plant-based natural products which are produced via pharmaceutical GMP, standardised and optimised

The WFSBP Taskforce solicited the academic and clinical input from 31 members from 15 countries. The team had a range of qualifications and skills, including psychiatrists, psychologists, natural product psychopharmacologists, epidemiologists, integrative medicine practitioners, nutritionists, preclinical scientists, pharmacists, and statisticians. The committee was set up with consideration of providing a mix of ages, ethnicity, gender, experience, geographic and socioeconomic background.

Due to the growth in the number of RCTs and meta-analyses, it was the consensus of the taskforce that there are now sufficient data to conduct an updated clinical guideline document to focus specifically on the two dominant aspects of TCIM biological interventions—i.e. the use of nutraceuticals and phytoceuticals. In preparation for the guidelines, we undertook two meta-reviews of the literature—one on nutraceuticals (Firth et al. 2019), and the other on phytoceuticals (Sarris, Marx et al. 2020). An updated search of meta-analyses was performed from May to September 2020, in addition to searching for more recent RCTs not covered in the meta-analyses. We adopted an evidence-grading approach based on the WFSBP grading system guidelines *cf.* (Hasan et al. 2019). The WFSBP evidence searching and grading system comprises of categories of evidence from levels A to F. However due to breadth of data in the field, we only examined evidence with Grade A (strong level of evidence), omitting inclusion of studies with weak or limited evidence (e.g. case studies, open label studies, isolated RCTs).

These WFSBP and CANMAT guidelines were aimed at providing a definitive evidence-informed approach to assist in greater clinical clarity around the use of nutraceuticals and phytoceuticals across major psychiatric disorders where evidence was available. We also provide discussion of safety and tolerability issues, in addition to clinical advice around prescription considerations for specific clinical indications.

Scope of this review

As mentioned above, the primary focus of this review was to provide an update to the CANMAT 2009 and 2016 guidelines on nutraceutical and phytoceutical therapies for use in psychiatric disorders. These previous reviews summarised a broad range of complementary medicines and therapies. The key difference with this present guideline is that we focussed solely on nutraceuticals and phytoceuticals, including no other complementary medicine modalities; further, we based our assessment of the data on the recent WFSBP guidance on clinical guidelines development (Hasan et al. 2019). This allowed for the assessment of both 'level of evidence' (LoE) (i.e. meta-analyses or RCTs), and in addition it provided scope for the assessment of the 'direction of the evidence' in respect to being either positive, neutral, or negative for each intervention for a particular mental health condition (covered in more detail below). This contrasts with previous guidelines in the area, which solely graded the level of evidence (and did not assign directionality

and subsequent clinical advice based on this determination). Finally, aside from assessing the level of evidence and directionality of the data, we also performed a literature search to assess the safety, tolerability, cost, and practicability of the interventions. This was also based on the WFBSP clinical guideline development paper (Hasan et al. 2019) which graded acceptability of an intervention with regard to considerations involving risk-benefit ratio, cost-benefit ratio, applicability/practicability (of prescribing the intervention), and ethical and legal aspects. Suggested dosage was based on a combination of the clinical trial data (including general evidence-based recommendations from a key text in the field) (Braun and Cohen 2015), regulatory guidelines and toxicology data, and clinician input as to real-world practice.

This WFSBP guideline provides clinicians with:

- An overview of the current breadth of data across the field
- A specific WFSBP grade of evidence assessing the quality of the data
- Reporting on the relative strength (or weakness) of evidence of the treatments
- A summary on the safety, cost (where an issue), and product quality considerations
- Clinical considerations and therapeutic recommendations when possible (e.g., for use in specific populations or clinical presentations).

Guideline aim

The aim of the guidelines was to provide a clear summary of top-tier clinical trial data and resultant prescriptive recommendations for clinicians and health professionals, health managers and policymakers pertaining to nutraceuticals and phytoceuticals use in adults across major psychiatric disorders (and for use in children with attention-deficit hyperactivity disorder [ADHD]).

Methods

Clinical questions defined

1. Are there any nutraceuticals or phytoceuticals with sufficient Grade A level evidence which can be recommended for therapeutic application as monotherapies or adjunctive interventions for any psychiatric disorders?
2. What clinical conclusions can we reach from the data and what recommendations can be provided to clinicians for therapeutic indications, dosage, safety, and tolerability considerations?

Guideline procedure

The WFSBP Taskforce was initially convened in 2019 (established between 2019 and 2021), aiming to build a team of academics and clinicians with expertise within psychiatry and TCIM fields. In order to provide balanced and globally-focussed guidelines, we engaged colleagues from 15 different countries (across the Asia-Pacific, North and South America, Europe, UK and Africa), with a mix of language/cultures, socioeconomic levels, and career levels. A balance between genders was also sought, though the finalised taskforce had a greater proportion of males.

Initial online taskforce discussions were undertaken to decide on the breadth/focus of the guidelines. It was decided via consensus to focus on biological interventions and to separate out mind-body interventions (e.g. yoga, meditation) and complementary therapies (e.g. acupuncture). This was due to the focus of the WFBSP being primarily on 'biological' interventions, and further due to the vast amount of literature available across the entire integrative medicine field (a such an approach would be logistically prohibitive). It was also decided to base the guidelines on a set of initial meta-reviews conducted by working groups of some of the taskforce members (Firth et al. 2019; Sarris, Marx et al. 2020), supplemented with a current additional literature search.

For the additional literature search (post-meta reviews), a draft of the search terms list of over 50 nutraceuticals and phytoceuticals (based on the previous meta-reviews) was initially provided to the taskforce. This was subsequently reviewed and amended before a full search was undertaken of the literature (during May to September 2020–detailed later). The intent was to locate any data not revealed by the initial meta-reviews and also to update results where newer additional data presented. Initially the review was conducted by JS, WM, LC, NM, with cross-checking by MB, AR, and LY where additional opinion was required to determine inclusion/exclusion of data. For further details of the methods underpinning the original meta-reviews please consult those papers *cf.* (Firth et al. 2019; Sarris, Marx et al. 2020).

The draft results were then provided to the taskforce core steering group (JS, MB, AR, LY, WM, JR, RJM) for review and editing before circulation to the wider group for discussion and modification. Two Zoom meetings took place at that point (to allow for time zone differences) with the process for voting and endorsing intervention recommendations discussed. It was decided that an online survey (Qualtrics) would be adopted and provided to the taskforce members

soliciting voting on endorsing or not endorsing each evidence grading and evidence statement for individual interventions. A level of 80% or more was considered the threshold for acceptance. Further, narrative feedback for each intervention (asking for a one or two sentence response for each) was solicited to receive information on how the evidence statement could be improved, and if not endorsing the current statement, what changes were advised so endorsement could occur.

The process consisted of three online voting rounds (with amendments to the grading and statements occurring between rounds) for the level of >80% consensus that was reached, and with the resultant grading and statements officially endorsed.

After full endorsements of the grading and evidence statements, the taskforce core-steering group synthesised the recommendations before preparing the manuscript and sending for a final review by the full taskforce membership. Finally, the draft manuscript was sent to CANMAT for external review, and endorsement was provided in May 2021.

Methodology summary

As per Table 1, the key tenets on which our practice guideline recommendations are based on involve: (1) the level of evidence and grading for each intervention; and (2) the acceptability of the intervention whereby we considered clinical factors such as safety and tolerability, cost, and availability and practical application of the intervention (Hasan et al. 2019). Grading ratings were based on both a critique of current Grade A evidence and any relevant clinical experience of taskforce members. Study eligibility was based on the PICO reporting structure (patient/population, intervention, comparison, outcome).

The grading system and LoE criteria that were adopted included three key elements:

- Type of evidence: Grades A (*Strong*) was included (meta-analyses OR 2 or more RCTs). We omitted Grade B (*Limited*), Grade C (*Low*), and Grade D (*No Evidence*) due to the breadth of research spanning all nutraceuticals and phytoceuticals for every mental health application.
- Evidence direction: +++ (Recommended), ++ (Provisionally Recommended*), + (Weakly Recommended), +/− (Not Currently Recommened [based on present mixed or undetermined evidence]), − (Not Recommended); see Table 1. The evidence grade was in part also assessed via giving greater weight to 'multi-jurisdictional' research involving more than one country or research group.
- An assessment of safety and tolerability: Ordered in descending strength, as either: *Robust, Acceptable, Fair,* or *Poor* (no intervention was found to be classed as having a *Poor* level). This grading was provided in addition to a narrative recommendation around any main safety or tolerability considerations. The ultimate decision for the safety and tolerability gradings were based on taskforce consensus guided by evidence from clinical trials, regulatory bodies, and pharmacovigilance databases.

**A Provisional Recommendation was classed as a tentatively supportive endorsement for use based off positive underlying data; however, either concerns over small sample sizes, non-multi-jurisdictional research, or potential issues with nutraceuticals/phytoceutical standardisation and/or quality, restricted a current endorsement of a clear 'Recommendation' for use.*

From these elements, individual guideline statements were provided, in addition to narrative summary points for potential applications and clinical considerations. This was also summarised in evidence summary tables (grouped via mental disorder).

Methodology underpinning the review of the evidence

As detailed above, the guidelines were primarily based on two meta-reviews (Firth et al. 2019; Sarris, Marx

Table 1. Adapted from the WFSBP Grading system (grades of recommendations).

Recommendation *FOR* or AGAINST using the intervention	Grade	Level of Evidence (LoE)
Recommended	+++	'A' LoE with robust positive data meta-analyses or meta-reviews involving underpinning RCTs, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Provisionally Recommended	++	'A' LoE with mainly positive data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average quality, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Weakly Recommended	+	'A' LoE mixture of (primarily) positive and negative data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average underpinning quality, tending towards positive findings, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Not Currently Recommended	+/−	'A' LoE mixture of positive and negative data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average or weak underpinning quality, with ROBUST, ACCEPTABLE, or FAIR tolerability
Not Recommended	−	'A' LoE with robust negative data from meta-analyses or meta-reviews or ≥2 RCTs and/or POOR safety/tolerability

Table 2. Guidelines Search Terms.

Participants (any mental disorder)
Depression OR depressive OR mental illness* OR mental disorder* OR mood disorder* OR affective disorder* OR anxiety OR panic disorder OR obsessive compulsive OR ADHD OR attention deficit OR attentional deficit OR phobia OR bipolar type OR bipolar disorder* OR psychosis OR psychotic OR schizophr* OR antipsychotic* OR post traumatic* OR personality disorder* OR stress disorder* OR dissociative disorder*
Interventions (any nutrient or nutraceutical)
Vitamin* OR mineral* OR nutrient* OR food supplement* OR meal replacement* OR nutritional supplement* OR health supplement* OR multivitamin* OR omega 3 OR fish oil* OR alpha lipoic acid OR alpha linolenic acid OR alpha linoleic acid OR eicosapentaenoic OR docosahexaenoic OR fatty acid* OR amino acid* OR taurine OR S-adenosyl methionine OR creatine OR acetylcysteine OR cysteine OR probiotic* OR tryptophan OR tocopherol OR alphatocopherol OR carotene OR retinol OR thiamine OR riboflavin OR niacin OR niacinamide OR nicotinic acid OR pantothenic OR pyridox* OR biotin OR methylfolate OR 5-MTH* OR levomefolic acid OR folate OR folinic acid OR folic acid OR inositol OR cyanocobalamin OR methylcobalamin OR cobalamin OR ascorbic acid OR cholecalciferol OR iron OR ferrous OR tocopherols OR trace element OR calcium OR phosphorus OR magnesium OR potassium OR manganese OR zinc OR selenium OR boron OR chromium OR lycopene OR isoflav* OR flavonoid* OR bioflavonoid* OR micronutrient OR carnitine OR herbal OR herbal medicine OR plant medicine OR phytomedicine OR supplement OR st John's wort OR kava OR ginseng OR saffron OR curcumin OR valerian OR ginkgo OR rhodiola OR *Bacopa monniera* OR *Centella asiatica* OR *Crocus sativus* OR *Curcuma longa* OR *Hypericum perforatum* OR *Galphimia* OR *Ginkgo biloba* OR *Lavandula* OR *Matricaria spp.* OR *Panax ginseng* OR *Passiflora incarnata* OR *Piper methysticum* OR *Rhodiola rosea* OR *Valeriana* OR *Withania somnifera*
Comparator (placebo-controlled trials)
Random* OR Placebo OR Control* or Adjunc* or Clinical Trial*
Outcomes (any from meta-analyses or randomised controlled trials or systematic reviews)
Meta-analy* OR Metaanaly* OR Clinical Trial OR RCT* OR systematic review

et al. 2020); supplemented with an additional systematic literature search for RCTs. The search strategies and data syntheses for the meta-reviews were conducted in line with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al. 2009). We adopted the assessment of multiple systematic reviews (AMSTAR) study quality rating system to provide an assessment of the quality of the meta-analyses reviewed in our published meta-reviews (Shea et al. 2007).

The full list of nutraceuticals and phytoceuticals search terms are presented in Table 2. For English language studies, initial systematic searches were conducted using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), PsycINFO and Ovid MEDLINE(R); in 2019 for nutraceuticals and in 2020 for phytoceuticals. The additional search for interventions not covered or included in the meta-reviews, occurred across May to September 2020. If the taskforce was aware of newer meta-analyses in late 2020, these were reviewed to determine whether to be added or replacing previous versions. An additional English language database, EMBASE, was also searched during this period. During this time other non-English language (Japanese, German, Chinese, Spanish, Portuguese, and African languages) databases were searched for additional meta-analyses or RCTs: Epistemonikos, Scielo, Lilacs, ICHUSHI, CAMBase, CAMQuest, PubPsych, Africa-Wide Information, Sabinet, and Nexus.

Eligibility criteria

Eligibility criteria were organised in accordance with the PICO reporting structure, as described below.

Participants

We included studies of individuals with common and severe mental disorders: depressive disorders (e.g. major depressive disorder [MDD] and bipolar disorder); anxiety disorders (e.g. generalised anxiety disorder [GAD]; schizophrenia; ADHD (including studies on either a child/adolescent or adult population, due to the nature of the disorder). Studies examining neurodegenerative disorders (e.g. dementia) or neurodevelopmental disorders (e.g. autism, intellectual disability), and sleep disorders, were not included. Note that obsessive compulsive disorder and trichotillomania were covered under 'anxiety disorders' for reading ease (though recognised these are not labelled so under DSM-5).

All studies of the above conditions were eligible provided that at least 75% of the sample had a confirmed mental illness or at-risk state, ascertained by either clinical diagnostic history or reaching established thresholds on validated screening measures.

Design, interventions and comparisons

All nutraceuticals and phytoceuticals were considered for inclusion, were used either as used either as adjunctive treatment or monotherapy (with such application being differentially advised within the context of both the existing evidence and the nature of the mental disorder). In the case of phytoceuticals, these could be either whole plant-medicines or isolated constituents (omitting cannabinoids and traditional Chinese medicine formulations as these were considered as complex and specialised areas beyond the remit of this taskforce). Comparisons needed to be an adequate placebo-controlled intervention or an established 'positive' biological control (e.g. an antidepressant in MDD). Only studies involving 'chronic' interventional time periods of $\geq$2 weeks were included (i.e. excluding acute dose studies). Individual RCTs with less than 10 participants per arm were excluded

to minimise Type I error. No restrictions were placed on the dosage or standardisation of the interventions (due to recognised variability in formulations).

Outcomes

All data on physical and/or mental health outcomes (including changes in clinical measures, response rates) from meta-analyses of RCTs or interventions with two or more RCTs examining any eligible disorder were included in our review of the data. A meta-analysis was classified as eligible if: (a) it had clearly stated inclusion, intervention and comparison criteria aligned with the participant, intervention and comparison criteria listed above; (b) it reported a systematic search with a screening procedure; (c) it had used systematic data extraction and reported pooled continuous or categorical outcome data from more than one study.

Where overlapping meta-analyses of a given intervention for a specific outcome/disorder existed, the most recently updated meta-analysis was used if it captured more than 75% of the trials in the earlier version. Where older meta-analyses presented unique findings, through inclusion of a greater number of studies or use of particular subgroup analyses, these data were also included in our review of the evidence.

Data extraction and analysis

In line with conventional interpretations, statistical significance was set at a p value of <0.05, while standardised mean differences (which additionally informed our guideline statements) were classified as negligible (<0.2), small (0.2–0.4), moderate (0.4–0.8), or large (>0.8). In cases where meta-analyses had provided effect sizes corrected for publication bias, these were reported in our original meta-reviews alongside the main effects observed and interpreted as the primary findings from the analysis.

For the primary outcome analyses summarised in the evidence statements, we extracted the number of participants (n), along with the number of trials/comparisons (k) from which the result (or pooled effect size in meta-analyses) was derived. Where reported, all relevant study characteristics were provided, detailing type of formulation, standardisation, and dose). Phytoceutical dosage recommendations are based on either raw dried material or specific extracts being standardised to key therapeutic constituents. The potential impact of publication bias was assessed in the underpinning meta-reviews wherever there were sufficient data for appropriate analyses.

Results

Guideline statements

Table 3 provides a summary of the interventions with Level A evidence (meta-analysis or 2 or more RCTs) identified in these guidelines. In summary, 15 nutraceuticals and 10 phytoceuticals had sufficient Level A evidence for inclusion in the guidelines. Further, individual findings are presented in Tables 4–7.

Nutraceuticals for mood disorders (major depressive disorder/bipolar depression) (Table 4)

Omega 3-fatty acids

> **Statement:** Omega-3 fatty acids at doses standardised to 1 g to 2 g of eicosapentaenoic acid (EPA) are *Recommended* for *Adjunctive* use in MDD; and *Not Currently Recommended* for *Monotherapy* use [although it may be still effective as a monotherapy in people with raised inflammation and/or obesity]

Evidence grade: A (a statistically significant meta-analysis and 5 RCTs; $k = 18$, $n = 1619$)
Strength of recommendation: Adjunctive: Recommended (+++), Monotherapy: Not Currently Recommended (±)

Clinical guideline statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD; while use as a monotherapy is weaker

Table 3. Intervention type, and mental disorders covered

Intervention type	Mental health disorder	Intervention
Nutraceuticals	Mood disorders	Omega-3 fatty acids (in particular eicosapentaenoic acid: EPA), vitamin D, N-acetyl cysteine, probiotics, zinc, folate-based compounds, S-adenosyl-methionine, vitamin C, tryptophan and 5-HTP, creatine, inositol, and magnesium
	Anxiety disorders	N-acetyl cysteine
	Psychotic disorders	Omega-3 fatty acids, vitamin D, N-acetyl cysteine, and folate-based compounds
	ADHD	Vitamin D, zinc, folate-based compounds, omega-3 and omega-9 fatty acids, broad-spectrum micronutrients, and acetyl-L-carnitine
Phytoceuticals	Mood disorders	St John's wort, saffron, curcumin, rhodiola, and lavender
	Anxiety disorders	Lavender, kava, ashwagandha, galphimia, and chamomile
	Psychotic disorders	Ginkgo
	ADHD	Ginkgo

Table 4. Depression (Unipolar and Bipolar).

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested dosage per day	Tolerability/ safety	Clinical advice	References
Omega-3	MDD (Adj)	A (Meta + 5 RCTs)	+++	1 g–2 g of EPA or mixed EPA/DHA	*ROBUST*	Potentially more effective adjunctively with antidepressants, and in raised inflammatory markers and/or obesity	MDD: (Mocking et al. 2016; Gabbay et al. 2018; Carney et al. 2019; Fristad et al. 2019; Chang et al. 2020; Jana et al. 2020)
	(Mono)		+/−		Caution with blood-thinning medication; Potential GI upset		
	BD (Adj)	A (Meta + 3 RCTs)	+				BD: (Murphy et al. 2012; Sarris, Mischoulon, et al. 2011; Wozniak et al. 2015; Shakeri et al. 2016)
Vitamin D	MDD (Adj/Mono)	A (Meta + 2 RCTs)	+	1500 IU–4000 IU	*ROBUST* Considered safe	Unlikely to be of benefit in those with sufficient skin exposure to sufficient non-winter sunlight and/or dietary intake	(Alghamdi et al. 2020; Cheng et al. 2020; Vellekkatt et al. 2020)
Probiotics	MDD (Adj/Mono)	A (Meta)	++	1–10 billion colony forming units (varying strains)	*ROBUST* Considered safe	The most appropriate probiotics strains for depression have not been confirmed, certain and variations are potentially more beneficial depending on an individual's genetics and diet	(Sanada et al. 2020)
Zinc	MDD (Adj)	A (Meta)	++	∼25 mg elemental	*ACCEPTABLE* Considered safe below 40mg per day, although nausea may occur on an empty stomach	May have a specialised use in cases of comorbid lowered immune response or raised inflammation, or high oxidative stress (especially if dietary deficient)	(Schefft et al. 2017)
Folate-based compounds	MDD (Adj)	A (Meta)		Methylfolate (15 mg)	*FAIR*	Methylfolate potentially more effective due to the metabolic bypass of the T677C polymorphism	(Bedson et al. 2014; Roberts et al. 2018)
	Folic acid		−		Fairly safe, however larger doses of synthetic folic acid have been linked to very slight increase of some cancers		
	MTHF/acid		++				
S-adenosyl methionine	MDD (Mono)	A (5 RCTs)	+/−	800 mg–3200 mg	*ACCEPTABLE* A safe compound, however, caution is advised in bipolar disorder	SAMe is an unstable compound and enteric coating and storage in blister packs under refrigeration may be advised	(Pancheri et al. 2002; George I. Papakostas et al. 2010; Mischoulon et al. 2014; Sarris et al. 2018; Sarris, Murphy, et al. 2020)
	(Adjunctive)		+				
Vitamin C	MDD (Adj)	A (2 RCTs)	+/−	∼1 g	*ROBUST* Considered safe, however excess doses may cause gastrointestinal disturbance (e.g. diarrhea)	While evidence is not supportive, there may be a potential role in cases of Vit C deficiency or comorbid immune system deficiency	(Amr et al. 2013; Sahraian et al. 2015)
Tryptophan & 5-HTP	MDD (Adj/Mono)	A (Meta +1 RCT)	+/−	∼1 g (tryptophan), 50 mg–200 mg (5-HTP)	*ACCEPTABLE* Caution is advised in co-use with antidepressants	Older research showing mixed efficacy. 5-HTP a preferred form as a precursor of serotonin. May be of benefit in the evening for comorbid insomnia	(Levitan et al. 2000; Shaw et al. 2002)
Creatine	MDD (Adj/Mono)	A (2 RCTs)	+/−	5 g	*FAIR* Caution in excess doses	May have a role in people with MDD and comorbid fatigue	(Lyoo et al. 2012, Nemets and Levine 2013)

(*continued*)

Table 4. Continued.

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested dosage per day	Tolerability/ safety	Clinical advice	References
					and in people with kidney issues		
Inositol	MDD (Adj)	A (Meta)	−	~12 g	*ACCEPTABLE* Considered safe, however may cause gastrointestinal discomfort at high doses	Not effective for use in MDD	(Mukai et al. 2014)
Magnesium	MDD (Adj)	A (2 RCTs)	−	100–400 mg elemental	*ROBUST* Considered safe	While evidence is not supportive for use in MDD, there may still be an application in deficiency	(Mehdi, Atlas et al. 2017; Ryszewska-Pokraśniewicz et al. 2018)
N-acetyl cysteine	BD (Adj)	A (4 RCTs)	+/−	1g–3 g	*ACCEPTABLE* Considered safe	May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress	(Berk et al. 2008, 2012; Bauer et al. 2017; Ellegaard et al. 2019)

Phytoceutical	Indications	Level of evidence	Grade (+ or −)	Suggested Dosage per Day	Safety	Clinical Advice	References
St John's wort	Mono	A (Meta)	+++	600 mg–1800 mg (standardised to hypericin 0.2–0.3% AND/ OR 5–6% hyperforin)	*ACCEPTABLE* Caution for use in Bipolar Disorder. May cause photosensitivity. Do not use with SSRIs or SNRIs due to potential of serotonin syndrome. Hyperforin-rich extracts may reduce serum levels of many drugs	Use of quality standardised extracts is vital to be confident of replicated effects shown in RCTs	(Apaydin et al. 2016)
Saffron	MDD (Adj/Mono)	A (Meta)	++	30 mg per day of stigma (standardised to safranal or crocin isomers)	*ACCEPTABLE* Considered safe, aside from potential minor adverse effects e.g. gastrointestinal symptoms, increased stimulation	Stigma/petal combinations may still provide antidepressant effects (and be much cheaper than stigma alone)	(Marx et al. 2019)
Curcumin	MDD (Adj/Mono)	A (Meta)	++	500 mg–1000 mg (curcumin)	*ACCEPTABLE* Considered safe	Potential adjuvant benefit in comorbid inflammatory disorders. Bioavailable forms are advised e.g. liposomal	(Fusar-Poli et al. 2020)
Rhodiola	MDD (Adj/Mono)	A (2 RCTs)	+/−	340–680 mg (standardised to rosvarin)	*ACCEPTABLE* Considered safe	Potential role in depression co-occurring with fatigue	(Darbinyan et al. 2007; Mao et al. 2015)
Lavender	MDD (Adj/Mono)	A (3 RCTs)	++	80 mg–160 mg per day of a specialised oil (in capsule form) or 500 mg–1.5 g of dried flower (standardised to linalool)	*ACCEPTABLE* Considered safe	Use of standardised capsule formulations advised over tea preparations of unknown quality	(Akhondzadeh et al. 2003; Nikfarjam et al. 2013, 2017)

*= Recommendation level; Grades= +++, ++, +, ± −Adj: Adjunctive; Mono: Monotherapy; MDD: Major Depressive Disorder; BD: Bipolar Disorder; Meta: Meta-analysis level data; RCTs: two or more randomised controlled trials; *ROBUST, ACCEPTABLE, POOR*: level of safety and tolerability as assessed via available clinical trial data, regulatory agencies, and pharmacovigilance databases.

Table 5. Anxiety disorders.

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested dosage per day	Tolerability/ safety	Clinical advice	References
N-acetyl cysteine	OCD (Adj/Mono)	A (Meta)	+	2 g–3 g	*ACCEPTABLE* Considered safe	May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress	OCD: (Gadallah et al. 2020; Li et al. 2020)
	Trichotillomania	A (RCTs)	+/−	2 g–3 g			Trichotillomania: (Grant et al. 2009; Bloch et al. 2013)

Phytoceutical	Indications	Level of Evidence	Grade (+ or −)	Suggested Dosage per Day○	Tolerability/ Safety	Clinical Advice	References
Kava	GAD (Mono)	A (Meta + 2 RCTs)	−	60mg-250mg of kavalactones	*FAIR* Caution for use in people with liver issues, and avoidance with alcohol and benzodiazepines	While not effective for GAD, potential use for acute or short-term management of general anxiety symptoms supported Important to recommend only the use of 'noble' varieties of the rootstock of the plant standardised to a sufficient level of kavalactones	(Barić et al. 2018; Kuchta et al. 2018; Sarris, Byrne, et al. 2020)
Ashwagandha	GAD (Adj/Mono)	A (3 RCTs)	++	300 mg–600 mg (standardised to 5% withanolides)	*ACCEPTABLE* Considered safe	May be of additional benefit in improving cognition in BD	(Andrade et al. 2000; Sud Khyati and Anup 2013; Fuladi et al. 2020)
Galphimia	GAD (Mono)	A (2 RCTs)	+	350 mg–700 mg (standardised to galphimine-B)	*FAIR* Considered safe	Not commonly used outside South America, sourcing could be an issue	(Herrera-Arellano et al. 2007, 2012)
Chamomile	GAD (Adj/Mono)	A (2 RCTs)	+/−	220 mg–1500 mg (potentially standardised to chrysin or apigenin)	*ROBUST* Robust safety data	Standardised extracts preferable to teas of unknown quality	(Amsterdam et al. 2009; Mao et al. 2016)
Lavender	GAD (Adj/Mono)	A (3 RCTs)	++	80 mg–160 mg per day of a specialised oil (in capsule form) or 500 mg–1.5 g of dried flower (standardised to linalool)	*ACCEPTABLE* Considered safe	Highly standardised essential oil based extracts potentially more effective than general dried raw material	(Kasper et al. 2014, 2015; Farshbaf-Khalili et al. 2018)

*= Recommendation level; Grades= **+++, ++, +, ± −** ; Adj: Adjunctive; Mono: Monotherapy; GAD: Generalised Anxiety Disorder; Meta: Meta-analysis level data; RCTs: two or more randomised controlled trials; *ROBUST, ACCEPTABLE, POOR*: level of safety and tolerability as assessed via available clinical trial data, regulatory agencies, and pharmacovigilance databases.

Table 6. Schizophrenia.

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested Dosage per Day	Tolerability/ Safety	Clinical Advice	References
Omega-3	Schz (Adj)	A (Meta) + 1 RCT	−	1 g–2 g of EPA or mixed EPA/DHA	*ROBUST* Caution with blood-thinning medication; Potential GI upset	Potentially more effective in raised inflammatory markers and in obesity (especially metabolic issues from antipsychotics)	(Çakici et al. 2019; Qiao et al. 2020)
Vitamin D	Schz (Adj)	A 2 RCTs	−	1500 IU–4000 IU	*ROBUST* Considered safe	Unlikely to be of benefit in those with sufficient skin exposure to sufficient non-winter sunlight and/or dietary intake	(Sheikhmoonesi et al. 2016; Krivoy et al. 2017)
N-acetyl cysteine	Schz (Adj)	A (Meta)	++	1 g–3 g	*ACCEPTABLE* Considered safe	May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress	(Yolland et al. 2020)
Folate-based compounds	Schz (Adj)	A (Meta)	++	Methylfolate (1–15 mg)	*FAIR* Fairly safe, however larger doses of synthetic folic acid have been linked to very slight increase of some cancers	5-MTHF potentially more effective due to the metabolic bypass of the T677C polymorphism	(Sakuma et al. 2018)

Phytoceutical	Indications	Level of evidence	Grade (+ or −)	Suggested dosage per day	Safety	Clinical advice	References
Ginkgo	Schz (Adj)	A (Meta)	+	120 mg–360 mg (2–3% ginkgoflavones)	*ACCEPTABLE* Caution with blood-thinning medication	Potential role for negative symptoms, tardive dyskinesia, and for enhancing cognition in this population	(Chen et al. 2015)

*= Recommendation level; Grades= +++, ++, +, ± − ; Adj: Adjunctive; Mono: Monotherapy; Schz: Schizophrenia; Meta: Meta-analysis level data; RCTs: two or more randomised controlled trials; *ROBUST, ACCEPTABLE, POOR*: level of safety and tolerability as assessed via available clinical trial data, regulatory agencies, and pharmacovigilance databases

Table 7. ADHD treatment guidelines.

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested dosage per Day○	Tolerability/ safety	Clinical advice	References
Omega-3 Fatty acids	ADHD (Mono/Adj)	A (Meta + 4 new RCTs) Children	+/−	120 mg–1200 mg	*ROBUST* Robust safety data	May be of benefit in deficiency; higher EPA preparations potentially more effective	(Cornu et al. 2018; Crippa et al. 2019; Mohammadzadeh et al. 2019; Rodriguez et al. 2019; Chang et al. 2020)
Omega-9 Fatty Acids (Efamol)	ADHD (Mono/Adj)	A (2 RCTs) Children	−	2 g–3 g	*ROBUST* Robust safety data	Not recommended for ADHD. Sufficient omega-9s highly available in most diets	(Aman et al. 1987; Arnold et al. 1989)
Micronutrient formula	ADHD (Mono)	A (Meta involving 2 RCTs: 1 Adult 1 Child)	+	Micronutrient formula (8–12 capsules)	*ACCEPTABLE* Considered safe, has been studied used for decades	This particular micronutrient formula's efficacy cannot necessarily be extended to other multivitamins	(Rucklidge et al. 2014, 2018; Johnstone et al. 2020)
Vitamin D	ADHD (Mono/Adj)	A (Meta) Mixed	+	1500–4000 IU	*ROBUST* Robust safety data	Unlikely to be of benefit in those with sufficient skin exposure to sufficient non-winter sunlight and/or dietary intake	(Gan et al. 2019)
Acetyl-L-Carnitine	ADHD (Mono/Adj)	A (2 RCTs) Children	−	1 g–3 g	*ACCEPTABLE* Fair safety data	Not effective for ADHD	(Arnold et al. 2007; Abbasi et al. 2011)
Zinc	ADHD (Adj)	A (5 RCTs) Children	+/−	15 mg–40 mg (elemental)	*ACCEPTABLE* Considered safe below 40 mg per day (for adults), although nausea may occur on an empty stomach	May have a specialised use in cases of comorbid lowered immune response or raised inflammation, or high oxidative stress (especially if dietary deficient)	(Akhondzadeh et al. 2004; Bilici et al. 2004; Arnold et al. 2011; Zamora et al. 2011; Noorazar et al. 2020)

Phytoceutical	Indications	Level of Evidence	Grade (+ or −)	Suggested Dosage per Day○	Tolerability/ Safety	Clinical Advice	References
Ginkgo	ADHD (Mono/Adj)	A (2 RCTs) Children	+/−	80 mg–120 mg (2–3% of ginkgoflavones)	*ACCEPTABLE* Caution with blood-thinning medication	Mixed evidence for ADHD. May potentially improve some elements of impaired cognition	(Salehi et al. 2010; Shakibaei et al. 2015)

*= Recommendation level; Grades= +++, ++, +, ± − Adj: Adjunctive; Mono: Monotherapy; ADHD: Attention Hyperactivity Deficit Disorder ○=Per Day (based on age and weight for children); Meta:Meta-analysis level data; RCTs: two or more randomised controlled trials; *ROBUST, ACCEPTABLE, POOR*: level of safety or tolerability as assessed via available clinical trial data, regulatory agencies, and pharmacovigilance databases.

- A major monotherapy RCT was not supportive of efficacy (Mischoulon et al. 2015)
- Evidence supports preparations with higher/sufficient EPA (≥1 g per day and can be potentially used up to 4 g per day in people with raised inflammatory markers)
- Use may be more beneficial in people with raised inflammation, obesity, or in cases of dietary deficiency (Rapaport et al. 2016)
- Robust safety data. However, caution is advised for use with anticoagulants and at higher doses prior to surgery
- Quality can be an issue with omega-3 supplements, with some containing higher levels of oxidation. Product choice is important

Cf. Omega-3 depression clinical guidelines (Guu et al. 2019)

> **Statement:** Omega-3 fatty acids at doses standardised to 1 g to 2 g of eicosapentaenoic acid (EPA) are *Weakly Recommended* for *Adjunctive* use in bipolar depression

Evidence grade: A (a statistically significant meta-analysis and 3 RCTs; $k = 8$, $n = 460$)
Strength of recommendation: Adjunctive: Weakly Recommended (+)

Clinical guideline statement:

- Meta-analytic level results and additional RCTs have shown mixed weakly supportive evidence for efficacy in treating depression in bipolar disorder
- Evidence tends to support preparations with higher/sufficient EPA (≥1 g per day)
- Robust safety data. However, caution is advised for use with anticoagulants and at higher doses prior to surgery
- Omega-3 has not been shown to be effective in attenuating mania or hypomania
- Quality can be an issue with omega-3 supplements, with some containing higher levels of oxidation. Product choice is important

Vitamin D

> **Statement:** Vitamin D at doses of between 1500 IU and 4000 IU per day are *Weakly Recommended* for *Adjunctive or Monotherapy* use in MDD

Evidence grade: A (a statistically significant meta-analysis and 2 RCTs; $k = 27$, $n = 7651$)
Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD
- The meta-analysis reviewed revealed methodologically weak underlying data
- Smaller daily or weekly doses may be more appropriate compared to singular mega-bolus dosage (i.e. 50,000 IU)
- Potentially of greater benefit in winter months (although Vitamin D levels could be a proxy marker for adequate sunshine – which may have additional neurochemical and psychological benefits) (Knippenberg et al. 2014; Sarris et al. 2014)
- Unlikely to be of benefit in those with sufficient skin exposure to sunlight and/or dietary intake (although some people may have absorption [e.g. from dark skin] or metabolic issues impeding Vitamin D levels)
- Robust safety data

Probiotics

> **Statement:** Probiotic strains (e.g. *Lactobacillus and Bifidobacterium spp.)* at doses of 1–10 billion units per day are *Provisionally Recommended* for *Adjunctive* use and *Weakly Recommended* for *Monotherapy use* in MDD

Evidence grade: A (a statistically significant meta-analysis; $k = 6$, $n = 302$)
Strength of recommendation: Adjunctive: Provisionally Recommended (++), Monotherapy: Weakly Recommended (+)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD (although most mood research on probiotics has focussed on depressive symptoms rather than diagnosed MDD
- The underlying RCTs mainly consist of small samples with modest effect sizes, so this probiotic use in MDD can only at present be modestly recommended in concert with adjunctive standard treatments
- The most appropriate probiotics strains for depression have not been confirmed, and it is likely that variations are more beneficial depending on an

individual's genetics and diet and microbiome composition
- The *Lactobacillus and Bifidobacterium spp*. are currently the most studied strains, however there are marked variations of products studied with vastly differing probiotic strains
- Robust safety data

Zinc

Statement: Zinc at doses of ~25 mg per day is *Provisionally Recommended* for *Adjunctive* use in MDD

Evidence grade: A (a statistically significant meta-analysis; $k = 3$, $n = 124$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Meta-analytic level results involving a small, pooled sample have shown supportive (primarily adjunctive) evidence for the efficacy of zinc (in forms such as sulphate or hydroaspartate) in treating MDD
- May have a specialised use in cases of comorbid lowered immunity, raised inflammation, or high oxidative stress (especially in dietary deficiency)
- Acceptable safety data. However, caution is advised in higher doses. May cause nausea on an empty stomach
- Certain chelations are recommended due to being more absorbable e.g. amino acid chelates or picolinate

Folate-based compounds

Statement: Methylfolate (15 mg) per day is *Provisionally Recommended* for A*djunctive* use in MDD. Folic acid is however *Not Recommended*

Evidence grade: A (a statistically significant meta-analysis; $k = 7$, $n = 966$)
Strength of recommendation: Methylfolate (15 mg) is Provisionally Recommended (++); Folic acid is Not Recommended (−)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD (for metabolically active forms of folate)
- A large RCT (Bedson et al. 2014) using folic acid, showed null results (being potentially less effective than active 'down-stream' forms which bypass the T677C polymorphism) (Fava and Mischoulon 2009)
- Fair safety data. However, larger doses of synthetic folic acid have been linked to very slight increase of some cancers (due potentially to stimulating an increase in cell proliferation)
- May have additional benefits in those with inflammation and/or obesity, or for use in preconception care or pregnancy (see Specialised Populations section below)

S-Adenosyl Methionine (SAMe)

Statement: SAMe at doses of 800 mg per day is *Not Currently Recommended* for *Monotherapy* use in MDD. SAMe at 1600 mg–3200 mg is *Weakly Recommended* for *Adjunctive* use in MDD

Evidence grade: A (5 individual RCTs; $k = 5$, $n = 711$)
Strength of recommendation: Monotherapy: Not Currently Recommended (±), Adjunctive: Weakly Recommended (+)

Background/Supporting statement:

- Five RCTs have been conducted; one with supportive adjunctive results (1600 mg–3200 mg per day used with antidepressants) and the other four with null findings for adjunctive or monotherapy use (800 mg and 1600 mg–3200 mg per day)
- Higher doses may potentially be more effective (i.e. ≥1600 mg)
- SAMe is an unstable compound and enteric coating and storage in blister packs under refrigeration may be advised
- Cost may be prohibitive at higher doses (e.g. >800 mg per day)
- Acceptable safety data. However, caution is advised in bipolar disorder due to the potential induction of mania

Vitamin C

Statement: Vitamin C at doses of ~1 g per day is *Not Currently Recommended* for *Adjunctive* or *Monotherapy* use in MDD

Evidence grade: A (1 null RCT and 1 positive RCT; $k = 2$, $n = 70$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- RCT results from small sample trials have shown mixed but generally non-supportive evidence for efficacy in MDD
- May have a potential use in deficiency or comorbid lowered immunity or raised oxidative stress
- Robust safety data. However, excess doses may cause gastrointestinal disturbance (e.g. diarrhoea) in some people

Tryptophan and 5-HTP

Statement: Tryptophan at doses of up to 1 g per day (or 5-HTP at 50 mg–200 mg per day) is *Not Currently Recommended* for *Adjunctive or Monotherapy* use in MDD

Evidence grade: A (a meta-analysis and an additional null RCTs; $k = 3$, $n = 94$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- The combination of a meta-analytic and RCT results involving small sample sizes, have overall not shown supportive evidence for efficacy in MDD
- The meta-analysis reviewed revealed methodologically weak underlying data
- 5-HTP is the preferred form as a precursor of serotonin
- May benefit symptomatic improvement of insomnia symptoms in depression
- Acceptable safety data
- Caution with co-use with antidepressants due to a potential rare risk of serotonin syndrome

Creatine

Statement: Creatine at a dose of 5 g per day is *Not Currently Recommended* for *Adjunctive* or *Monotherapy* use in MDD

Evidence grade: A (1 positive RCT and 1 null RCT; $k = 2$, $n = 64$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- RCT results have shown mixed evidence for efficacy in MDD
- May have a role in people with MDD and comorbid fatigue
- Fair safety data
- Caution in excess doses and in people with kidney issues due to increased demand on renal clearance

Inositol

Statement: Inositol at doses up to 12 g per day is *Not Recommended* for *Adjunctive* or *Monotherapy* use in MDD

Evidence grade: A (a statistically non-significant meta-analysis; $k = 2$, $n = 69$)
Strength of recommendation: Not Recommended (−)

Background/Supporting statement:

- Meta-analytic level results have not shown supportive evidence for efficacy in MDD
- Acceptable safety data, although due to the high dose required, it may cause gastrointestinal discomfort

Magnesium

Statement: Magnesium at doses of 100 mg to 400 mg elemental per day is *Not Recommended* for *Adjunctive* or *Monotherapy* use in MDD

Evidence grade: A (2 non-significant RCTs; $k = 2$, $n = 49$)
Strength of recommendation: Not Recommended (−)

Background/Supporting statement:

- Meta-analytic level results involving small sample sizes have shown non-supportive evidence for efficacy in MDD
- Robust safety data within a therapeutic dosage range, however, at higher doses may compete with (and reduce) the absorption of other minerals such as calcium. Gastrointestinal upset may occur in higher doses

N-Acetyl Cysteine (NAC)

Statement: NAC at doses of 1 g to 3 g per day is *Not Currently Recommended* for *Adjunctive* use in bipolar disorder

Evidence grade: A (4 mixed RCTs; $k = 4$, $n = 328$)

Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- Data from 4 bipolar disorder RCTs (2 positive and 1 mixed, and 1 null [which was the largest and most robust study])
- May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress
- Acceptable safety data based on long-standing use in acetaminophen overdose

Phytoceuticals for mood disorders (major depressive disorder/bipolar disorders) (Table 4)

St John's wort (Hypericum perforatum)

Statement: St John's wort flowers at doses of 600 mg to 1800 mg (3:1–7:1 extract depending on product) per day standardised to a dose of approximately 0.2–0.3% hypericin and/or 5–6% hyperforin (once to three times per day depending on extract) is *Recommended* for *Monotherapy* use in MDD (mild-to-moderate depression)

Evidence grade: A (a statistically significant meta-analysis; $k = 35$, $n = 6993$)
Strength of recommendation: Recommended (+++)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD (being superior to placebo and being equivalent to antidepressants)
- While the recommendation is extended to mild-to-moderate depression, there is one RCT showing superiority of St John's wort (WS 5570) over paroxetine ($n = 251$) in moderate to severe level depression (HAMD $\geq$ 22)(Szegedi et al. 2005)
- Quality and standardisation are potential issues, and data from highly standardised quality extracts cannot be extended to inferior preparations (Kasper et al. 2010)
- Acceptable safety data, although there may be clinically important interactions with commonly used medications such as oral contraceptives
- Caution for use in bipolar disorder due to the potential induction of mania
- May cause photosensitivity
- Do not use with SSRIs or SNRIs due to potential of serotonin syndrome
- Hyperforin-rich extracts may induce metabolic pathways (i.e. P-glycoprotein pump and cytochrome P450 3A4) thereby reducing serum levels of many drugs

Saffron (*Crocus sativus*)

Statement: Saffron at a dose of approximately 30 mg of the stigma, or standardised to safranal or crocin isomers (once to three times per day depending on extract) is *Provisionally Recommended* for *Monotherapy* or *Adjunctive* use in MDD (mild to moderate depression)

Evidence grade: A (a statistically significant meta-analysis; $k = 14$, $n = 620$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD
- A larger international RCT is now required to more confidently support saffron for use in the treatment of MDD
- Acceptable safety data, aside from potential minor adverse effects e.g. gastrointestinal symptoms, increased perceived mental stimulation
- Quality and standardisation of saffron extracts (which can be expensive) are essential

Curcumin (*Curcuma longa*)

Statement: Curcumin extract at a dose of approximately 500 mg to 1000 mg per day (depending on extract) is *Provisionally Recommended* for *Monotherapy* or *Adjunctive* use in MDD (mild to moderate depression)

Evidence grade: A (a statistically significant meta-analysis; $k = 10$, $n = 531$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating MDD
- Most RCTs have small sample sizes, and a large multi-centre study is required to more firmly validate its use in MDD
- Potential adjuvant benefit in comorbid inflammatory disorders

- Formulations with evidence of sufficient bioavailability are advised (e.g. consider liposomal forms)
- Acceptable safety data (used within therapeutic guidelines)

Rhodiola (*Rhodiola rosea*)

Statement: Rhodiola root at a dose of approximately 340–680 mg (once to three times per day depending on extract) is *Not Currently Recommended* for *Monotherapy* or *Adjunctive* use in MDD

Evidence grade: A (1 positive RCT and 1 null RCT; $k = 2$, $n = 146$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- RCT level results have shown mixed evidence for efficacy in treating MDD
- The RCTs have small sample sizes and a further large multi-centre study is required to more accurately assess its use in MDD
- Russian research (purported to have occurred 50–70 years ago) has been suggested as providing supportive evidence for antifatigue and antidepressant effect; however, these data have not been translated and provided for public scrutiny
- Acceptable safety data (used within therapeutic guidelines)

Lavender (*Lavandula officinalis*)

Statement: Lavender at doses of 80 mg to 160 mg of essential oil per day (in the form of soft gels), or 500 mg to 1.5 g of dried flower (preferably in the form of standardised formulations), twice per day is *Weakly Recommended* for *Monotherapy* or *Adjunctive* use in MDD

Evidence grade: A (3 supportive RCTs; $k = 3$, $n = 325$)
Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- RCT level results have shown supportive evidence for efficacy in treating MDD (currently no meta-analytic MDD data)
- Most RCTs have small sample sizes, and an additional large multi-centre study is required to validate its use in MDD
- Acceptable safety data (used within therapeutic guidelines with treatment as usual)
- Use of standardised dosage forms is advised over tea preparations of unknown quality

Nutraceuticals for anxiety disorders (Table 5)

N-Acetyl Cysteine (NAC)

Statement: A) NAC at doses of 2 g to 3 g per day is *Weakly Recommended* for *Adjunctive* use in obsessive compulsive disorder
B) NAC at doses of 2g to 3g per day is *Not Currently Recommended* for *Adjunctive* use in Trichotillomania

Evidence grade: A (a statistically significant meta-analysis and 3 RCTs; $k = 8$, $n = 312$)
Strength of recommendation:
OCD: Weakly (+); Trichotillomania = Not Currently Recommended (±)

Background/Supporting statement:

- Data from a meta-analysis for OCD revealed a significant effect in favour of NAC; however, underpinning RCT data are mixed
- Two individual RCTs showed mixed results for use in Trichotillomania
- NAC may have a preferential benefit in ameliorating compulsive symptoms as opposed to addressing cognitive ruminations
- May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress
- Acceptable safety data based off long-standing use in acetaminophen overdose

Phytoceuticals for anxiety disorders (Table 5)

Kava (*Piper methysticum*)

Statement: Kava rootstock extracts standardised to kavalactones at 60 mg to 250 mg is *Not Recommended* for *Adjunctive* or *Monotherapy* use for generalised anxiety disorder (GAD)

Evidence grade: A (a statistically non-significant meta-analysis for anxiety disorders and 2 RCTs; $k = 6$, $n = 473$)
Strength of recommendation: Not Recommended (−)

Background/Supporting statement:

- Meta-analytic level results have not shown supportive evidence for efficacy in treating GAD

- A recent additional large multicentre RCT confirms non-superiority to placebo in GAD (Sarris, Byrne, et al. 2020)
- Potential use for acute or short-term management of general anxiety symptoms is however supported by robust evidence (Sarris 2016)
- Caution for use in people with liver issues, and avoidance with alcohol and benzodiazepines
- Important to recommend only the use of 'noble' varieties of the rootstock of the plant standardised to a sufficient level of kavalactones
- Fair safety data, although further data would be beneficial in determining causations of very rare liver issues (noted 15–20 years ago, potentially due to poor-quality kava (Teschke et al. 2011)

Ashwagandha (*Withania somnifera*)

Statement: Ashwagandha root extract at doses of 300 mg to 600 mg (standardised to 5% withanolides) per day is *Provisionally Recommended* for *Monotherapy or Adjunctive* use (application with 'treatment as usual') in GAD

Evidence grade: A (3 statistically significant RCTs; $k = 3$, $n = 165$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Three individual RCTs have shown efficacy in treating anxiety disorders (in particular GAD); however, a larger more definitive study is required to validate efficacy
- As an 'adaptogen', may have application in presentations of fatigue/burn-out and/or insomnia (Choudhary et al. 2017)
- Other data from a bipolar disorder study showing Ashwagandha may also have 'pro-cognitive' effects (Chengappa et al. 2013)
- Acceptable safety data (used within therapeutic guidelines)

Galphimia (*Galphimia glauca*)

Statement: Galphimia aerial parts extract at doses of 350 mg to 700 mg twice per day (standardised to galphimine B) is *Weakly Recommended* for *Monotherapy* use in GAD

Evidence grade: A (2 statistically significant RCTs; $k = 2$, $n = 343$)
Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- Two individual RCTs (both versus the positive control lorazepam) have shown efficacy in treating GAD
- Replicated international placebo-controlled research is needed to validate efficacy
- Fair safety data with no major adverse effects noted from clinical trials

Chamomile (*Matricaria spp.*)

Statement: Chamomile flowers standardised at doses of 220 mg to 1500 mg per day (depending on standardisation of volatile compounds or apigenin or chrysin) is *Not Currently Recommended* for *Monotherapy or Adjunctive* use in GAD

Evidence grade: A (a statistically significant RCT and 1 non-significant RCT; $k = 2$, $n = 236$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- Two individual RCTs (1 positive RCT and 1 null RCT)
- May be a potential low-cost adjunctive intervention in tea form to assist with lessening anxiety symptoms
- Robust safety data and has 'generally recognised as safe' (GRAS) status in the US

Lavender (*Lavandula officinalis*)

Statement: Lavender at doses of 80 mg to 160 mg per day of a specialised oil (in capsule form) or 500 mg to 1.5 g of dried flower (preferably in the form of standardised formulations), twice per day is *Provisionally Recommended* for *Monotherapy or Adjunctive* use (application with 'treatment as usual') in GAD

Evidence grade: A (3 statistically significant RCTs; $k = 3$, $n = 813$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Three individual RCTs have shown efficacy in treating anxiety disorders (in particular GAD)

- Also has been shown to have therapeutic effects in the treatment on somatic symptoms, including insomnia complaints and fatigue, and on reduced physical health in patients with anxiety disorders (Von Kanel et al. 2021)
- Acceptable safety data
- Use of standardised capsule formulations is advised over tea preparations of unknown quality

Nutraceuticals for psychotic disorders (Table 6)

Omega 3-fatty acids

Statement: Omega-3 fatty acids at doses of 1 g to 2 g are *Not Recommended* for *Adjunctive* or *Monotherapy* use in schizophrenia

Evidence grade: A (a statistically non-significant meta-analysis and 1 RCT; $k = 15$, $n = 400$)
Strength of recommendation: Not Recommended (−)

Clinical guideline statement:

- Meta-analytic level results have not shown supportive evidence for efficacy in schizophrenia (with mixed data showing a potential to prevent transition of at-risk youth to schizophrenia)(Hsu et al. 2020)
- May be more beneficial in people with raised inflammation, obesity (including when initiating antipsychotics to potentially assist in the reduction of metabolic issues), or in cases of dietary deficiency
- Robust safety data. However, caution is advised for use with anticoagulants and at higher doses prior to surgery

Vitamin D

Statement: Vitamin D at doses of between 1500 IU and 4000 IU per day is *Not Recommended* for *Adjunctive* use in schizophrenia

Evidence grade: A (2 RCTs; $k = 2$, $n = 104$)
Strength of recommendation: Not Recommended (−)

Background/Supporting statement:

- RCT results involving small samples have not shown supportive evidence for adjunctive efficacy in reducing symptoms of schizophrenia
- Unlikely to be of benefit in those with sufficient skin exposure to sunlight and/or dietary intake (although some may have absorption [e.g. from dark skin] or metabolic issues impeding Vitamin D levels)
- Robust safety data. However, it may be toxic at very large doses

N-Acetyl cysteine

Statement: NAC at doses of 1 g to 3 g per day is *Provisionally Recommended* for *Adjunctive* use in schizophrenia (primarily for negative symptoms)

Evidence grade: A (a statistically significant meta-analysis; $k = 7$, $n = 440$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in reducing symptoms in schizophrenia (primarily for negative symptoms)
- May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress
- Acceptable safety data based off long-standing use in acetaminophen overdose

Folate-based compounds

Statement: Methylfolate (1 mg to 15 mg) per day is *Provisionally Recommended* for *Adjunctive* use in schizophrenia (primarily for negative symptoms)

Evidence grade: A (a statistically significant meta-analysis; $k = 10$, $n = 840$)
Strength of recommendation: Provisionally Recommended (++)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in treating schizophrenia (primarily for negative symptoms)
- The meta-analysis reveals methodologically weak underlying data
- Potentially less effective than active 'down-stream' forms which bypass the T677C polymorphism (Fava and Mischoulon 2009)

- Fair safety data, although larger doses of synthetic folic acid have been linked to very slight increase of some cancers (due potentially to stimulating an increase in cell proliferation)
- May have additional benefits in inflammation and/or obesity, or for use in preconception care or pregnancy (see Specialised Populations section below)

Phytoceuticals for psychotic disorders (Table 6)

Ginkgo (*Ginkgo biloba*)

Statement: Ginkgo extract at doses of 120 mg to 360 mg (50:1 standardised extract) is *Weakly Recommended* for *Adjunctive* use in schizophrenia (primarily for negative symptoms)

Evidence grade: A (a statistically significant meta-analysis; $k = 8$, $n = 571$)
Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for total and negative symptoms in schizophrenia
- There are concerns regarding the underlying RCT data which are all obtained from a single region (i.e. the data are not multi-jurisdictional)
- Potential role for negative symptoms, tardive dyskinesia, and for enhancing cognition in this population
- Acceptable safety data; caution with blood-thinning medication
- Highly standardised products can have added costs

Nutraceuticals for attention deficit hyperactivity disorder (Table 7)

Omega-3 Fatty Acids

Statement: Omega-3 fatty acids at doses of 120 mg to 1200 mg is *Not Currently Recommended* for *Monotherapy* or *Adjunctive* use in ADHD in children

Evidence grade: A (one statistically significant meta-analysis; $k = 7$, $n = 534$ plus recent negative/null RCTs; $k = 4$, $n = 344$, in children)
Strength of recommendation: Not Currently Recommended (±)

Clinical guideline statement:

- Meta-analytic level results have shown weakly supportive evidence of efficacy in treating ADHD in children, however, four more recent RCTs showed negative or null results
- Evidence tends to support preparations with higher/sufficient EPA compared to DHA alone (however the data do not show a clear dose-response relationship)
- May be potentially more effective in children with fatty acids deficiency
- There is a deficit of data assessing its use in adults with ADHD
- Robust safety data, however, caution is advised for use with anticoagulants and at higher doses prior to surgery
- Quality can be an issue with omega-3 supplements, with some containing higher levels of oxidation. Product choice is important

Omega 9-fatty acids (Evening Primrose oil)

Statement: Omega-9 fatty acids at doses of 2 g to 3 g are *Not Recommended* for *Monotherapy* or *Adjunctive* use in ADHD in children

Evidence grade: A (2 statistically non-significant RCTs in children; $k = 2$, $n = 49$)
Strength of recommendation: Not Recommended (−)

Clinical guideline statement:

- RCT level results with small sample sizes have not shown definitive efficacy of omega-9 fatty acids in treating ADHD in children
- Sufficient omega-9 levels usually found in most diets
- Robust safety data

Micronutrient Formula

Statement: A broad-spectrum micronutrient (13 vitamins and 15 minerals) formula taken as 8–12 capsules per day is *Weakly Recommended* for *Monotherapy* use in ADHD (children and adults)

Evidence grade: A (a statistically significant meta-analysis; $k = 2$, $n = 173$) with statistically significant RCTs in adult and child samples

Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for efficacy in ADHD as a monotherapy
- More replicated evidence required (in both adults and children)
- This particular micronutrient formula's efficacy cannot necessarily be extended to other multi-nutrient formulas
- Dosing may need to be supervised (and titrated) via a health profession
- Cost and compliance may be an issue due to a recommended dosage of 8–12 capsules per day
- Acceptable safety data

Vitamin D

Statement: Vitamin D at doses of approximately 1500 IU to 4000 IU per day is *Weakly Recommended* for *Adjunctive* use in ADHD in children

Evidence grade: A (a statistically significant meta-analysis; $k = 4$, $n = 256$)
Strength of recommendation: Weakly Recommended (+)

Background/Supporting statement:

- Meta-analytic level results have shown supportive evidence for adjunctive efficacy in ADHD
- Meta-analysis has revealed methodologically weak underlying data
- Smaller daily or weekly doses may be more appropriate compared to singular mega-bolus dosage (i.e. 50,000 IU)
- Unlikely to be of benefit in those with sufficient skin exposure to sunlight and/or dietary intake (although some may have absorption [e.g. from dark skin] or metabolic issues impeding Vitamin D levels)
- Robust safety data. However, it may be toxic at very large doses

Acetyl-L-Carnitine (ALC)

Statement: ALC at doses of 1 g to 3 g per day is *Not Recommended* for *Adjunctive or Monotherapy* use in ADHD in children

Evidence grade: A (2 individual RCTs; $k = 2$, $n = 152$)
Strength of recommendation: Not Recommended (−)

Clinical guideline statement:

- RCT level results have shown no efficacy in treating ADHD in children
- Acceptable safety data

Zinc

Statement: Zinc at doses of 15 mg-40mg (elemental), depending on weight/age, per day is *Not Currently Recommended* for *Monotherapy* or *Adjunctive* use in ADHD in children

Evidence grade: A (mixed findings in 5 RCTs involving children; $k = 5$, $n = 596$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- Mixed evidence, although zinc may improve some cognitive and behavioural indices depending on the individual
- May have a specialised use in cases of comorbid lowered immunity or raised inflammation, or high oxidative stress (especially with dietary deficiency)
- Acceptable safety data, however, caution is advised in higher doses. May cause nausea on an empty stomach

Phytoceuticals for attention-deficit hyperactivity disorder (Table 7)

Ginkgo (*Ginkgo biloba*)

Statement: Ginkgo at doses of 80 mg to 120 mg (50:1 standardised extract) is *Not Currently Recommended* for *Monotherapy* or *Adjunctive* use in ADHD in children

Evidence grade: A (2 RCTs with mixed findings in children; $k = 2$, $n = 116$)
Strength of recommendation: Not Currently Recommended (±)

Background/Supporting statement:

- RCT level results have shown mixed evidence in treating ADHD in children
- Ginkgo may improve some cognitive and behavioural indices depending on the individual

- Acceptable safety data, however, caution with blood-thinning medication
- Highly standardised preparations can have added costs

Safety and tolerability

With the significant prevalence of natural product use worldwide, (Harris et al. 2012; Harnett et al. 2019) in some cases without the knowledge of the patient's primary practitioner (Xue et al. 2007), the risk of potential adverse events or drug interactions is of clinical concern. Evidence relating to nutraceutical/phytoceutical side effects and drug interactions can vary significantly and be challenging to interpret, due in part to variability in product standardisation, quality assurance processes, manufacturing methods, routes of administration, and dose (Coxeter et al. 2004). The nutraceuticals/phytoceuticals reviewed in these guidelines have undergone a consensus-based grading process that has taken into account currently available clinical and pharmacological evidence, along with the findings of several governmental regulatory agencies. Safety and tolerability in this context is multifaceted, and must take into consideration both product(s) and patient characteristics and context of use. Aside from any inherent potential side effects of these products, patient symptom severity, comorbidities, and current pharmaceutical interventions are also key considerations.

Of particular importance is the potential for pharmacodynamic and pharmacokinetic interactions, with available evidence for clinicians being complex to navigate, absent, or largely theoretical. In some cases these interactions can be of therapeutic benefit; for example, research on a broad spectrum micronutrient approach shows a clear pharmacodynamic interaction, referred to as 'potentiation', such that those who lower their doses of medications alongside taking micronutrients tend to experience relatively fewer side effects and greater clinical benefit (Popper et al. 2017). Clinicians should remain assiduous to the potential likelihood of such interactions (whether beneficial or harmful) occurring and their subsequent clinical consequences, including medication adjustments, particularly with narrow therapeutic index drugs (such as warfarin) (Chavez et al. 2006).

Pharmacokinetic interactions via either induction or inhibition of isoenzymes of the hepatic Cytochrome P450 system or the drug transporter P-glycoptrotein (P-gp) are noted in the literature for many of the agents covered in this review. Most prominent is St John's wort, which can significantly induce CYP3A4, CYP2E1 and 2C19 and the P-gp, which may lead to clinically significant interactions, including (but not limited to) cyclosporine, anticonvulsants, oral contraceptives, warfarin, digoxin, anaesthetics, antineoplastics, and anti-HIV medications (Henderson et al. 2002; Borrelli and Izzo 2009). Serotonin syndrome is also possible with St John's wort and tryptophan/5-HTP with concurrent SSRI/SNRI use (Turner et al. 2006; Borrelli and Izzo 2009). Caution should also be advised due to possible additive effects of omega-3 supplements or ginkgo with blood-thinning medications, (Ramsay et al. 2005) whilst kava should be avoided in patients with liver issues or concurrent alcohol, benzodiazepine, or other sedative medication use (Sarris, LaPorte et al. 2011).

The tolerability of nutraceutical/phytoceutical agents are generally mild, with the majority of side effects being gastrointestinal related (e.g. zinc, omega-3, n-acetylcysteine, vitamin C). Other important considerations include photosensitivity (St John's wort) and allergy or sensitivity, such as to plants of the *Asteraceae* (e.g. Chamomile) or *Solanaceae* (e.g. Ashwagandha) families. Further, ingredient substitution (e.g. species adulteration of plant material), (Srirama et al. 2017), whether deliberate or accidental, along with contamination and adulteration of products with pesticide residues, pharmaceuticals, heavy metals, or microbial contaminants further increases risk of adverse events, (Posadzki et al. 2013) and highlights the importance for strict manufacturing quality assurance requirements. One meta-analysis shows that prescription omega-3 fatty acid products (RxOME3FAs) are generally safe and well tolerated but not free of adverse effects (Chang et al. 2017).

Specialised populations

Several factors need to be considered when recommending nutraceuticals and/or phytoceuticals for different populations. For example, during pregnancy and breastfeeding, many women prefer to minimise dosages of psychotropic drugs or avoid psychotropics altogether (Calderon-Margalit et al. 2009). In this population, nutraceuticals and/or phytoceuticals are frequently used under the misconception that, because they are 'natural', they are safe (Freedman et al. 2018). Unfortunately, relatively few of these have been rigorously studied for safety or efficacy when used in the perinatal period. Large robustly conducted studies are required to evaluate the safety of natural product supplement use during pregnancy and

breastfeeding, including risks of teratogenicity to the foetus, obstetrical complications during pregnancy and childbirth, neonatal complications, and longer-term implications for children exposed *in utero*.

To date, the best studied natural supplements for psychiatric disorders during the perinatal period are omega-3 fatty acids (i.e. n-3 PUFAs) for MDD, with a meta-analysis revealing the important role of n-3 fatty acid deficits in perinatal depression (Lin et al. 2017). Randomised controlled trials have suggested modest efficacy for the acute treatment of perinatal depressed mood, especially postpartum depression (Mocking et al. 2020; Sarris and Freeman 2020). Omega-3 fatty acids may be more effective for depressed mood during mid-to-late pregnancy (Mocking et al. 2020). Notably, there may be obstetrical benefits to omega-3 fatty acid supplementation, such as modestly lengthening gestation (Kar et al. 2016). Deficiencies of certain vitamins, including D3 (cholecalciferol) and others, can cause obstetrical complications and poor infant outcomes (Sharef et al. 2020). Folic acid is also a critically important nutritional supplement for women of reproductive age, especially women who are planning pregnancy or are already pregnant. Folic acid supplementation during pregnancy is known to prevent birth defects and a growing number of studies support its long-term benefits on neurodevelopment of children (Lassi et al. 2013); however, as noted in the present guidelines, data are not supportive of folic acid supplementation per se for psychiatric disorders (Bedson et al. 2014; Roberts et al. 2018). A recent review of nutraceutical research, highlighted the common prenatal use of folic acid, phosphatidylcholine, and Vitamins A and D, and found a potential application (within safe dosage levels) for both potentially impacting long term prevention of psychiatric disorders in the mother, and their effects on healthy neurodevelopment in the foetus (Freedman et al. 2018).

With respect to paediatric considerations, there is a long history of using single nutrients to treat psychiatric disorders in children with overall limited success. The majority of studies investigating nutraceuticals and phytoceuticals in children and adolescents focus on ADHD (Chang et al. 2018), with a few studies on other paediatric psychiatric disorders, such as mood and anxiety disorders (Fristad et al. 2019; Trebatická et al. 2020). No phytoceutical was identified as efficacious for ADHD; while we found only weak evidence for vitamin D as a potential monotherapy or adjunctive treatment of ADHD, with other isolated nutraceuticals showed mixed or no effects above placebo. While there was provisional evidence for modest beneficial effects of a broad spectrum micronutrient in paediatric ADHD, large placebo-controlled studies are needed to determine whether broad spectrum micronutrients are more efficacious than combinations of select micronutrients. Current evidence for omega-3 fatty acids used as a monotherapy or adjunct to medications for ADHD is mixed, and limited evidence suggests that omega-3 fatty acid supplementation may be beneficial in cases of deficiency (Chang et al. 2018; Cornu et al. 2018; Crippa et al. 2019). This raises the broader issue about whether baseline nutrient status informs efficacy. In general, it is intuitive that efficacy might be greater in instances of baseline deficiency, but this hypothesis largely remains unexplored. If validated, it would support precision approaches to nutraceutical therapy.

The evidence base for omega-3 fatty acids for the treatment of mood disorders in children is also evolving (Fristad et al. 2019; Trebatická et al. 2020). The potential safety issues associated with psychostimulant medication use in this age group invites rigorous consideration of nutraceuticals that potentially address ADHD and other paediatric psychiatric disorders (Correll and Carlson 2006). However, the safe appropriate use of nutraceuticals in children and adolescents must take into account metabolic differences that affect treatment response, and any relevant safety concerns.

With respect to nutraceutical use in older populations, it is recognised that nutritional deficiencies are more prevalent in older adults, and that individual differences in the microbiome may lead to differences in effective dosages. Emerging findings point to the impact of age, genetics (including pharmacogenomics), and inter-individual variations in metabolism and the microbiome that affect the pharmacokinetics and pharmacodynamics of nutraceuticals and phytoceuticals. For example, microbial dysbiosis may be more prevalent in the elderly and lead to individuals with an increased oxidative and inflammatory load (including the digestive system) (Nagpal et al. 2018). These areas are being increasingly researched, and in time it is hoped that data will provide more direction for personalised interventions, especially involving prebiotic or probiotic products.

The findings of a recent systematic review suggest that a balanced wholefood diet may help reduce the risk of depression and reduce the severity of depressed mood in the elderly (Klimova et al. 2020). Many elderly individuals are also at risk of malnutrition because of social isolation and fixed incomes and may not meet minimum recommended dietary allowances (RDA) of essential micronutrients, amino acids and

essential fatty acids. This may result in abnormal low serum levels of essential amino acids and nutrient co-factors required for synthesis of serotonin and other neurotransmitters involved in mood regulation. Poor nutrition or unhealthy food choices in the elderly can also negatively impact the microbiome resulting in incomplete absorption of essential nutrients and/or inflammation, both of which are implicated in the pathogenesis of depressed mood and other psychiatric disorders (Donini et al. 2013).

Recent advances in 'nutragenomics' and 'herbomics' are providing valuable insights to the specific neurochemical pathways associated with the pathogenesis of the psychiatric disorders and a better understanding of the pharmacodynamics and neurochemistry influenced by natural product supplements (Sarris et al. 2012; Reddy et al. 2018). The application of omic studies to assist in quantifying both therapeutically active and toxic constituents of nutraceuticals and their effects on animal models may provide many valuable insights. For instance, metabolomics has significantly advanced phytotherapy in recent years by allowing for better identification of plant material, and the ability to develop standardised extracts that contain minimum levels of known active constituents (Sarris et al. 2012; Reddy et al. 2018).

Research priorities in the area include increasing our knowledge of the epigenetic effects by nutrients and plants, and determining which isolated agents or complex formulations have the most advantageous effects on particular individuals. Specific epigenetic effects from standardised extracts have previously been observed to be replicated, suggesting that it may be possible to patent specific phytoceuticals for specific therapeutic epigenetic effects (DellaPenna 1999). Many micronutrients and macronutrients are also known to indirectly influence genomic pathways that methylate DNA, resulting in changes in neurotransmitter synthesis (DellaPenna 1999). Such epigenetic modifications of the genetic material represent a link between nutrition and mental health. The effects of nutrition on mental health are mediated by changes in expression of multiple genes. Further, beneficial effects of particular micronutrients or macronutrients on mood, cognitive function and behaviour may be related to genetic variability at the level of each person (Parletta et al. 2013).

Finally, since efficacy and side effects of nutraceutical/phytoceutical can vary according to product standardisation, quality assurance processes, manufacturing methods etc, developing a standardised chemotype that presents with consistency of composition across preparations could allow nutraceuticals/phytoceuticals address a specific range of symptoms and/or psychiatric condition that is reproducible and undeniable. This should be also considered within the context of the prescription length needed, and the half-life of the compounds to determine the dosage frequency advised.

Conclusion

These WFSBP and CANMAT nutraceutical/phytoceutical clinical guidelines are the most comprehensive to date and aim to provide clarity and confidence in the prescriptive decisions for using (or not using) these agents in a range of psychiatric disorders. Our methodology employed, based on existing WFSBP guideline methodology recommendations, provided both structure for an in-depth literature review, a standardised assessment and grading of the evidence (adapted for current purpose), and drew on a depth of multi-disciplinary clinical experience.

The top-line findings of the WFSBP Taskforce reveal over two dozen nutraceuticals and phytoceuticals that have been evaluated in rigorous double-blind RCTs. The use of nutraceuticals and phytoceuticals in psychiatry is steadily gathering the necessary evidence base. However, the taskforce recognises that the methodology employed in some of the underlying studies did not adhere to the highest standard. Methodological flaws encountered included small sample sizes, markedly varied doses, insufficient communication of trial designs (especially regarding blinding processes), and failure to standardise active constituents (in some phytoceutical studies), thus limiting replicability and potential clinical confidence.

Nevertheless, our findings showed that adjunctive omega-3 fatty acids and monotherapy St John's wort are recommended for mood disorder treatment; while adjunctive probiotics, zinc, methylfolate, and adjunctive or monotherapy saffron and curcumin are provisionally recommended. Adjunctive or monotherapy vitamin D and lavender, monotherapy probiotics, and adjunctive SAMe were weakly recommended for this application. In the case of monotherapy omega-3 fatty acids and SAMe, adjunctive NAC, and adjunctive and monotherapy vitamin C, tryptophan, creatine, and rhodiola for unipolar depression treatment, there were mixed data or a lack of confidence in the methodological quality of the RCTs, or very small sample sizes and potential underpowering. Adjunctive or monotherapy folic acid, inositol, and magnesium showed no efficacy, and thereby cannot be recommended.

In the treatment of anxiety disorders, adjunctive or monotherapy ashwagandha and lavender were provisionally recommended, while adjunctive NAC and monotherapy galphimia were weakly recommended. In the case of adjunctive or monotherapy chamomile, there was mixed data. Monotherapy use of kava in GAD showed no efficacy and thereby cannot be recommended for this specific application. In the treatment of psychotic disorders, adjunctive NAC, and methylfolate were provisionally recommended for negative symptoms in schizophrenia, while adjunctive vitamin D or ginkgo were weakly recommended. Adjunctive and monotherapy omega-3 fatty acids showed no efficacy in schizophrenia and thereby cannot be recommended for this condition. Weak support however existed for omega-3 in bipolar depression (while NAC was not currently recommended for use in this application). In the treatment of ADHD, monotherapy micronutrients and adjunctive or monotherapy vitamin D were weakly recommended, while there was mixed data in the case of adjunctive or monotherapy omega-3 fatty acids, zinc, and ginkgo. Adjunctive or monotherapy omega-9 fatty acids and ALC showed no efficacy and thereby cannot be recommended in ADHD.

Many members of the taskforce expressed concern and advised caution when prescribing or recommending nutraceuticals and/or phytoceuticals as monotherapies in cases of severe psychiatric disorders. For this reason, we recommend that they be considered in individuals diagnosed with severe MDD, bipolar disorder or schizophrenia, only when used with conventional care, and only when there are no contraindications to adjunctive use of a particular agent with the prescribed psychotropic medication. In the face of this limitation, it is still recognised that a range of nutraceuticals/phytoceuticals may be safely used to augment conventional therapies to enhance treatment outcomes.

With respect to promising clinical applications, as noted in our guidelines, many factors need to be taken into account when prescribing these agents. These include differences in clinical presentation, previous treatment history, and available biomarker data (if any). With respect to particular brands of nutraceuticals or phytoceuticals that may be recommended for use, this can entail considerable ambiguity for both clinicians and consumers. For example, it is often challenging to determine the quality and relevant standardisation of a natural supplement, especially phytoceuticals. While it is outside the auspices of this taskforce to recommend brands, it is advised that only highly reputable manufacturers be recommended.

Regarding future steps in the field, the taskforce acknowledges that several of the agents reviewed in these guidelines still need to be investigated in large multicentre RCTs to further elucidate their efficacy and safety. While select nutraceuticals and/or phytoceuticals reviewed in this paper are substantiated by consistent positive findings from large, well-designed studies, many are only supported by provisional evidence at this time. In such cases, as usual, further research is recommended. Another important future research direction should be aimed at optimisation of nutraceuticals and/or to enhance synergistic effects in combination with psychotropic medications. At present, research and development of these agents often does not include optimisation during preclinical and early phase human studies, much less during production and manufacture. Another important future research area is to investigate the influences of the microbiome on psychiatric illness and prescription by using more sophisticated biomarker assays (ideally at point-of-care) (Marx et al. 2021; Ratsika et al. 2021). Advances in biomics could also lead to tailoring nutraceuticals for the individual based on for example: pre-existing deficiencies, genetic and microbiome data, or relevant biochemical assays. Finally, most data have tested these interventions between 4 and 12 weeks, and there is a general deficit of longer-term data, and research around any potential preventative effects.

In conclusion, this WFSBP Taskforce provides a range of recommendations for the evidence-based application of nutraceuticals and phytoceuticals in the field of psychiatry, which can now be adopted and integrated globally into psychiatric treatment protocols.

Statement of interest

JS has conducted a range of clinical trials on nutraceuticals or phytoceuticals, and has received either presentation honoraria, travel support, clinical trial grants, book royalties, or independent consultancy payments from nutraceutical/phytoceutical companies: Integria Healthcare & MediHerb, Pfizer, Scius Health, Key Pharmaceuticals, Taki Mai, Fiji Kava, FIT-BioCeuticals, Blackmores, Soho-Flordis, Healthworld, HealthEd, HealthMasters, Kantar Consulting, Angelini Pharmaceuticals, Grunbiotics, Polistudium, Australian Natural Therapeutics Group, Research Reviews, Elsevier, Chaminade University, International Society for Affective Disorders, Complementary Medicines Australia, SPRIM, Terry White Chemists, ANS, Society for Medicinal Plant and Natural Product Research, Sanofi-Aventis, Omega-3 Centre, the National Health and Medical Research Council, CR Roper Fellowship. **MB** has received Grant/Research Support from

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Ltd, received travel funding from Nutrition Society of Australia, received consultancy funding from Nutrition Research Australia, and has received speakers honoraria from The Cancer Council Queensland and the Princess Alexandra Research Foundation. **JR** has received academic funding for conducting broad-spectrum micronutrient research. **DM** has received research support from Nordic Naturals and heckel medizintechnik GmbH. He has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy, Harvard Blog, and PeerPoint Medical Education Institute, LLC. He also works with the MGH Clinical Trials Network and Institute (CTNI), which has received research funding from multiple pharmaceutical companies and NIMH. **BH** has participated in advisory boards, received honoraria from Servier, and received research funding from Servier, Lundbeck, Deakin University, Cannabis Science Inc, HG&H Pharmaceuticals and the South African Medical Research Council. **OMD** is a R.D. Wright Biomedical NHMRC Career Development Fellow [APP1145634] and has received grant support from the Brain and Behaviour 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. **JSS** has previously served on the scientific advisory board of Bioceuticals. **HC** has received Research Support from Dr. Willmar Schwabe GmbH & Co. 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Wolfgang has previously received funding from the NHMRC, Clifford Craig Foundation, Cancer Council Queensland and university grants/fellowships from La Trobe University, Deakin University, University of Queensland, and Bond University, received industry funding and has attended events funded by Cobram Estate Pty. 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