# Chapter 11
# Herbal Remedies and Nutraceuticals as Augmentation or Adjunct for Mood and Anxiety Disorders: Evidence for Benefit and Risk

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**Abstract** Background: Complementary and alternative medicine (CAM) therapies have considerable patient appeal. Perceived as better, safer and more economical than conventional treatments, such as pharmacotherapy and psychotherapy, they are often used by patients to self-treat symptoms of depression and anxiety, usually in combination with existing medications and without medical supervision. CAM therapies include physical therapies (e.g. exercise), herbal remedies (e.g. St. John's wort) and nutraceuticals/dietary supplements (e.g. omega-3 fatty acids). This chapter will review the published evidence for the use of herbal and dietary supplements as augmenting or adjunctive agents in depressive and anxiety disorders.

Methods: A PubMed search was conducted for all randomized controlled trials, open trials and case reports available and published up to May 2012 on the use of herbal remedies and dietary supplements, as augmentation or combination, particularly to medications, in the treatment of unipolar depression, bipolar disorder and anxiety conditions.

Results: Overall, the published literature is sparse. Among available data in depressive disorders, there is a moderate level of evidence to support adjunctive use of Free and Easy Wanderer Plus (FEWP) and folate in unipolar depression, and FEWP and omega-3 fatty acids in bipolar depression. Several other herbal remedies and

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume II: Use of Polypharmacy in the "Real World"*, DOI 10.1007/978-94-007-5799-8_11,

nutraceuticals have preliminary evidence of benefit as augmentation to pharmacotherapy, including S-adenosylmethionine (SAM-e), dehydroepiandrosterone (DHEA), folate, and zinc, in unipolar depression; magnesium in mania; N-acetylcysteine (NAC) in bipolar depression; and E. M. Power Plus (EMP+) in bipolar disorder. Surprisingly, there is no published evidence to support the benefit of St. John's wort as adjunct to antidepressants. Similarly, evidence of benefits for other herbal and dietary supplements remains limited. In anxiety disorders, there is, as yet, little evidence that herbal and dietary supplements are useful as augmenting agents.

Limitations: The overall evidence base remains limited and studies often had methodological problems, including small samples, variability in dose, short duration of treatment, and unknown quality of the agent. Though the supplements were generally well tolerated in reported studies, there is limited long-term safety and tolerability data, and drug-drug interaction information.

Conclusions: While several herbal and dietary supplements have evidence of benefit as add-on agents in depressive disorders, none can currently be recommended for anxiety conditions, and safety issues should be carefully considered prior to use in clinical practice. Larger well-designed studies are needed to provide a broad and reliable base of data for further evaluations.

## Abbreviations

| | |
|---|---|
| 5-HTP | 5-hydroxy tryptophan |
| CAM | Complementary and alternative medicine |
| CBZ | Carbamazepine |
| DBRCT | Double-blind randomized controlled trial |
| DHA | Docosahexaenoic acid |
| DHEA | Dehydroepiandrosterone |
| DNA | Dioxyribonucleic acid |
| EMP | E. M. Power Plus |
| EPA | Eicosapentanoic acid |
| FEWP | Free and Easy Wanderer Plus |
| GABA | Gamma-aminobutyric acid |
| GAD | Generalized anxiety disorder |
| HPA | Hypothalamic-pituitary adrenocortical |
| HRT | Hormone replacement therapy |
| MDD | Major depressive disorder |
| NAC | N-acetylcysteine |
| NMDA | N-methyl-D-aspartic acid |
| OCD | Obsessive-compulsive disorder |
| PD | Panic disorder |
| PTSD | Post-traumatic stress disorder |
| RCT | Randomized controlled trial |

| | |
|---|---|
| RNA | Ribonucleic acid |
| SAD | Social anxiety disorder |
| SAM-e | S-adenosylmethionine |
| STEP-BD | Systematic Treatment Enhancement Program for Bipolar Disorder |
| SSRI | Selective serotonin reuptake inhibitor |
| TCA | Tricyclic antidepressant |
| TRD | Treatment-resistant depression |

## 11.1 Introduction

Depressive and anxiety disorders are the most common psychiatric conditions found in the general population. Depressive disorders, which encompass unipolar depression and bipolar disorder, have an estimated 12-month prevalence of up to 11%, while anxiety conditions, which include generalized anxiety disorder (GAD), panic disorder (PD), obsessive-compulsive disorder (OCD), social anxiety disorder (SAD) and post-traumatic stress disorder (PTSD), have a 1 year prevalence of up to 18% [1, 2].

Despite the wide range of pharmacological and psychological interventions available for depressive and anxiety conditions, up to a quarter of patients show partial or no response even with adequate treatment, and for many, a chronic course of illness is common [3–5]. Side effects (with medications), time and accessibility (with psychotherapy), and cost factors can be further obstacles to patient compliance and full recovery [6, 7]. These limitations are frequently cited among the reasons that many patients turn to complementary and alternative medication (CAM) therapies for symptom relief, under the perception that these 'natural' therapies are more effective, affordable and tolerable [8–10]. It is quite common for patients to use CAM therapies without medical supervision, and while also receiving conventional treatments [11, 12].

CAMs fall into three main categories: physical therapies (e.g. exercise, acupuncture), nutraceuticals (i.e. dietary and nutritional supplements such as vitamins and minerals) and herbal remedies (i.e. plants and plant extracts) [9]. Although the data on the utility of such treatments is not as extensive as that for more conventional treatments, the field of research is growing in response to patient interest and use. Published data suggests that several CAMs have shown some benefits in depression and anxiety, both as monotherapy and as adjunctive treatments to pharmacotherapy. As the benefits and risks of physical therapies have been reviewed extensively and recently elsewhere [e.g. 13–15], this chapter will focus on the data relating to nutraceuticals and herbal remedies as augmentation or combination with conventional treatments for mood and anxiety disorders.

A search of the psychiatric literature, using PubMed, was conducted for all articles relating to the use of herbal and dietary supplements as augmenting agents in mood and anxiety disorders and published in English up to May 2012. The range of disorders covered in this review include: Major depressive disorder (MDD), dysthymia,

psychotic depression, treatment resistant depression (TRD), chronic depression, bipolar disorder, generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Information was summarized on the design, methods and outcomes of these studies. Study results were evaluated using the standard methodology for considering the strength of evidence for efficacy and tolerability.

The data reviewed below on herbal and dietary supplements used as augmenting or combination agents in depressive and anxiety disorders is also summarized in Tables 11.1, 11.2, 11.3 and 11.4. In published literature, "augmentation" refers to the addition of an agent to an existing treatment regime, usually antidepressants [65]. "Combination" refers to the concurrent use of two or more agents, who individually have antidepressant/anti-anxiety effects on their own, as treatment. "Add-on" refers to either strategy. The studies described below used one or other of these strategies.

## 11.2 Supplements

### *11.2.1 Herbal Remedies*

Herbal remedies are non-prescription, natural health products derived from plants and plant extracts, such as leaves, flowers, roots, bark and berries. They are frequently used individually or in combination to support general wellness or resolve symptoms of physical or mental stress. A literature search on the use of herbs as augmenting or combination agents found research evidence relating to St. John's wort, lavender, and kava kava, as well as specific Chinese and Japanese herbal compounds.

Several other herbs that have been evaluated only as monotherapy in depressive and anxiety disorders, and are therefore not reviewed in this chapter. These include saffron (*Crocus sativus*), roseroot (*Rhodiola rosea*), borage (*Echium amoenum*), gingko biloba, passionflower (*Passiflora incarnate*) and valerian (*Valeriana officinalis*) see reviews [9, 66, 67].

#### 11.2.1.1 St. John's Wort

St. John's wort (*Hypericum perforatum*) is a flowering plant whose extracts, which include hypericin and hyperforin, are candidates for its active ingredients [68]. Though St. John's wort has shown some efficacy in depressive and anxiety conditions, its mechanism of action is not fully elucidated. It is proposed that such action may be mediated by its effect on monoaminergic systems and modulation of hypothalamic-pituitary adrenocortical (HPA) axis activity [66, 68].

**Table 11.1** Evidence for CAM therapies as augmentation in depression and co-morbid anxiety

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| *St. John's wort* | | | | | | | |
| [16] | Sarris et al. (2009) | DBRCT, cross-over design | MDD with co-morbid GAD/SAD/PD = 28 | 8 weeks | St. John's wort (1,800 mg) + kava kava (2,660 mg) | Placebo | Combination > placebo for depression in first phase (p = 0.003), but combination = placebo after cross-over.<br>No treatment effects on anxiety. |
| [17] | Muller et al. (2003) | Open trial, randomized | MDD with GAD = 2,462 | 6 weeks | St. John's wort (600 mg) + valerian (500 mg)<br>St. John's wort (600 mg) + Valerian (1,000 mg) | None | Both groups improved similarly, but p values not reported. |
| *Kava Kava* | | | | | | | |
| [16] | Sarris et al. (2009) | DBRCT, cross-over design | MDD with co-morbid GAD/SAD/PD = 28 | 8 weeks | St. John's wort (1,800 mg) + kava kava (2,660 mg) | Placebo | Combination > placebo for depression in first phase (p = 0.003), but no group differences after cross-over.<br>No treatment effects on anxiety. |
| [18] | Cagnacci et al. (2003) | Open trial, randomized | Subsyndromal depression with moderate anxiety (self-reported) = 68 | 3 months | Calcium (1,000 mg) + kava kava (100 mg)<br>Calcium (1,000 mg) + kava kava (200 mg) | Calcium (1,000 mg) | Calcium + kava groups similar and > calcium alone for anxiety (p < 0.001).<br>All groups improved depression comparably (p < 0.002). |

[a] Results statistically significant at p < 0.05

**Table 11.2** Evidence for CAM therapies as augmentation in unipolar depression

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| *Lavender* | | | | | | | |
| [19] | Akhondzadeh et al. (2003) | DBRCT | MDD = 45 | 4 weeks | Lavandula (200 mg) + placebo<br>Lavandula (200 mg) + imipramine (100 mg) | Imipramine (100 mg) + placebo | Lavandula + imipramine > mipramine + placebo ($p < 0.001$) > Lavandula + placebo ($p < 0.001$). |
| *Herbal compound: FEWP* | | | | | | | |
| [20] | Qin et al. (2011) | Meta-analysis | Total = 14 (unipolar depression, bipolar depression)<br>Monotherapy = 6<br>Combination = 8 | 4–12 weeks | FEWP<br>Existing psychotropics + FEWP | Placebo or Psychotropics<br>Existing psychotropics | FEWP monotherapy > placebo ($p < 0.00001$) and = psychotropics. FEWP combination > psychotropics alone ($p < 0.009$). |
| *Herbal compound: Jio-zai* | | | | | | | |
| [21] | Yamada et al. (2005) | Open trial | MDD = 20 | 4 weeks | Existing antidepressants + Jio-zai (15 g) | None | Clinically significant improvement in 60%, but only 30% were much improved. No p values were reported. |
| *SAM-e* | | | | | | | |
| [22] | Papakostas et al. (2010) | DBRCT | TRD = 73 | 6 weeks | Existing SSRIs/SNRIs + SAM-e (1,600 mg) | Existing SSRIs/SNRIs + placebo | SAM-e > placebo in response ($p = 0.01$) and remission ($p = 0.02$). |
| [23] | Alpert et al. (2004) | Open trial | TRD = 45 | 6 weeks | Existing SSRIs/SNRIs + SAM-e (800–1,600 mg) | None | Significant improvement ($p < 0.0001$). |

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|---|---|---|---|---|---|---|---|
| *DHEA* | | | | | | | |
| [24] | Woklowitz et al. (1999) | DBRCT | Total = 22<br>MDD = 20<br>Bipolar II depression = 2<br>Medicated = 15<br>Unmedicated = 7 | 6 weeks | DHEA (30–90 mg)<br>Existing antidepressants + DHEA (30–90 mg) | Placebo<br>Existing antidepressants + placebo | Both DHEA groups > placebo groups ($p < 0.04$). |
| *Tryptophan* | | | | | | | |
| [25] | Levitan et al. (2000) | DBRCT | MDD = 30 | 8 weeks | Fluoxetine (20 mg) + l-tryptophan (1–4 g) | Fluoxetine (20 mg) + placebo | Earlier improvement with tryptophan ($p < 0.001$), but tryptophan = placebo at end of treatment. |
| [26] | Lam et al. (1997) | Open trial | Seasonal affective disorder = 16, resistant to previous light therapy | 2 weeks | Existing light therapy + l-tryptophan (3 g) | None | Significant improvement ($p < 0.001$). |
| *Folate* | | | | | | | |
| [27] | Coppen et al. (1986) | DBRCT | Total = 75 (not clinically depressed, mean baseline BDI = 8)<br>Unipolar depression = 53<br>Bipolar disorder = 17<br>Schizoaffective disorder = 5 | 12 months | Existing lithium + folic acid (200 μg) | Existing lithium + placebo | Folic acid > placebo only for unipolar depression ($p < 0.02$). Results limited by non-symptomatic patient sample. |
| [28] | Godfrey et al. (1990) | DBRCT | Total = 41<br>MDD = 24<br>Schizophrenia = 17 | 6 months | Existing TCAs/MAOIs + methylfolate (15 mg) | Existing TCAs/MAOIs + placebo | Folate > placebo ($p < 0.01$). |

(continued)

**Table 11.2** (continued)

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| [29] | Coppen and Bailey (2000) | DBRCT | MDD = 127 | 10 weeks | Fluoxetine (20 mg) + folic acid (500 μg) | Fluoxetine (20 mg) + placebo | Folic acid > placebo for female patients ($p<0.005$). |
| [30] | Alpert et al. (2002) | Open trial | TRD = 22 | 8 weeks | Existing SSRIs + folinic acid (15–30 mg) | None | Significant improvement ($p<0.01$), but low response (27%) and remission (18%) rates. |
| [31] | Resler et al. (2008) | DBRCT | MDD = 27 | 6 weeks | Fluoxetine (20 mg) + folic acid (10 mg) | Fluoxetine (20 mg) + placebo | Folic acid > placebo ($p=0.04$). |
| [32] | Basoglu et al. (2009) | Open trial, randomized | MDD = 35 | 6 weeks | Escitalopram (10 mg) + folic acid (2.5 mg) | Escitalopram (10 mg) | Escitalpram alone > folic acid combination ($p=0.016$). |
| [33] | Ginsberg et al. (2011) | Retrospective analysis | MDD = 242<br>Monotherapy = 147<br>Combination = 95 | Variable | SSRIs/SNRIs + l-methylfolate (7.5 mg or 15 mg) | SSRIs/SNRIs | Methylfolate combination > SSRIs/SNRIs alone in response ($p<0.01$), onset of |
| *Inositol* | | | | | | | |
| [34] | Taylor et al. (2004) | Meta-analysis | Total = 4 (unipolar depression, bipolar depression)<br>Monotherapy = 1<br>Augmentation = 2 | 4–6 weeks | Inositol<br>Existing SSRIs + inositol | Placebo<br>Existing SSRIs + placebo | Inositol groups = placebo groups. |
| [35] | Levine et al. (1999) | DBRCT | MDD = 27 | 4 weeks | SSRIs + inositol (12 g) | SSRIs + placebo | Inositol = placebo. |
| [36] | Nemets et al. (1999) | DBRCT | MDD = 42 | 4 weeks | Existing SSRIs + inositol (12 g) | Existing SSRIs + placebo | Inositol = placebo. |
| *Zinc* | | | | | | | |

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|---|---|---|---|---|---|---|---|
| [37] | Lai et al. (2012) | Meta-analysis | Total = 4<br><br>Combination = 2 (healthy volunteers) + 2 (unipolar depression) | 10–12 weeks | Multivitamins with zinc<br><br>Existing antidepressants + zinc | Multivitamins<br><br>Existing antidepressants + placebo | Mixed results for zinc in healthy subjects. Zinc > placebo for depression ($p < 0.00001$). |
| [38] | Novak et al. (2003) | DBRCT | MDD = 14 | 12 weeks | SSRIs/TCAs + zinc (25 mg) | SSRIs/TCAs + placebo | Zinc > placebo ($p < 0.05$). |
| [39] | Siwek et al. (2009) | DBRCT | MDD = 60 | 12 weeks | Imipramine (40 mg) + zinc (25 mg) | Imipramine (40 mg) + placebo | Zinc = placebo. Zinc > placebo for TRD subgroup only at midpoint ($p < 0.05$), but with trend at endpoint ($p = 0.056$) in TRD subgroup. |
| *Amino acid formulations* | | | | | | | |
| [40] | Ille et al. (2007) | DBRCT | MDD = 40 | 4 weeks | Mirtazapine (30–60 mg) + amino acid mixture (15 g) | Mirtazapine (30–60 mg) + placebo | Amino acids > placebo in clinical improvement ($p < 0.0001$) and response ($p = 0.002$), but only numerically, not statistically, superior in remission rates. |

[a]Results statistically significant at $p < 0.05$

**Table 11.3** Evidence for CAM therapies as augmentation in bipolar disorder

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| *Herbal compound: FEWP* | | | | | | | |
| [41] | Zhang et al. (2007a) | DBRCT | Total = 235<br>Bipolar depression = 124<br>Bipolar mania = 111 | 12 weeks | CBZ (300 mg) + FEWP (36 mg) | CBZ (300 mg) + placebo<br>Placebo | Depression: CBZ + FEWP > CBZ + placebo ($p = 0.032$) > placebo alone ($p = 0.044$).<br>Mania: CBZ + FEWP = CBZ + placebo, and > placebo ($p < 0.05$). |
| [42] | Zhang et al. (2007b) (Contination phase of Zhang et al. 2007a) | DBRCT | Total = 188<br>Bipolar depression = 93<br>Bipolar mania = 84 | 26 weeks | CBZ (300 mg) + FEWP (36 mg) | CBZ (300 mg) + placebo | CBZ + FEWP = CBZ + placebo for continued improvement. CBZ + FEWP > CBZ + placebo for discontinuation ($p = 0.009$). |
| [20] | Qin et al. (2011) | Meta-analysis | Total = 14 (unipolar depression, bipolar depression)<br>Monotherapy = 6<br>Combination = 8 | 4–12 weeks | FEWP<br>Existing psychotrop- | Placebo or Psychotropics<br>Existing psychotropics | FEWP monotherapy > placebo ($p < 0.00001$), and = psychotropics. FEWP combination > to psychotropics alone ($p < 0.009$). |
| *Omega-3 fatty acids* | | | | | | | |
| [43] | Sarris et al. (2012) | Meta-analysis | Total = 6 (bipolar depression)<br>Augmentation = 6 | 4–16 weeks | Existing psychotropics | Existing psychotropics + placebo | Omega-3 > placebo for bipolar depression ($p < 0.029$), but not for mania ($p < 0.099$). |
| *DHEA* | | | | | | | |

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|---|---|---|---|---|---|---|---|
| [24] | Woklowitz et al. (1999) | DBRCT | Total = 22<br>MDD = 20<br>Bipolar II depression = 2<br>Medicated = 15<br>Unmedicated = 7 | 6 weeks | DHEA (30–90 mg)<br>Existing antidepressants + DHEA (30–90 mg) | Placebo<br>Existing antidepressants + placebo | Both DHEA groups > placebo groups ($p < 0.04$). |
| *Choline* | | | | | | | |
| [44] | Lyoo et al. (2003) | DBRCT | Rapid cycling bipolar disorder = 8 | 12 weeks | Existing lithium + choline bitartrate (15–30 g) | Existing lithium + placebo | No treatment effects on depression or mania. |
| [45] | Stoll et al. (1996) | Open case series | Rapid cycling bipolar disorder = 6 | Not well reported. Potentially 1–16 weeks | Existing lithium + choline bitartrate (15–30 g) | None | Clinically significant improvement in depression and mania, but no p values reported. |
| *Folate* | | | | | | | |
| [27] | Coppen et al. (1986) | DBRCT | Total = 75 (not clinically depressed, mean baseline BDI = 8)<br>Unipolar depression = 53<br>Bipolar disorder = 17<br>Schizoaffective disorder = 5 | 12 months | Existing lithium + folic acid (200 μg) | Existing lithium + placebo | Folic acid > placebo only for unipolar depression ($p < 0.02$). Results limited by non-symptomatic patient sample. |

(continued)

**Table 11.3** (continued)

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| [46] | Behzadi et al. (2009) | DBRCT | Mania = 88 | 3 weeks | Valproate (900–1,600 mg) + folic acid (3 g) | Valproate (900–16 mg) + placebo | Both groups improved ($p < 0.0001$); folic acid > placebo only at week 3 ($p = 0.005$). |
| *Inositol* | | | | | | | |
| [34] | Taylor et al. (2004) | Meta-analysis | Total = 4 (unipolar depression, bipolar depression) | 4–6 weeks | Inositol | Placebo | Inositol groups = placebo groups. |
| | | | Monotherapy = 1<br>Augmentation = 2 | | Existing SSRIs + inositol | Existing SSRIs + placebo | |
| [47] | Chengappa et al. (2000) | DBRCT | Bipolar depression = 24 | 6 weeks | Existing mood stabilizers + inositol (12 g) | Existing mood stabilizers + placebo | Inositol = placebo. |
| [48] | Eden Evins et al. (2006) | Two phases: DBRCT, then open label continuation | Bipolar depression = 17 | RCT: 6 weeks | RCT: Existing mood stabilizers + inositol (9.5–16.5 g) | RCT: Existing mood stabilizers + placebo | DBRCT: Inositol = placebo; with trend for inositol ($p = 0.053$). |
| | | | | Open: 8 weeks | Open: Existing mood stabilizers + inositol (9.5–16.5 g) | | Open: Generally positive results with inositol, but no significance values reported. |

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|---|---|---|---|---|---|---|---|
| [49] | Nierenberg et al. (2006) | Open trial, randomization | Bipolar depression = 66 | Up to 16 weeks | Existing psychotropics (mood stabilizers + at least 1 antidepressant) + | Existing psychotropics + lamotrigine (150–250 mg)<br>Existing psychotropics + risperidone (1–6 mg) | Inositol = lamotrigine = risperidone. |
| *Magnesium* | | | | | | | |
| [50] | Heiden et al. (1999) | Open case series | Bipolar mania = 10 | 1–3 weeks | Existing mood stabilizers or benzodiazepines + IV magnesium sulfate (200 mg/h) | None | Clinically significant improvement, but no p values reported. |
| [51] | Giannini et al. (2000) | DBRCT | Bipolar mania = 20 | 16 weeks | Existing verapamil + magnesium oxide (375 mg) | Existing verapamil + placebo | Magnesium > placebo ($p = 0.02$) |
| *Amino acid formulations* | | | | | | | |
| [52] | Scarna et al. (2003) | DBRCT | Bipolar mania = 25 | 1 week | Existing psychotropics (antipsychotics and/or mood stabilizers and/or benzodiazepines) + branched-chain amino acid drink (60 g) | Existing psychotropics + placebo | Amino acid = placebo at end of treatment. However, amino acid > placebo for early onset of action ($p = 0.02$), and at 1-week follow-up ($p < 0.01$). |

(continued)

**Table 11.3** (continued)

| Refs. | Study | Type | N | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| *NAC* | | | | | | | |
| [53] | Berk et al. (2008) | DBRCT, maintenance study | Bipolar disorder = 75<br>Euthymic = 37<br>Depressed = 27<br>Manic = 11 | 6 months | Existing psychotropics + NAC (2 g) | Existing psychotropics + placebo | NAC > placebo for depression ($p = 0.002$), quality of life ($p = 0.006$) and functioning ($p = 0.002$), but only a trend for NAC in mania |
| [54] | Berk et al. (2011) | Two-phase maintenance study: | Bipolar depressed | Open: 2 months | Open: Existing psychotropics + NAC (2 g) | RCT: Existing psychotropics + placebo | Open: Significant improvement in depressive symptoms ($p < 0.001$) and quality of life ($p < 0.05$), with trend in mania ($p = 0.078$). |
| | | Open label, then DBRCT<br>Only open data currently published | Open = 149<br>RCT = pending | RCT: 6 months | RCT: Existing medications + NAC (2 g) | | DBRCT: Results pending. |
| *Nutraceutical compound: EMP+* | | | | | | | |
| [55] | Kaplan et al. (2000) | Open case series | Bipolar disorder = 11<br>Medicated = 10<br>Unmedicated = 1 | 6 months | Existing psychotropics + EMP + (32 capsules)<br>EMP + (32 capsules) | None | Significant improvement in depressive ($p < 0.01$) and mania ($p < 0.01$), and medication use reduced by >50% ($p < 0.01$). |

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|---|---|---|---|---|---|---|---|
| [56] | Popper (2001) | Open case series | Bipolar disorder = 22 (10 adults, 12 children and adolescents)<br>Medicated = 15<br>Unmedicated = 7 | Up to 6–9 months | Existing psychotropics + EMP + (32 capsules)<br>EMP + (32 capsules) | None | Clinically significant improvement in 45%; 73% of medicated patients discontinued psychotropics. No p values reported. |
| [57] | Simmons (2003) | Open case series | Bipolar disorder = 19 (treatment-resistant)<br>Medicated = 16<br>Unmedicated = 3 | Up to 13 months | Existing psychotropics + EMP + (32 capsules)<br>EMP + (32 capsules) | None | Clinically significant improvement in 63%; 69% of medicated patients discontinued psychotropics. No p values reported. |
| [58] | Rucklidge et al. (2010) | Database analysis | Bipolar disorder = 120 (children and adolescents)<br>Medicated = 95<br>Unmedicated = 25 | 3–6 months | Existing psychotropics + EMP + (32 capsules)<br>EMP + (32 capsules) | None | Significant improvement ($p<0.001$); 52% of medicated patients stopped psychotropics while the rest reduced medication use by 74%. |

[a]Results statistically significant at $p<0.05$

**Table 11.4** Evidence for CAM therapies as augmentation in anxiety disorders

| Refs. | Study | Type | *N* | Duration | Agent | Comparator | Efficacy results[a] |
|---|---|---|---|---|---|---|---|
| Generalized anxiety disorder | | | | | | | |
| *Kava kava* | | | | | | | |
| [59] | De Leo et al. (2001) | DBRCT | GAD = 40 | 6 months | HRT (50 μg) + kava kava (100 mg)<br>ERT (50 μg) + kava kava (100 mg) | HRT (50 μg) + placebo<br>ERT (50 μg) + placebo | Kava groups > placebo groups ($p < 0.05$). |
| *Magnesium* | | | | | | | |
| [60] | Hanus et al. (2004) | DBRCT | GAD = 264 | 3 months | Elemental magnesium + hawthorn + California poppy (375 mg) | Placebo (375 mg) | Magnesium combination > placebo ($p = 0.005$). |
| Obsessive-compulsive disorder | | | | | | | |
| *Omega-3 fatty acids* | | | | | | | |
| [61] | Fux et al. (2004) | DBRCT, cross-over design | OCD = 11 | 12 weeks | Existing SSRIs + Omega-3 fatty acids (EPA 2 g) | Existing SSRIs + placebo | EPA = placebo. |
| Inositol | | | | | | | |
| [62] | Fux et al. (1999) | DBRCT, cross-design | OCD = 10 | 12 weeks | Existing SRIs + inositol (18 g) | Existing SRIs + placebo | Inositol = Placebo. |
| [63] | Seedat and Stein (1999) | Open trial | OCD = 10 | 6 weeks | Existing SRIs + inositol (18 g) | None | No significant improvement. |
| Post-traumatic stress disorder | | | | | | | |
| *Omega-3 fatty acids* | | | | | | | |
| [64] | Zeev et al. (2005) | Open trial | PTSD = 6<br>Medicated = 4<br>Unmedicated = 2 | 3 months | Existing SSRIs + Omega-3 fatty acids (EPA 2 g)<br>Omega-3 fatty acids alone (EPA 2 g) | None | No improvement with EPA. |

[a]Results statistically significant at $p < 0.05$

A number of randomized controlled trials (RCTs) and meta-analyses have supported the efficacy of St. John's wort as a monotherapy for mild to moderate unipolar depression, against both placebo and antidepressant comparators [e.g. 69, 70]. Surprisingly, it has not yet been evaluated as add-on to psychotropic medications, but the literature does report on two studies of St. John's wort in combination with other herbs for MDD and co-morbid anxiety. Among these, one small cross-over placebo-controlled RCT evaluated the combination of kava kava (*Piper methysticum*), a leafy plant though to have similar mood modulating effects [71], with St. John's wort. The St. John's Wort + kava kava combination was significantly superior to placebo alone in reducing depressive symptoms in the initial phase, but there were no group differences in the second phase, after cross-over [16]. Neither treatment improved anxiety symptoms, and though no serious side effects were reported, drop out rates were high, likely due to lack of efficacy. In a second, large open trial, patients were randomized to low-dose or high-dose valerian (*Valeriana officinalis*), another flowering plant with putative antidepressant and anxiolytic properties [72], combined with St. John's Wort [17]. Depressive and anxiety symptoms improved significantly and comparably in both treatment groups, though exact significance values were not reported [17]. The combination was well tolerated.

St. John's wort has been evaluated only to a limited extent in anxiety conditions. Small placebo-controlled RCTs found no benefit to St. John's wort monotherapy in SAD or OCD subjects [73, 74], though a small positive open trial in OCD [75] and case reports in GAD [76, 77] have suggested some benefits. No studies were found of St. John's wort as augmentation or combination for anxiety disorders.

Thus, St. John's wort has only preliminary evidence as add-on to valerian for the treatment of depression and co-morbid anxiety, though it can be questioned whether the lack of a placebo control influenced results. As well, despite its seeming tolerability in these studies, caution has been advised in its use in clinical practice. Adverse effects include photosensitivity and drug interactions, leading to reduced efficacy of immunoregulatory compounds, anticoagulants, anti-infective agents, and oral contraceptives, which is attributed in part to its effect on cytochrome P450 enzymes [78]. As well, serotonin syndrome when used in combination with antidepressants [79] and induction of mania and hypomania have also been reported in the literature [80].

#### 11.2.1.2 Lavender

Lavender (*Lavandula angustifolia*) is a flowering plant from the mint family, and is popularly used for extraction of essential oils for perfumes and aromatherapy. In herbal medicine, it is used as a relaxant, appetite stimulant and an anti-spasmodic [81]. Its active ingredients include linalool and linalyl acetate and its potential neuropsychiatric action is thought to be multimodal, via its effects on gamma-aminobutyric acid (GABA) receptors, as well as glutaminergic and cholinergic systems and ion channel functioning [81].

Monotherapy trials of lavender in depressive disorders are lacking, but one augmentation study was found. A small, 3-arm, placebo-controlled RCT found significant benefit in MDD symptoms with all treatments, but impramine + lavender was superior to imipramine + placebo, with lavender + placebo showing least efficacy [19]. Reported side effects were mild and transient.

In anxiety disorders, a recent small review of the few available monotherapy trials found lavender superior to placebo (for subsyndromal anxiety), as effective as benzodiazepines (in GAD), and well tolerated see review [81]. However, there are no published studies of lavender as augmentation or combination for anxiety conditions.

Lavender shows preliminary evidence of benefit in combination with medication for MDD, which needs confirmation through larger RCTs. It has also generally been well tolerated, except for a few reported cases of allergic reaction (dermatitis) and gastrointestinal symptoms after excessive intake [81, 82].

#### 11.2.1.3 Kava Kava

Kava kava (*Piper methysticum*) is a leafy plant whose roots are ground for herbal medicine purposes, primarily for mental and physical relaxation [83]. Its active ingredients are proposed to be several kavalactones, which are still being individually isolated [68, 83]. The kavalactones are proposed to act on GABAergic and ß-adrenergic systems, and on monoamine oxidase B (MAO-B) activity, mediating its neuropsychiatric effects [68]. In addition, effects on several monoaminergic systems have also been proposed, all of which suggests it may benefit both depressive and anxiety conditions [71].

Kava kava has not been evaluated as monotherapy or augmentation to medications in depressive disorders. However, it has been investigated in combination with other herbs in two studies of unipolar depression with co-morbid anxiety. One small placebo-controlled RCT, with a St. John's wort + kava kava combination (previously described), had inconclusive results [16]. In a small open trial, patients randomized to calcium combined with high-dose or low-dose kava kava showed significantly greater benefit for anxiety than those on calcium alone, but all three groups showed significant and similar reduction in depression [18]. Side effects were mild and tolerable. A limitation of the study is that patients were included based only on self-reported moderate anxiety and subsyndromal depressive symptoms, and not evaluated by objective ratings.

Though placebo-controlled RCTs in anxiety disorders have had mixed results with kava kava monotherapy [66], a single open label monotherapy trial had positive results [84] and the only medication comparator RCT found it as effective as conventional anxiolytics [85]. Small meta-analyses of six monotherapy RCTs each have found it superior to placebo in reducing anxiety, though effect sizes were small [86, 87]. No studies have evaluated kava kava as add-on to pharmacotherapy in anxiety disorders, but one study has investigated its benefit in combination with non-psychotropics. In a small RCT, GAD symptoms in menopausal women

improved significantly more with the combination of hormone replacement therapy (progesterone included [HRT] or excluded [ERT]), with kava kava, than with HRT + placebo or ERT + placebo [59]. Subjects did not report any side effects.

The limited literature suggests that kava kava's proposed utility in depression has not been substantiated, but it may have some potential benefit as a combination agent for anxiety conditions. No serious side effects were reported in the above studies, however, recent case reports of liver toxicity have raised concerns about its long-term use, and have led to its being withdrawn from markets in several countries [83, 88]. Excessive intake has also been linked to skin and neurological disorders, and rare cases of drug-drug interactions, including with psychotropics, anticonvulsants, and drugs for neurological, kidney or liver function, have been reported [88, 89].

#### 11.2.1.4 Herbal Compounds

Herbal compounds consist of herbs with individual health-promoting properties, which are thought to have synergistic effects when combined into a single product. Several reports have evaluated herbal compounds as adjunct in depressive disorders, but there are no such studies in anxiety conditions.

Among available publications, two large RCTs evaluated the efficacy of a well-established Chinese polyherbal compound called Free and Easy Wanderer Plus (FEWP) in bipolar disorder. Its 11 ingredients are reported to act on multiple monoaminergic and benzodiazepine receptors, as well as neurosteroid and cytokine function, accounting for its antidepressant and anxiolytic effects [90–92]. A three-arm RCT found the combination of carbamazepine (CBZ) and FEWP more effective than CBZ + placebo in improving bipolar depressive symptoms, with placebo alone being least useful [41]. The CBZ combination groups also improved mania significantly, compared to placebo. Reported side effects were mild, with CBZ + FEWP better tolerated than CBZ + placebo, suggesting that FEWP may alleviate some of the adverse effects of CBZ. A continuation phase included only the CBZ combination groups and found that further symptom improvement was comparable between groups, but that discontinuation rates were much lower with CBZ + FEWP [42]. It should be noted that FEWP has been investigated in several RCTs in depressive disorders published only in Chinese, which are therefore not reviewed in this chapter; Results from these mostly positive studies were included in a recent large systematic review of 26 studies [93] and a meta-analysis of 14 studies (which included 8 augmentation studies) [20]. While the former included small studies with methodological issues [94], publications for the meta-analysis were selected more rigorously [20]. Both reports found FEWP to be effective and tolerable as monotherapy and augmentation to medication in various depressive disorders, including major depression, dysthymia and bipolar depression [20, 93], and was also better tolerated (as monotherapy or augmentation) than conventional agents alone [20]. FEWP has no published reports as monotherapy or augmentation in anxiety disorders.

Among other reports, a small open trial augmentation of current antidepressants with a Japanese herbal compound, Jio-zai (a combination of two other well-established compounds, Rokumigan and Hachimijiogan), was found to reduce residual symptoms in MDD, but only a small percentage of patients were reported to be "much improved" [21]. Statistical significance of efficacy was not reported. Side effects were few and tolerable. The mechanism of antidepressant action of the compound, or its ingredients, is unclear. There are no reports of Jio-zai as monotherapy in depressive, nor any reports (as monotherapy or augmentation) in anxiety conditions.

While FEWP has reasonable evidence of benefit as an augmentation agent in both unipolar and bipolar depression, there is insufficient evidence to evaluate Jio-zai. Though both compounds were well tolerated, the sparse safety data available in English publications, and their limited use outside their countries of origin, would encourage caution in clinical use.

## *11.2.2 Nutraceuticals*

Nutraceuticals are non-prescription, natural health products that are usually concentrated forms of naturally occurring substances, such as vitamins and minerals. They are often used individually or in combination to support good nutrition and general wellness. A literature search on the use of nutraceuticals as adjunctive agents found information relating to omega-3 fatty acids, S-adenosylmethionine (SAM-e), Dehydroepiandrosterone (DHEA), tryptophan, the B vitamins, inositol, magnesium, zinc, amino acid formulations, and proprietory vitamin-mineral formulations.

Several other nutraceuticals that have been evaluated only as monotherapy in depressive and anxiety disorders, and are therefore not reviewed in this chapter, include alpha-lactalbumin (a tryptophan-rich protein fraction), acetyl-L-carnitine (a modified amino acid and acetyl ester of quaternary ammonium compound, L-carnitine) and lysine (an amino acid and precursor of L-carnitine) see reviews [9, 66, 67].

### 11.2.2.1 Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids involved in multiple biological systems, including the nervous system. Omega-3 fatty acid formulations include highly purified estyl esters of eicosapentanoic acid (EPA) or docosahexaenoic acid (DHA) or a combination of both. Their possible neuropsychiatric effect may result from modulation of neuronal communication and their impact on monoaminergic neural systems [94, 95]. A large meta-analysis of 14 studies recently noted a correlation between low omega-3 levels and depressive disorders [96], and low omega-3 levels have also been linked to anxiety conditions [97–99].

The efficacy of omega-3 fatty acids as monotherapy or augmentation in depressive disorders has been the subject of several medium-size meta-analyses that included seven to nine studies each. In both unipolar and bipolar depression, results

from several meta-analyses that included both monotherapy and augmentation studies have been inconclusive, with significant heterogeneity between studies noted, as well as speculation about publication bias, with positive results more likely to be reported than negative ones [e.g. 100–102]. The meta-analyses included studies from a range of diagnostic categories, e.g. unipolar and bipolar depression, schizophrenia, as well as other psychiatric or medical conditions in which depressed mood was exhibited, which may have affected results. However, a recent meta-analysis that focused only on six augmentation studies in bipolar disorder reported clear benefit for omega-3 as add-on to antidepressants or mood stabilizers for bipolar depression, but only a trend favouring it as augmentation in mania [43]. The study populations were more homogeneous, and the likelihood of publication bias was noted to be low, though effect sizes were larger in studies with smaller samples. In all studies, omega-3 fatty acids were well tolerated, with reported side effects being mild.

The question has also been raised about which of the omega-3 fatty acids is more useful in depression. Meta-analyses suggest that EPA may be more effective than DHA or EPA + DHA, but due to confounding factors (i.e. degree of baseline depressive severity and variability of omega-3 formulation used), definitive conclusions could not be reached [103, 104].

There are no monotherapy trials of omega-3 fatty acids in anxiety disorders. Data on their use as augmentation is limited to two studies. In one small cross-over RCT, there was no reduction in OCD symptoms with either EPA or placebo augmentation of SSRIs, though EPA was well tolerated [61]. Similar non-efficacy but good tolerability of EPA (as monotherapy or augmentation to SSRIs) was seen in a small open-label case series in PTSD [64].

In conclusion, omega-3 fatty acids have moderate evidence of benefit in depressive disorders, with more robust effects seen in bipolar samples. There is no current evidence for its benefit in anxiety disorders. The mild side effects reported with omega-3 use include diarrhoea, nausea and a fishy aftertaste, but these rarely lead to discontinuation [105, 106]. While there is also evidence to support its cardioprotective benefits [107], it has been noted to increase bleeding tendencies among patients on the anticoagulant, coumadin (warfarin) and anti-platelet medications (acetylsalicylic acid, clopidogrel), with a need for monitoring [108]. Induced hypomania has been reported in a few cases, but this risk has not been noted in systematic reviews or meta-analyses of studies in bipolar depression [e.g. 43, 101, 109].

#### 11.2.2.2 S-Adenosylmethionine (SAM-e)

SAM-e is a naturally occurring molecule found in the body and a derivative of the amino acid, methionine. It serves as a methyl donor in many biological processes [110]. As with several other CAM agents, its benefits has been attributed to its enhancement of monoaminergic neurotransmission [110]. However, studies that examined the association between low SAM-e levels and depression have had mixed results [111–113]. Synthetic SAM-e is available as a non-prescription oral natural health product in North America, but requires medical prescription in Europe.

While several systematic reviews and meta-analyses support the benefit of SAM-e as monotherapy in unipolar depression (as superior to placebo and comparable to TCAs) [e.g. 114–116], only two studies of adjunctive SAM-e in depressive disorders were found, and none in anxiety. In one small RCT in treatment-resistant major depression (TRD), SAM-e augmentation of SSRIs or selective norepinephrine reuptake inhibitors (SNRIs) produced significantly higher response and remission than placebo add-on [22]. Side effects were mild, and discontinuation due to adverse effects was similar between groups, but that due to lack of efficacy was higher with placebo. Similar efficacy and tolerability were noted in a small open trial of oral SAM-e augmentation to SSRIs/SNRIs in TRD [23].

No data was found for SAM-e as monotherapy or augmentation in anxiety disorders.

The limited data above offers only preliminary support for SAM-e as augmentation in TRD, but further investigation is encouraged by the evidence for its benefit as monotherapy. SAM-e is generally well tolerated with few adverse events, which include nausea, jitteriness, and loose stools [106]. Case reports suggests the risk of induction of manic episodes in vulnerable patients, and of serotonin syndrome when it is added to first-line antidepressants [117], though neither have been reported in systematic reviews or in the studies described above.

#### 11.2.2.3 Dehydroepiandrosterone (DHEA)

DHEA is a natural adrenosteroid that converts to the sex hormones, testosterone and estrogen, in the body. Often used as an anti-aging supplement (though with uncertain benefits) [118], it is thought to modulate monoaminergic and glutaminergic neurotransmission, as well as provide neuroprotective and anti-oxidant benefits [119–121]. The association between DHEA levels and affective symptomatology is unclear; some studies have linked low DHEA levels to depressive symptoms [122, 123], while others have found an association with high DHEA levels [124, 125]. Curiously, both low and high DHEA levels have been linked to depressive symptoms in women [126, 127]. High levels of DHEA have also found in anxiety conditions [128, 129].

The literature on the use of DHEA in depressive disorders is very small. The few published monotherapy studies have reported benefits in MDD and dysthymia [130–132]. Only one augmentation study in depressive disorders was found. In that small RCT, DHEA (either as monotherapy or augmentation to antidepressants) significantly improved depressive symptoms in unipolar and bipolar patients, compared to placebo, and was also well tolerated [24]. Of note, the bipolar sample was limited to two patients.

No published data was found for DHEA as monotherapy or augmentation in anxiety disorders.

This pilot data suggest that further investigation of DHEA an augmenting agent in mood disorders may be fruitful. Though no serious side effects were reported in

the above studies, DHEA, as a precursor of more potent sex hormones, has potential for side effects that may include acne and hirsutism, and several studies have excluded patients with prostatism or family history of breast cancer [130, 131]. Safety data also suggest monitoring for potential effects of DHEA on blood clotting, liver damage, induction of mania in vulnerable individuals, and dose-related increase in adverse effects [133, 134].

#### 11.2.2.4 Tryptophan

Tryptophan is a dietary amino acid that is converted to 5-hydroxy tryptophan (5-HTP) and then into serotonin (5-HT), both centrally and peripherally. Thus, it is thus thought to enhance serotonergic neurotransmission through "precursor loading" [135]. It is a prescription drug in Canada, and recently was reintroduced in the US. Tryptophan depletion is associated with worsening of mood and cognitive functioning both in patients with a history of depression and those at risk for depression [136, 137]. In studies, tryptophan has been used in both 5-HTP and l-tryptophan formulations.

Several early studies have evaluated 5-HTP as monotherapy or augmentation to SSRIs and TCAs in unipolar and bipolar depression, with generally positive results seen in the mostly monotherapy open trials, but equivocal results in 'blinded' RCTs see review [138]. However, a small monotherapy meta-analysis [135] and a large review (that included six augmentation studies) [138] noted the many methodological flaws in the included studies (all published prior to 1992) and reported inconclusive efficacy of 5-HTP [135, 138]. More recently, a small placebo-controlled RCT found fluoxetine + l-tryptophan combination produced early onset of improvement in MDD, but which was not sustained to endpoint, though the combination was well tolerated [25]. A small open CAM study found l-tryptophan augmentation significantly improved depressive symptoms in patients with seasonal affective disorder who did not initially respond to light therapy, and it was also well tolerated [26]. However, due to the lack of a comparison group, it can be questioned whether longer treatment with light therapy alone might have produced a similar result.

In anxiety disorders, the data on tryptophan is very sparse. One early RCT found 5-HTP monotherapy no different from placebo and inferior to TCAs for PD [139]. There are no studies of tryptophan as add-on in anxiety conditions.

The preliminary support for tryptophan as an augmenting agent in depressive disorders needs verification through further RCTs. It has no evidence of benefit in anxiety disorders at this time. Side effects usually reported with tryptophan include drowsiness, dry mouth, nausea, and other gastrointestinal symptoms, but reports of serotonin syndrome are relatively rare in RCTs [135, 138]. In 1989, tryptophan ingestion was associated with an outbreak of Eosinophilia-Myalgia Syndrome that resulted in significant mortality, but this was attributed to a contaminated batch from a single manufacturer, and no such reports have emerged since then [135, 138].

#### 11.2.2.5 The B Vitamins

The water-soluble B vitamins are found in foods and are vital to the growth, division and metabolism of cells, as well as for immune and nervous system functioning. They consist of thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid or folate (B9) and assorted cobalamins (B12). Vitamin B9 (folate) is implicated in monoaminergic synthesis [140], and is the most studied as a CAM therapy, but Vitamins B6 and B12 have also been investigated. Folate and Vitamin B12 are both necessary for production of homocysteine which is converted to methionine, a precursor to S-adenosyl methionine, which is a methyl donor involved in neurotransmitter function [140, 141]. Several studies have noted low levels of folate (in particular) and Vitamin B12 in depressed patients [e.g. 142, 143], though others have failed to confirm this association [e.g. 144, 145]. Similarly, studies evaluating the association between low Vitamin B6 levels and depression have had both positive [e.g. 146, 147] and negative [e.g. 144, 145] results. No associations have been noted between these B vitamins and anxiety disorders, thus far. Other research has focused on choline, a nutrient in the B vitamin family that is a precursor for the neurotransmitter, acetylcholine, and which also supports phosphate production in the brain [44]. Low levels of acetylcholine and of phosphates have been linked to mania [44, 148], as have low levels of choline [45, 149], but the data is not robust. Elevated choline levels have been found in depression [150, 151], while low levels have been correlated with anxiety [152, 153].

*Folate*: Several investigations have evaluated the efficacy of folate in depressive disorders. In an early placebo-controlled RCT, folic acid augmentation significantly improved depressive symptoms in unipolar depressed patients, but not in bipolar or schizophrenia patients [27]. However, the patients were only marginally depressed at the start of the study, which was a limitation. Side effects were comparable and tolerable across groups. Another early placebo-controlled RCT found methylfolate augmentation of tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) significantly superior to placebo in improving depressive symptoms in MDD and schizophrenia, though tolerability data was not reported and sample size was small [28]. Subsequently, an adequately-sized RCT found fluoxetine + folic acid combination superior to fluoxetine + placebo in MDD, but only among female patients, and it was also better tolerated than the placebo combination [29]. This was followed by a small open trial that found folinic acid augmentation of SSRIs to be significantly effective in improving TRD and well tolerated, but only a small percentage of patients achieved response or remission levels [30]. The findings of these four studies were included in recent small systematic reviews of folate in unipolar depression, which found it effective as both monotherapy and augmentation [154, 155], and well tolerated [154]. More recently, folic acid augmentation of fluoxetine was found significantly superior to placebo augmentation in a small RCT in MDD; tolerability data is unknown [31]. Paradoxically, a small open randomized trial found escitalopram monotherapy significantly superior to escitalopram + folic acid combination in MDD, but with tolerability data not reported [32]. A recent large retrospective analysis of 242 cases, which compared the efficacy of l-methylfolate co-initiated with antidepressant therapy to antidepressant therapy alone in MDD,

found that the folate combination was associated with significantly better treatment response, faster onset of improvement and less discontinuation due to side effects than antidepressants alone [33]. In the only study in bipolar disorder, an adequate-sized RCT found that both valproate + folic acid and valproate +placebo combinations significantly improved manic symptoms and were well tolerated; the folic acid combination showed statistical superiority to placebo only at end of the brief treatment period [46]. There is no data on folate as monotherapy or augmentation in anxiety disorders.

*Vitamin B12*: Literature on the use of Vitamin B12 is very sparse. A single early monotherapy RCT found no difference between Vitamin B12 and placebo in seasonal affective disorder [156]. No augmentation or combination studies were found with Vitamin B12 in other mood and anxiety conditions.

*Vitamin B6*: A recent small systematic review of the efficacy of Vitamin B6 as monotherapy or augmentation in unipolar depression found no benefit for its use, and noted limitations of small sample size and heterogeneity of patient populations [157]. The only published augmentation study, a small placebo-controlled RCT which used a B complex vitamin (comprised of Vitamins B1, B2 and B6), as add-on to TCAs, was included in the review, and also had negative results [158]. There are no reports of Vitamin B6 as monotherapy or augmentation in anxiety conditions.

*Choline*: There are no studies of choline monotherapy in depressive disorders. Choline augmentation has been evaluated in bipolar disorder in two studies, with mixed results. In a small open label case series, choline bitartrate augmentation of lithium significantly improved depressive and manic symptoms in most patients and was well tolerated, but important study data was not published, including duration of treatment and statistical significance values [45]. In a small RCT, choline bitartrate or placebo augmentation of lithium had no effect on bipolar depression or mania; no tolerability data was reported [44]. No investigations of choline as monotherapy or augmentation in anxiety conditions are currently available.

Thus, evidence is lacking for Vitamin B6, Vitamin B12 or choline as augmentation in depressive disorders. However, there is reasonable evidence for folate as augmentation or combination to medication for MDD. Folate was well tolerated in all reported studies, and there are no known drug interactions or contradictions to the use of methylfolate [140]. However, there is evidence that high folate doses (>800 mcg) may lead to increased levels of unmetabolized serum folic acid, which can lower levels of natural killers cells and brain l-methylfolate and deplete monoamines, and may worsen depression [140, 154]. Folic acid, in high doses (e.g. 15 μg), has been associated with increased depression in some studies, and sleep difficulties, irritability, hyperactivity and discomfort have also been reported in healthy volunteers [140, 159].

#### 11.2.2.6 Vitamin D

Vitamin D is a fat-soluble secosteroid that is found in foods and is also naturally produced by the body during adequate sun exposure. Essential to bone health, it acts through prevention of bone demineralization and promotion of calcium absorption,

and is also thought to influence cellular and kidney function [160, 161]. It has been postulated that Vitamin D may affect mood through its modulation of serotonin synthesis and glucocorticoid activity, and may also be neuroprotective [162, 163]. While several epidemiological studies have reported an association between low serum vitamin D levels and depression e.g. [164–166], others have not confirmed such links [167, 168]. It has also been suggested that any relationship may be seasonally influenced [169, 170] and may have a female gender skew [171].

Reviews of the limited research on Vitamin D monotherapy in depression have noted only modest benefit in seasonal affective disorder and methodological weaknesses in many of the studies found, limiting the generalizability of results [161, 167]. Thus, the role of Vitamin D in depressive disorders (as a cause, consequence or associate) also remains unelucidated [157, 167]. No published studies have evaluated Vitamin D as an add-on in depressive disorders, or as monotherapy or augmentation in anxiety conditions.

Evidence is currently lacking to recommend Vitamin D as an agent for depressive or anxiety disorders. However, it continues to be recommended as a dietary supplement for general health benefits at a dosage of up to 2,000 IU per day [172]. Toxicity has been reported at dosages over 20,000 IU per day, and has included gastrointestinal symptoms, low appetite and hypercalcemia [172, 173].

#### 11.2.2.7 Inositol

Inositol is a carboxylic polyol, an isomer of glucose that is integral to the production of cellular secondary messengers, such as inositol triphosphate, that mediates neurotransmitter receptor activity, and in turn, intracellular processes [34]. The association between low inositol levels and depression is equivocal, with some studies noting a correlation [174–176], but others not [177]. Low levels of inositol have also been linked to anxiety in animal models [178, 179].

There is a small body of literature on the use of inositol in depressive disorders. No group differences were noted in two small placebo-controlled RCTs of inositol add-on to SSRIs in MDD [35, 36]. It had comparable tolerability to placebo in the first study [35], but in the other, drop out due to side effects (including one case of serotonin syndrome) was greater with inositol than with placebo [36]. In bipolar disorder, a small RCT failed to find group differences between inositol or placebo augmentation of mood stabilizers in bipolar depression, though it was well tolerated [47]. A small meta-analysis of four studies in depressive disorders, which included these three studies (and one placebo-controlled monotherapy RCT), also found no evidence of benefit for inositol as monotherapy or augmentation in unipolar or bipolar depression [34]. More recently, a two-phase study in bipolar depression failed to note any benefit to inositol augmentation of mood stabilizers in its placebo-controlled RCT phase (though a trend favoured inositol) [48]. The subsequent open label continuation phase supported inositol augmentation, though significance values were not reported. Another small open trial, an arm of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, found randomized

augmentation with lamotrigine, inositol or risperidone to be comparable in efficacy and tolerability in bipolar depression [49].

In anxiety disorders, a small review found modest benefits with inositol monotherapy in PD and OCD, with inositol showing superiority to placebo, comparable efficacy to SSRIs, and good tolerability [67]. However, these benefits were not replicated in the only two augmentation studies with inositol, both in OCD. No significant benefit was noted to inositol augmentation of SSRIs/TCAs in either a cross-over placebo-controlled RCT [62], or an open trial [63]. Side effect data, available for only one of the studies, found inositol to be well tolerated [63].

Thus, overall, there is insufficient evidence to recommend inositol as an augmenting agent in either depressive or anxiety disorders. It appears to be well tolerated, but induction of mania or hypomania, and hospitalization due to worsening of psychiatric symptoms, have been reported in case reports, as well as in some patients in clinical trials [35, 47, 48, 180].

#### 11.2.2.8 Magnesium

Magnesium is an essential mineral that is integral to cellular and neuronal functioning in the brain [181]. It modulates both N-methyl-D-aspartic acid (NMDA) and GABA neurotransmission, suggesting a possible route of antidepressant action, but is also thought to modulate HPA axis activity, and thus stress and anxiety pathways [182–184]. Magnesium deficiency is associated with increased vulnerability to stress reactivity, depression and anxiety in animal models [181, 185], and to postpartum depression in humans [186].

Data on magnesium supplementation in mood and anxiety disorders is limited. A recent small review of mostly early studies noted that monotherapy with magnesium supplements appeared to benefit depression, mania and anxiety, but heterogeneity of study populations, variation in formulations used and lack of RCT data limit the value of the findings [187]. Only two augmentation studies were found in depressive disorders, both in bipolar patients. In the first, a small open case series, intravenous (IV) magnesium sulfate augmentation of existing mood stabilizers or benzodiazepines improved refractory mania, though no statistical significance values were reported [50]. Significant side effects of brachycardia (frequent) and burning sensation in the veins (rare) were resolved with reduction in IV dosage. In the other, a small RCT, magnesium oxide augmentation of verapamil was found significantly superior to placebo augmentation for mania, but tolerability data was not reported [51].

Any published evidence for magnesium monotherapy for anxiety symptoms is challenged by methodological flaws, particularly the lack of distinct syndromal anxiety patient samples [187]. In the only add-on study available, a large RCT in GAD combined hawthorn (*Crataegus oxyacantha*; a fruit-bearing shrub), and California poppy (*Eschscholtzia californica*; a flowering plant), both thought to have anxiolytic properties [188, 189], with elemental magnesium and found the combination to be significantly superior to placebo in improving GAD symptoms [60]. Side effects were mild with both treatments.

This preliminary data is promising, but there is currently insufficient evidence to recommend magnesium augmentation for depressive or anxiety disorders. Though magnesium is generally well tolerated in over-the-counter formulations, the absence of long-term safety data is also a cautionary note, in particular as excess intake of magnesium has been linked to gastrointestinal upset and cardiac arrhythmia [186, 190].

#### 11.2.2.9 Zinc

Zinc is an essential mineral that is involved in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) metabolism, signal transduction, and gene expression, and is a component in enzymes, amino acids and proteins [191]. Its exact role in the pathophysiology of mood and anxiety disorders remains unclear. One hypothesis is that deficiency of zinc (found in highest concentrations in the hippocampus and amygdala) [192], leads to reduced hippocampal neurogenesis [193], and in turn to the decreased hippocampal volumes reported with depression and anxiety [194, 195]. Zinc is also suggested to modulate NMDA-receptor activity, pharmacological antagonists of which have been shown to benefit both depression and anxiety [196, 197]. It is also posited to support serotonergic signaling [198, 199], and to improve neuroplasticity by increasing BDNF gene expression [200, 201] and glutathione levels [202], an effect similar to that of antidepressants [203, 204]. Thus, it may have several modes of antidepressant and anxiolytic action. Zinc deficiency is associated with anxiety in animal models [205, 206], while human studies have noted a correlation between zinc deficiency and depression [e.g. 207, 208].

There are no monotherapy studies of zinc as intervention in depressive disorders. A recent small meta-analysis of four studies (two monotherapy studies in healthy subjects and two augmentation RCTs in depressed subjects) found zinc to be superior to placebo as augmentation to SSRIs/TCAs in unipolar depression [37]. However, methodological flaws restrict generalizability of the results. Both RCTs had small MDD samples [38, 39]. Furthermore, in one RCT, the zinc combination was superior to placebo add-on only in the antidepressant-resistant subgroup and only at midpoint, with only a trend to superiority in this subgroup at endpoint [39]. Zinc was well tolerated in both studies.

There are no published studies of zinc as monotherapy or augmentation in anxiety disorders.

This limited but promising data suggest that more and larger placebo-controlled RCTs would be useful to help determine the utility of zinc for depression. In the above studies, zinc supplementation was well tolerated and no drug-drug interactions were reported. However, there are reports of excess zinc consumption being associated with ataxia, lethargy, iron and copper deficiency, and cerebral ischemia [209–211].

#### 11.2.2.10 Other Dietary Supplements

Additional studies on adjunctive use of other dietary supplements in mood and anxiety disorders have reported on the benefits of several amino acid formulations or proprietary vitamin-mineral formulations.

While several amino acids are produced by the body, others are only found in foods. Though mostly known for their key role in protein synthesis, amino acids are also important in many physiological processes, including synthesis of neurotransmitters, by which effect they may influence affective state [212, 213]. Disturbances in amino acid levels have been reported with depression, and improvement in amino acid levels has been seen with antidepressant treatment response [214, 215]. Among individual amino acids, a few small and mostly early RCTs found acetyl-L-carnitine as monotherapy to be superior to placebo and comparable to atypical antipsychotics in unipolar depression, and to be well tolerated [216–219]. However, there is no published data to support its benefit as augmentation. On the other hand, while amino acid formulations have not been evaluated as monotherapy in depressive disorders, there are two augmentation studies in the literature. In a small RCT with an amino acid mixture (comprised of ten amino acids, 11 vitamins and three minerals), response in severe MDD was significantly greater with mirtazapine + amino acid mixture than mirtazapine + placebo, though remission rates and tolerability were similar [40]. Another small RCT found augmentation with a branched-chain amino acid drink (consisting of three amino acids) produced faster onset of improvement in bipolar mania than placebo; group differences disappeared by end of treatment, but re-emerged in favour of amino acids at 1-week follow-up [52]. The amino acid drink was well tolerated. There are no studies of amino acids as monotherapy or augmentation in anxiety disorders.

N-acetylcysteine (NAC) is acetylated derivative of the amino acid, cysteine, which is the precursor of glutathione, the main antioxidant in the brain [220]. Impaired glutathione metabolism is linked to increased oxidative stress, which, in turn, is thought to underl the pathophysiology of several psychiatric disorders, including depression [220, 221]. NAC has no monotherapy data in depressive disorders, but there are two maintenance augmentation studies in bipolar disorder. A small placebo-controlled maintenance RCT found NAC augmentation to existing psychotropics (antidepressants, mood stabilizers, antipsychotics, etc.) produced significant improvement in bipolar depressive symptoms, quality of life and functioning; a trend to improvement in manic symptoms may have been moderated by the low mania scores at study onset [53]. There were no group differences in time to mood episode, and NAC was generally well tolerated. Similar benefits with NAC augmentation of existing psychotropics were also noted in the results from the large open trial stage of a two-phase maintenance RCT by the same research group, though side effect data were not reported [54]. Results of the subsequent double-blind phase are pending. No studies were found with NAC as monotherapy in anxiety disorders, but a single case report suggests its benefit as augmentation to SSRIs [222].

A proprietary nutritional supplement made up of 36 chelated trace vitamins and minerals, called E. M. Power Plus (EMP+), has also been investigated in bipolar disorder. It is thought to alleviate bipolar-like symptoms by correcting nutritional deficiencies that may contribute to metabolic dysfunction [55]. Three case series with adult patients have noted significant improvement in bipolar depressive and manic symptoms with EMP + (as monotherapy or augmentation), leading to significant reduction in psychotropic medication use [55–57]. Only one of the case series reported significance values, but it had a small sample and almost all patients were male, limiting generalizability [55]. In general, EMP + was well tolerated in these studies, with few side effects. Hypomanic switch was reported in two cases, as well as symptom recurrence in some subjects post-study, needing resumption of psychotropics [57]. A recent large database analysis of open label EMP + monotherapy or augmentation in child and adolescent bipolar patients noted similar efficacy and tolerability with EMP+, but lack of RCTs hinder definitive conclusions [58]. A systematic review of the safety and tolerability of EMP + found that it was well tolerated in both adult and youth populations, with mild and transitory GI symptoms and headache most reported, no abnormal lab results or toxicity, and fewer adverse events and lower weight gain than with psychotropics [223]. There is no data on the use of EMP + as monotherapy or augmentation in anxiety conditions.

There is only preliminary evidence for the benefit of amino acid compounds, and due to the variability in formulation between studies, data is insufficient to make recommendations. The pilot data on NAC augmentation for bipolar depression appears promising and if the pending data from the double-blind phase of the latest study [54] is positive, it may support the use of NAC in this disorder. While the preliminary efficacy data with EMP + in bipolar disorder also appears to warrant further placebo-controlled investigations, it must be noted that the only such trial registered on clinicaltrials.gov was discontinued due to recruitment difficulties, large expectancy effects and uninformative results [224]. Side effects reported with the above supplements appear to be mild and tolerable, for most part. However, due to the general paucity of evidence, their utility in clinical practice remains undefined.

## 11.3 Conclusions and Future Directions

Although clinical trials of herbal and dietary supplements as augmentation or combination in mood and anxiety disorders are being increasingly reported, they are still significantly fewer than those with conventional pharmacological agents. As this review has also shown, research on the supplementary use of these compounds is much more common for depressive disorders than for anxiety conditions.

It is of note that despite the general dearth of efficacy and tolerability data with the CAM agents reviewed in this chapter, there is relatively good information on the basic physiological mechanism of action of many of them. Enhancement of monoaminergic

and glutaminergic neurotransmission, impact on HPA axis functioning, and enhanced neurogenesis, have been reported to result from the use of several of these agents, as with conventional antidepressants. Large head-to-head effectiveness trials against first-line antidepressants may prove to be valuable.

Based on the evidence from available studies, the herbal and dietary supplements that appear to hold most promise as adjunctive agents to pharmacotherapy include the herbal supplement, FEWP (in unipolar depression, bipolar depression or mania), and the nutraceuticals, omega-3 fatty acids (in bipolar depression) and folate (in MDD). There is also preliminary evidence of benefit for combination with some other herbal remedies, such as lavandula (in MDD), and dietary supplements, such as SAM-e (in TRD), DHEA (in MDD), magnesium (in mania), zinc (in MDD), amino acid formulations (in unipolar depression and mania), NAC (as maintenance in bipolar depression), and EMP + (in bipolar disorder). Among the other supplements reviewed, St. John's wort (for depression and co-morbid anxiety), kava (for anxiety symptoms), and tryptophan (for seasonal affective disorder) only have data in combination with non-pharmacological agents, thus far. Currently, there is insufficient evidence to support other herbal and nutraceutical agents (i.e. Jio-zai, inositol and Vitamin D) as augmentation for depressive and anxiety disorders.

While these agents were frequently effective and usually well tolerated in published studies, limited numbers of good quality RCTs and/or limited familiarity of use in clinical practice has meant that most guidelines would recommend their use usually as augmentation, and often later in the treatment algorithm. In particular, there is sparse information on their potential interaction with conventional psychiatric drugs, and as such, longer-term efficacy and safety data may help to increase support for wider clinical application.

## References

1. Andrade L, Caraveo-Anduaga JJ, Berglund P et al (2000) Cross-national comparisons of the prevalences and correlates of mental disorders. WHO international consortium in psychiatric epidemiology. Bull World Health Organ 78:413–426
2. Demyttenaere K, Bruffaerts R, Posada-Villa J et al (2004) WHO world mental health survey consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization world mental health surveys. JAMA 291:2581–2590
3. Goldberg JF, Garno JL, Harrow M (2005) Long-term remission and recovery in bipolar disorder: a review. Curr Psychiatry Rep 7:456–461
4. Rush AJ, Fava M, Wisniewski SR et al (2004) Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials 25:119–142
5. Yonkers KA, Bruce SE, Dyck IR et al (2003) Chronicity, relapse, and illness—course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 17:173–179
6. Keller MB, McCullough JP, Klein DN et al (2000) A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 342:1462–1470
7. Zivin K, Madden JM, Graves AJ et al (2009) Cost-related medication nonadherence among beneficiaries with depression following Medicare Part D. Am J Geriatr Psychiatry 17:1068–1076

8. Andreescu C, Mulsant BH, Emanuel JE (2008) Complementary and alternative medicine in the treatment of bipolar disorder—a review of the evidence. J Affect Disord 110:16–26
9. Ravindran AV, Lam RW, Filteau MJ et al (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. J Affect Disord 117(Suppl 1):S54–S64
10. van der Watt G, Laugharne J, Janka A (2008) Complementary and alternative medicine in the treatment of anxiety and depression. Curr Opin Psychiatry 21:37–42
11. Kessler RC, Soukup J, Davis RB et al (2001) The use of complementary and alternative therapies to treat anxiety and depression in the United States. Am J Psychiatry 158:289–294
12. Wahlström M, Sihvo S, Haukkala A et al (2008) Use of mental health services and complementary and alternative medicine in persons with common mental disorders. Acta Psychiatr Scand 118:73–80
13. da Silva TL, Ravindran LN, Ravindran AV (2009) Yoga in the treatment of mood and anxiety disorders. Asian J Psychiatry 2:6–16
14. Ströhle A (2009) Physical activity, exercise, depression and anxiety disorders. J Neural Transm 116:777–784
15. Tuunainen A, Kripke DF, Endo T (2004) Light therapy for non-seasonal depression. Cochrane database Syst Rev (2):CD004050
16. Sarris J, Kavanagh DJ, Deed G et al (2009) St. John's wort and Kava in treating major depressive disorder with comorbid anxiety: a randomised double-blind placebo-controlled pilot trial. Hum Psychopharmacol 24:41–48
17. Müller D, Pfeil T, von den Driesch V (2003) Treating depression comorbid with anxiety—results of an open, practice-oriented study with St John's wort WS 5572 and valerian extract in high doses. Phytomedicine 10(Suppl 4):25–30
18. Cagnacci A, Arangino S, Renzi A et al (2003) Kava-Kava administration reduces anxiety in perimenopausal women. Maturitas 44:103–109
19. Akhondzadeh S, Kashani L, Fotouhi A et al (2003) Comparison of Lavandula angustifolia Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. Prog Neuropsychopharmacol Biol Psychiatry 27:123–127
20. Qin F, Wu XA, Tang Y et al (2011) Meta-analysis of randomized controlled trials to assess the effectiveness and safety of Free and easy wanderer plus, a polyherbal preparation for depressive disorders. J Psychiatr Res 45:1518–1524
21. Yamada K, Yagi G, Kanba S (2005) Effectiveness of herbal medicine (Rokumigan and Hachimijiogan) for fatigue or loss of energy in patients with partial remitted major depressive disorder. Psychiatry Clin Neurosci 59:610–612
22. Papakostas GI, Mischoulon D, Shyu I et al (2010) S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry 167:942–948
23. Alpert JE, Papakostas G, Mischoulon D et al (2004) S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 24:661–664
24. Wolkowitz OM, Reus VI, Keebler A et al (1999) Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry 156:646–649
25. Levitan RD, Shen JH, Jindal R et al (2000) Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. J Psychiatry Neurosci 25:337–346
26. Lam RW, Levitan RD, Tam EM et al (1997) L-tryptophan augmentation of light therapy in patients with seasonal affective disorder. Can J Psychiatry 42:303–306
27. Coppen A, Chaudhry S, Swade C (1986) Folic acid enhances lithium prophylaxis. J Affect Disord 10:9–13
28. Godfrey PS, Toone BK, Carney MW et al (1990) Enhancement of recovery from psychiatric illness by methylfolate. Lancet 336:392–395

29. Coppen A, Bailey J (2000) Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 60:121–130
30. Alpert JE, Mischoulon D, Rubenstein GE, Bottonari K, Nierenberg AA, Fava M (2002) Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry 14:33–38
31. Resler G, Lavie R, Campos J et al (2008) Effect of folic acid combined with fluoxetine in patients with major depression on plasma homocysteine and vitamin B12, and serotonin levels in lymphocytes. Neuroimmunomodulation 15:145–152
32. Basoglu C, Ates MA, Algul A et al (2009) Adjuvant folate with escitalopram treatment and homocystein, folate, vitamin B-12 levels in patients with major depressive disorder. Bull Clin Psychopharmacol 19:135–142
33. Ginsberg LD, Oubre AY, Daoud YA (2011) L-methylfolate Plus SSRI or SNRI from treatment initiation compared to SSRI or SNRI monotherapy in a major depressive episode. Innov Clin Neurosci 8:19–28
34. Taylor MJ, Wilder H, Bhagwagar Z, et al (2004) Inositol for depressive disorders. Cochrane Database Syst Rev (2):CD004049
35. Levine J, Mishori A, Susnosky M et al (1999) Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. Biol Psychiatry 45:270–273
36. Nemets B, Mishory A, Levine J et al (1999) Inositol addition does not improve depression in SSRI treatment failures. J Neural Transm 106:795–798
37. Lai J, Moxey A, Nowak G et al (2012) The efficacy of zinc supplementation in depression: systematic review of randomised controlled trials. J Affect Disord 136:e31–e39
38. Nowak G, Siwek M, Dudek D et al (2003) Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. Pol J Pharmacol 55:1143–1147
39. Siwek M, Dudek D, Paul IA et al (2009) Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J Affect Disord 118:187–195
40. Ille R, Spona J, Zickl M et al (2007) "Add-On"-therapy with an individualized preparation consisting of free amino acids for patients with a major depression. Eur Arch Psychiatry Clin Neurosci 257:222–229
41. Zhang ZJ, Kang WH, Tan QR et al (2007a) Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. J Psychiatr Res 41:360–369
42. Zhang ZJ, Kang WH, Li Q et al (2007b) The beneficial effects of the herbal medicine Free and Easy Wanderer Plus (FEWP) for mood disorders: double-blind, placebo-controlled studies. J Psychiatr Res 41:828–836
43. Sarris J, Mischoulon D, Schweitzer I (2012) Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 73:81–86
44. Lyoo IK, Demopulos CM, Hirashima F et al (2003) Oral choline decreases brain purine levels in lithium-treated subjects with rapid-cycling bipolar disorder: a double-blind trial using proton and lithium magnetic resonance spectroscopy. Bipolar Disord 5:300–306
45. Stoll AL, Sachs GS, Cohen BM et al (1996) Choline in the treatment of rapid-cycling bipolar disorder: clinical and neurochemical findings in lithium-treated patients. Biol Psychiatry 40:382–388
46. Behzadi AH, Omrani Z, Chalian M et al (2009) Folic acid efficacy as an alternative drug added to sodium valproate in the treatment of acute phase of mania in bipolar disorder: a double-blind randomized controlled trial. Acta Psychiatr Scand 120:441–445
47. Chengappa KN, Levine J, Gershon S et al (2000) Inositol as an add-on treatment for bipolar depression. Bipolar Disord 2:47–55
48. Eden Evins A, Demopulos C, Yovel I et al (2006) Inositol augmentation of lithium or valproate for bipolar depression. Bipolar Disord 8:168–174
49. Nierenberg AA, Ostacher MJ, Calabrese JR et al (2006) Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry 163:210–216

50. Heiden A, Frey R, Presslich O et al (1999) Treatment of severe mania with intravenous magnesium sulphate as a supplementary therapy. Psychiatry Res 89:239–246
51. Giannini AJ, Nakoneczie AM, Melemis SM et al (2000) Magnesium oxide augmentation of verapamil maintenance therapy in mania. Psychiatry Res 93:83–87
52. Scarna A, Gijsman HJ, McTavish SF et al (2003) Effects of a branched-chain amino acid drink in mania. Br J Psychiatry 182:210–213
53. Berk M, Copolov DL, Dean O et al (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468–475
54. Berk M, Dean O, Cotton SM et al (2011) The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. J Affect Disord 135:389–394
55. Kaplan B, Simpson J, Ferre R et al (2001) Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder. J Clin Psychiatry 62:936–944
56. Popper CW (2001) Do vitamins or minerals (apart from lithium) have mood-stabilizing effects? J Clin Psychiatry 62:933–935
57. Simmons M (2003) Nutritional approach to bipolar disorder. J Clin Psychiatry 64:338
58. Rucklidge JJ, Gately D, Kaplan BJ (2010) Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. BMC Psychiatry 10:74
59. De Leo V, la Marca A, Morgante G et al (2001) Evaluation of combining kava extract with hormone replacement therapy in the treatment of postmenopausal anxiety. Maturitas 39:185–188
60. Hanus M, Lafon J, Mathieu M (2004) Double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium in mild-to-moderate anxiety disorders. Curr Med Res Opin 20:63–71
61. Fux M, Benjamin J, Nemets B (2004) A placebo-controlled cross-over trial of adjunctive EPA in OCD. J Psychiatr Res 38:323–325
62. Fux M, Benjamin J, Belmaker RH (1999) Inositol versus placebo augmentation of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: a double-blind cross-over study. Int J Neuropsychopharmacol 2:193–195
63. Seedat S, Stein DJ (1999) Inositol augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive-compulsive disorder: an open trial. Int Clin Psychopharmacol 14:353–356
64. Zeev K, Michael M, Ram K et al (2005) Possible deleterious effects of adjunctive omega-3 fatty acids in post-traumatic stress disorder patients. Neuropsychiatr Dis Treat 1:187–190
65. Lam RW, Kennedy SH, Grigoriadis S et al (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. J Affect Disord 117(Suppl 1):S26–S43
66. Lakhan SE, Vieira KF (2010) Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review. Nutr J 9:42
67. Saeed SA, Bloch RM, Antonacci DJ (2007) Herbal and dietary supplements for treatment of anxiety disorders. Am Fam Physician 76:549–556
68. Sarris J, Kavanagh DJ (2009) Kava and St. John's Wort: current evidence for use in mood and anxiety disorders. J Altern Complement Med 15:827–836
69. Kasper S, Dienel A (2002) Cluster analysis of symptoms during antidepressant treatment with hypericum extract in mildly to moderately depressed out-patients. A meta-analysis of data from three randomized, placebo-controlled trials. Psychopharmacology (Berl) 164:301–308
70. Linde K, Berner MM, Kriston L (2008) St John's wort for major depression. Cochrane Database Syst Rev (4):CD000448
71. Baum SS, Hill R, Rommelspacher H (1998) Effects of kava extract and individual kavapyrones on neurotransmitter levels in the nucleus accumbens of rats. Prog Neuropsychopharmacol Biol Psych 22:1105–1120

72. Hattesohl M, Feistel B, Sievers H et al (2008) Extracts of Valeriana officinalis L. s.l. show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine 15:2–15
73. Kobak KA, Taylor LV, Bystritsky A et al (2005) St John's wort versus placebo in obsessive-compulsive disorder: results from a double-blind study. Int Clin Psychopharmacol 20:299–304
74. Kobak KA, Taylor LV, Warner G et al (2005) St. John's wort versus placebo in social phobia: results from a placebo-controlled pilot study. J Clin Psychopharmacol 25:51–58
75. Taylor LH, Kobak KA (2000) An open-label trial of St. John's wort (Hypericum perforatum) in obsessive-compulsive disorder. J Clin Psychiatry 61:575–578
76. Davidson JR, Connor KM (2001) St. John's wort in generalized anxiety disorder: three case reports. J Clin Psychopharmacol 21(6):635–636
77. Kobak KA, Taylor L, Futterer R et al (2003) St. John's wort in generalized anxiety disorder: three more case reports. J Clin Psychopharmacol 23:531–532
78. Golan DE, Tashjian AH, Armstrong EJ et al (2007) Principles of pharmacology: the pathophysiologic basis of drug therapy. Lippincott Williams & Wilkins, New York, pp 49–62
79. Knuppel L, Linde K (2004) Adverse effects of St. John's wort: a systematic review. J Clin Psychiatry 65:1470–1479
80. Rodriguez-Landa JF, Contreras CM (2003) A review of clinical and experimental observations about antidepressant actions and side effects produced by Hypericum perforatum extracts. Phytomedicine 10:688–699
81. Kasper S, Gastpar M, Müller WE et al (2010) Efficacy and safety of silexan, a new, orally administered lavender oil preparation, in subthreshold anxiety disorder – evidence from clinical trials. Wien Med Wochenschr 160:547–556
82. Cavanagh H, Wilkinson J (2005) Lavender essential oil: a review. Austr Infect Coun 10:35–37. Available at: http://www.publish.csiro.au/?act=view_file&file_id=HI05035.pdf. Accessed May 1, 2012
83. Bilia AR, Gallon S, Vincieri FF (2002) Kava-kava and anxiety: growing knowledge about the efficacy and safety. Life Sci 70:2581–2597
84. Scherer J (1998) Kava-kava extract in anxiety disorders: an outpatient observational study. Adv Ther 15:261–269
85. Boerner RJ, Sommer H, Berger W et al (2003) Kava-Kava extract LI 150 is as effective as Opipramol and Buspirone in Generalised Anxiety Disorder – an 8-week randomized, double-blind multi-centre clinical trial in 129 out-patients. Phytomedicine 10:38–49
86. Pittler MH, Ernst E (2003) Kava extract for treating anxiety. Cochrane Database Syst Rev (1):CD003383
87. Witte S, Loew D, Gaus W (2005) Meta-analysis of the efficacy of the acetonic kava-kava extract WS1490 in patients with non-psychotic anxiety disorders. Phytother Res 19:183–188
88. Gounder R (2006) Kava consumption and its health effects. Pac Health Dialog 13:131–135
89. Stevinson C, Huntley A, Ernst E (2002) A systematic review of the safety of kava extract in the treatment of anxiety. Drug Saf 25:251–261
90. Liao JF, Jan YM, Huang SY et al (1995) Evaluation with receptor binding assay on the water extracts of ten CNS-active Chinese herbal drugs. Proc Natl Sci Coun Repub China 19:151–158
91. Mizowaki M, Toriizuka K, Hanawa T (2001) Anxiolytic effect of Kami-Shoyo-San (TJ-24) in mice: possible mediation of neurosteroid synthesis. Life Sci 69:2167–2177
92. Sugiyama K, Muteki T, Kano T (1996) The Japanese herbal medicine 'saikokeishi- to' activates GABAA receptors of rat sensory neurons in culture. Neurosci Lett 216:147–150
93. Zhang Y, Han M, Liu Z, et al. (2012) Chinese herbal formula xiao yao san for treatment of depression: a systematic review of randomized controlled trials. Evid Based Complement Alternat Med 2012;931636. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3159992/pdf/ECAM2012-931636.pdf
94. Glen AIM, Ross BM (2004) Eicosanoids in the central nervous system. In: Curtis-Prior P (ed) The eicosanoids. Wiley, London, pp 210–220

95. Stahl SM (2000) Essential psychopharmacology: neuroscientific basis and practical applications, 2nd edn. Cambridge University Press, Cambridge
96. Lin PY, Huang SY, Su KP (2010) A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol Psychiatry 68:140–147
97. Green P, Hermesh H, Monselise A et al (2006) Red cell membrane omega-3 fatty acids are decreased in nondepressed patients with social anxiety disorder. Eur Neuropsychopharmacol 16:107–113
98. Ross BM (2009) Omega-3 polyunsaturated fatty acids and anxiety disorders. Prostaglandins Leukot Essent Fatty Acids 81:309–312
99. Yehuda S, Rabinovitz S, Mostofsky DI (2005) Mixture of essential fatty acids lowers test anxiety. Nutr Neurosci 8:265–267
100. Appleton KM, Rogers PJ, Ness AR (2010) Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. Am J Clin Nutr 91:757–770
101. Bloch MH, Hannestad J (2011) Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry Sep 20. doi:10.1038/mp.2011.100. [Epub ahead of print]
102. Kraguljac NV, Montori VM, Pavuluri M et al (2009) Efficacy of omega-3 fatty acids in mood disorders—a systematic review and metaanalysis. Psychopharmacol Bull 42:39–54
103. Martins JG, Bentsen H, Puri BK (2012) Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. Mol Psychiatry Apr 10. doi:10.1038/mp.2012.25. [Epub ahead of print]
104. Ross BM, Seguin J, Sieswerda LE (2007) Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis 6:21
105. Freeman MP, Fava M, Lake J et al (2010) Complementary and alternative medicine in major depressive disorder: the American psychiatric association task force report. J Clin Psychiatry 71(6):669–681
106. Nahas R, Sheikh O (2011) Complementary and alternative medicine for the treatment of major depressive disorder. Can Fam Physician 57:659–663
107. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 354:447–455
108. Freeman MP, Hibbeln JR, Wisner KL et al (2006) Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry 67:1954–1967
109. Montgomery P, Richardson AJ (2008) Omega-3 fatty acids for bipolar disorder. Cochrane Database Syst Rev (2):CD005169
110. Alpert JE, Papakostas GI, Mischoulon D (2008) One-carbon metabolism and the treatment of depression: roles of S-adenosyl-l-methionine and folate. In: Mischoulon D, Rosenbaum J (eds) Natural medications for psychiatric disorders: considering the alternatives, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 68–83
111. Bottiglieri T, Hyland K (1994) S-adenosylmethionine levels in psychiatric and neurological disorders: a review. Acta Neurol Scand Suppl 154:19–26
112. Bottiglieri T, Godfrey P, Flynn T et al (1990) Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry 53:1096–1098
113. Maj M, Zizolfi S, Del Vecchio M (1981) Blood levels of S-adenosylmethionine in unmedicated schizophrenic and depressive patients. Neuropsychobiology 7:188–191
114. Papakostas GI (2009) Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. J Clin Psychiatry 70(Suppl 5):18–22
115. Williams AL, Girard C, Jui D, Sabina A, Katz DL (2005) S-adenosylmethionine (SAMe) as treatment for depression: a systematic review. Clin Invest Med 28:132–139
116. Bressa GM (1994) S-adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neurol Scand Suppl 154:7–14

117. Natural Medicines Comprehensive Database (2009) SAMe monograph. Available at: http://www.naturaldatabase.com/(S(e4rus0neempxru55g2cipjqg))/nd/Search.aspx?cs=&s=ND&pt=100&id=786&ds=&name=SAMe. Accessed 1 May 2012
118. Bhagra S, Nippoldt TB, Nair KS (2008) Dehydroepiandrosterone in adrenal insufficiency and ageing. Curr Opin Endocrinol Curr Opin Endocrinol Diabetes Obes 15:239–243
119. Maninger N, Wolkowitz OM, Reus VI et al (2009) Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol 30:65–91
120. Pérez-Neri I, Méndez-Sánchez I, Montes S et al (2008) Acute ehydroepiandrosterone treatment exerts different effects on dopamine and serotonin turnover ratios in the rat corpus striatum and nucleus accumbens. Prog Neuropsychopharmacol Biol Psychiatry 32:1584–1589
121. Pérez-Neri I, Montes S, Ríos C (2009) Inhibitory effect of dehydroepiandrosterone on brain monoamine oxidase activity: in vivo and in vitro studies. Life Sci 85:652–656
122. Markianos M, Tripodianakis J, Sarantidis D et al (2007) Plasma testosterone and dehydroepiandrosterone sulfate in male and female patients with dysthymic disorder. J Affect Disord 101:255–258
123. Morsink LF, Vogelzangs N, Nicklas BJ et al (2007) Health ABC study. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: results from the health ABC study. Psychoneuroendocrinology 32:874–883
124. Assies J, Visser I, Nicolson NA et al (2004) Elevated salivary dehydroepiandrosterone-sulfate but normal cortisol levels in medicated depressed patients: preliminary findings. Psychiatry Res 128:117–122
125. Goodyer IM, Herbert J, Tamplin A (2003) Psychoendocrine antecedents of persistent first-episode major depression in adolescents: a community-based longitudinal enquiry. Psychol Med 33:601–610
126. Morrison MF, Freeman EW, Lin H et al (2011) Higher DHEA-S (dehydroepiandrosterone sulfate) levels are associated with depressive symptoms during the menopausal transition: results from the PENN ovarian aging study. Arch Womens Ment Health 14:375–382
127. Morrison MF, Ten Have T, Freeman EW et al (2001) DHEA-S levels and depressive symptoms in a cohort of African American and Caucasian women in the late reproductive years. Biol Psychiatry 50:705–711
128. Gill J, Vythilingam M, Page GG (2008) Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. J Trauma Stress 21:530–539
129. Hsiao CC (2006) Positive correlation between anxiety severity and plasma levels of dehydroepiandrosterone sulfate in medication-free patients experiencing a major episode of depression. Psychiatry Clin Neurosci 60:746–750
130. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR (1999) Dehydroepiandrosterone treatment of midlife dysthymia. Biol Psychiatry 45:1533–1541
131. Schmidt PJ, Daly RC, Block M et al (2005) Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. Arch Gen Psychiatry 62:154–162
132. Wolkowitz OM, Reus VI, Roberts E et al (1997) Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry 41:311–318
133. Natural Medicines Comprehensive Database. DHEA monograph (2009) Available at: http://www.naturaldatabase.com/(S(e4rus0neempxru55g2cipjqg))/nd/Search.aspx?cs=&s=ND&pt=100&id=331&ds=&name=DHEA. Accessed 1 May 2012
134. Natural Standard. DHEA professional monograph (2009) Available at: http://www.naturalstandard.com/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/dhea.asp%3Fprintversion%3Dtrue. Accessed 1 May 2012
135. Shaw K, Turner J, Del Mar C (2002) Are tryptophan and 5-hydroxytryptophan effective treatments for depression? A meta-analysis. Aust N Z J Psychiatry 36:488–491
136. Booij L, Van der Does AJ, Haffmans PM et al (2005) The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. J Psychopharmacol 19:267–275

137. Feder A, Skipper J, Blair JR et al (2011) Tryptophan depletion and emotional processing in healthy volunteers at high risk for depression. Biol Psychiatry 69:804–807
138. Turner EH, Loftis JM, Blackwell AD (2006) Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. Pharmacol Ther 109:325–338
139. Kahn RS, Westenberg HG, Verhoeven WM et al (1987) Effect of a serotonin precursor and uptake inhibitor in anxiety disorders; a double-blind comparison of 5-hydroxytryptophan, clomipramine and placebo. Int Clin Psychopharmacol 2:33–45
140. Farah A (2009) The role of l-methylfolate in depressive disorders. CNS Spectr 14(1 Suppl 2):2–7
141. Bottiglieri T (2005) Homocysteine and folate metabolism in depression. Prog Neuro-Psychopharmacol Biol Psychiatry 29:1103–1112
142. Coppen A, Bolander-Gouaille C (2005) Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol 19:59–65
143. Ng TP, Feng L, Niti M et al (2009) Folate, vitamin B12, homocysteine, and depressive symptoms in a population sample of older Chinese adults. J Am Geriatr Soc 57:871–876
144. Kamphuis MH, Geerlings MI, Grobbee DE et al (2008) Dietary intake of B(6-9-12) vitamins, serum homocysteine levels and their association with depressive symptoms: the Zutphen elderly study. Eur J Clin Nutr 62:939–945
145. Watanabe H, Suganuma N, Hayashi A, Hirowatari Y, Hirowatari T, Ohsawa M (2010) No relation between folate and homocysteine levels and depression in early pregnant women. Biosci Trends 4:344–350
146. Hvas AM, Juul S, Bech P et al (2004) Vitamin B6 level is associated with symptoms of depression. Psychother Psychosom 73:340–343
147. Skarupski KA, Tangney C, Li H et al (2010) Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time. Am J Clin Nutr 92:330–335
148. Leiva DB (1990) The neurochemistry of mania: a hypothesis of etiology and rationale for treatment. Prog Neuropsychopharmacol Biol Psychiatry 14:423–429
149. DelBello MP, Cecil KM, Adler CM et al (2006) Neurochemical effects of olanzapine in first hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology 31:1264–1273
150. Kumar A, Thomas A, Lavretsky H et al (2002) Frontal white matter biochemical abnormalities in late-life major depression detected with proton magnetic resonance spectroscopy. Am J Psychiatry 159:603–636
151. Steingard RJ, Yurgelun-Todd DA, Hennen J et al (2000) Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. Biol Psychiatry 48:1053–1061
152. Bjelland I, Tell GS, Vollset SE et al (2009) Choline in anxiety and depression: the Hordaland health study. Am J Clin Nutr 90:1056–1060
153. Coplan JD, Mathew SJ, Mao X et al (2006) Decreased choline and creatine concentrations in centrum semiovale in patients with generalized anxiety disorder: relationship to IQ and early trauma. Psychiatry Res 147:27–39
154. Fava M, Mischoulon D (2009) Folate in depression: efficacy, safety, differences in formulations, and clinical issues. J Clin Psychiatry 70(suppl 5):12–17
155. Morris DW, Madhukar HT, Rush AJ (2008) Folate and unipolar depression. J Altern Comp Med 14:277–285
156. Oren DA, Teicher MH, Schwartz PJ et al (1994) A controlled trial of cyanocobalamin (vitamin B12) in the treatment of winter seasonal affective disorder. J Affect Disord 32:197–200
157. Williams AL, Cotter A, Sabina A et al (2005) The role for vitamin B-6 as treatment for depression: a systematic review. Fam Pract 22:532–537
158. Bell IR, Edman JS, Morrow FD et al (1992) Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction. J Am Coll Nutr 11:159–163

159. Lazarou C, Kapsou M (2010) The role of folic acid in prevention and treatment of depression: An overview of existing evidence and implications for practice. Comp Ther Clin Pract 16:161–166
160. Christakos S, Dhawan P, Benn B et al (2007) Vitamin D: molecular mechanism of action. Ann N Y Acad Sci 1116:340–348
161. Parker G, Brotchie H (2011) 'D' for depression: any role for vitamin D? 'Food for thought' II. Acta Psychiatr Scand 124:243–249
162. Gaines S (2005) The saddest season. Minnesota Med 88:25–32
163. Obradovic D, Gronemeyer H, Lutz B et al (2006) Cross-talk of vitamin D and glucocorticoids in hippocampal cells. J Neurochem 96:500–509
164. Ganji V, Milone C, Cody MM et al (2010) Serum vitamin D concentrations are related to depression in young adult US population: the third national health and nutrition examination survey. Int Arch Med 3:29
165. Hoang MT, Defina LF, Willis BL et al (2011) Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the cooper center longitudinal study. Mayo Clin Proc 86:1050–1055
166. Hoogendijk WJ, Lips P, Dik MG et al (2008) Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 65:508–512
167. Bertone-Johnson ER (2009) Vitamin D, and the occurrence of depression: causal association or circumstantial evidence? Nutr Rev 67:481–492
168. Chan R, Chan D, Woo J et al (2011) Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. J Affect Disord 130:251–259
169. Berk M, Sanders KM, Pasco JA et al (2007) Vitamin D deficiency may play a role in depression. Med Hypotheses 69:1316–1319
170. Nanri A, Mizoue T, Matsushita Y et al (2009) Association between serum 25-hydroxyvitamin D and depressive symptoms in Japanese: analysis by survey season. Eur J Clin Nutr 63:1444–1447
171. Milaneschi Y, Shardell M, Corsi AM et al (2010) Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. J Clin Endocrinol Metab 95:3225–3233
172. Heaney RP (2008) Vitamin D: criteria for safety and efficacy. Nutr Rev 66(10 Suppl 2):S178–S181
173. Penckofer S, Kouba J, Byrn M et al (2010) Vitamin D and depression: where is all the sunshine? Issues Ment Health Nurs 31:385–393
174. Barkai AI, Dunner DL, Gross HA et al (1978) Reduced myo-inositol levels in cerebrospinal fluid from patients with affective disorder. Biol Psychiatry 13:65–72
175. Coupland NJ, Ogilvie CJ, Hegadoren KM et al (2005) Decreased prefrontal myoinositol in major depressive disorder. Biol Psychiatry 57:1526–1534
176. Shimon H, Agam G, Belmaker RH et al (1997) Reduced frontal cortex inositol levels in postmortem brain of suicide victims and patients with bipolar disorder. Am J Psychiatry 154:1148–1150
177. Levine J, Kurtzman L, Rapoport A et al (1996) CSF inositol does not predict antidepressant response to inositol. J Neural Transm 103:1457–1462
178. Einat H, Belmaker RH (2001) The effects of inositol treatment in animal models of psychiatric disorders. J Affect Disord 62:113–121
179. Kofman O, Einat H, Cohen H et al (2000) The anxiolytic effect of chronic inositol depends on the baseline level of anxiety. J Neural Transm 107:241–253
180. Levine J, Barak Y, Gonzalves M et al (1995) Double-blind, controlled trial of inositol treatment of depression. Am J Psychiatry 152:792–794
181. Sartori SB, Whittle N, Hetzenauer A et al (2012) Magnesium deficiency induces anxiety and HPA axis dysregulation: modulation by therapeutic drug treatment. Neuropharmacology 62: 304–312

182. Haddad JJ (2005) N-methyl-D-aspartate (NMDA) and the regulation of mitogenactivated protein kinase (MAPK) signaling pathways: a revolving neurochemical axis for therapeutic intervention? Prog Neurobiol 77:252–282
183. Murck H (2002) Magnesium and affective disorders. Nutr Neurosci 5:375–389
184. Murck H, Steiger A (1998) Mg2þ reduces ACTH secretion and enhances spindle power without changing delta power during sleep in men—possible therapeutic implications. Psychopharmacology (Berl) 137:247–252
185. Siwek M, Wróbel A, Dudek D et al (2005) The role of copper and magnesium in the pathogenesis and treatment of affective disorders. Psychiatr Pol 39:911–920
186. Eby GA, Eby KL (2006) Rapid recovery from major depression using magnesium treatment. Med Hypotheses 67:362–370
187. Eby GA, Eby KL (2010) Magnesium for treatment-resistant depression: a review and hypothesis. Med Hypoth 74:649–660
188. Schäfer HL, Schafer H, Schneider W et al (1955) Sedative action of extract combination of *Eschscholtzia California* and *Corydalis cava*. Arzneimittelforschung 45:124–126
189. Walker AF, Marakis G, Morris AP et al (2002) Promising hypotensive effect of hawthorn extract: a randomised doubleblind pilot study of mild, essential hypotension. Phytother Res 16:48–54
190. Delva P (2003) Magnesium and cardiac arrhythmias. Mol Aspects Med 24(1–3):53–62
191. Hambidge KM, Krebs NF (2007) Zinc deficiency: a special challenge. J Nutr 137:1101–1105
192. Takeda A, Tamano H (2009) Insight into zinc signaling from dietary zinc deficiency. Brain Res Rev 62:33–44
193. Suh SW, Won SJ, Hamby AM et al (2009) Decreased brain zinc availability reduces hippocampal neurogenesis in mice and rats. J Cereb Blood Flow Metab 29:1579–1588
194. Revest JM, Dupret D, Koehl M et al (2009) Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Mol Psychiatry 14:959–967
195. Sahay A, Hen R (2007) Adult hippocampal neurogenesis in depression. Nat Neurosci 10:1110–1115
196. Dziedzicka-Wasylewska M, Rogóż Z, Solich J et al (2002) Effect of joint administration of imipramine and amantadine on binding of [3H]7-OH-DPAT to dopamine D3 receptors in peripheral blood lymphocytes of the patients with drug-resistant unipolar depression. Pol J Pharmacol 54:703–706
197. Pittenger C, Coric V, Banasr M et al (2008) Riluzole in the treatment of mood and anxiety disorders. CNS Drugs 22:761–786
198. Cichy A, Sowa-Kućma M, Legutko B et al (2009) Zinc-induced adaptive changes in NMDA/glutamatergic and serotonergic receptors. Pharmacol Rep 61:1184–1191
199. Szewczyk B, Poleszak E, Wlaź P et al (2009) The involvement of serotonergic system in the antidepressant effect of zinc in the forced swim test. Prog Neuropsychopharmacol Biol Psychiatry 33:323–329
200. Nowak G, Legutko B, Szewczyk B et al (2004) Zinc treatment induces cortical brain-derived neurotrophic factor gene expression. Eur J Pharmacol 492:57–59
201. Shimizu E, Hashimoto K, Okamura N et al (2003) Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 54:70–75
202. Franco JL, Posser T, Brocardo PS et al (2008) Involvement of glutathione, ERK1/2 phosphorylation and BDNF expression in the antidepressant-like effect of zinc in rats. Behav Brain Res 188:316–323
203. Schmidt HD, Duman RS (2007) The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behaviour. Beh Pharmacol 18:391–418
204. Slamon ND, Pentreath VW (2000) Antioxidant defense against antidepressants in C6 and 1321N1 cells. Chem Biol Interact 127:181–199

205. Cope EC, Levenson CW (2010) Role of zinc in the development and treatment of mood disorders. Curr Opin Clin Nutr Metab Care 13:685–689
206. Joshi M, Akhtar M, Najmi A, et al (2012) Effect of zinc in animal models of anxiety, depression and psychosis. Hum Exp Toxicol May 1. [Epub ahead of print]
207. Salimi S, Kianpoor M, Abassi MR et al (2008) Lower total serum protein, albumin and zinc in depression in an Iranian population. J Med Sci 8:587–590
208. Siwek M, Dudek D, Schlegel-Zawadzka M et al (2010) Serum zinc level in depressed patients during zinc supplementation of imipramine treatment. J Affect Disord 126:447–452
209. Fosmire GJ (1990) Zinc toxicity. Am J Clin Nutr 51:225–227
210. Shuttleworth CW, Weiss JH (2011) Zinc: new clues to diverse roles in brain ischemia. Trends Pharmacol Sci 32:480–486
211. Sommerville RB, Baloh RH (2011) Anemia, paresthesias, and gait ataxia in a 57-year-old denture wearer. Clin Chem 57:1103–1106
212. Fernstrom JD (2005) Branched-chain amino acids and brain function. J Nutr 135 (6 Suppl):1539S–1546S
213. Markus CR (2008) Dietary amino acids and brain serotonin function; implications for stress-related affective changes. Neuromolecular Med 10:247–258
214. Altamura C, Maes M, Dai J et al (1995) Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. Eur Neuropsychopharmacol 5(Suppl):71–75
215. Maes M, Verkerk R, Vandoolaeghe E et al (1998) Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. Acta Psychiatr Scand 97:302–308
216. Bella R, Biondi R, Raffaele R et al (1990) Effect of acetyl-L-carnitine on geriatric patients suffering from dysthymic disorders. Int J Clin Pharmacol Res 10:355–360
217. Garzya G, Corallo D, Fiore A et al (1990) Evaluation of the effects of L-acetylcarnitine on senile patients suffering from depression. Drugs Exp Clin Res 16:101–106
218. Tempesta E, Casella L, Pirrongelli C et al (1987) L-acetylcarnitine in depressed elderly subjects. A cross-over study vs placebo. Drugs Exp Clin Res 13:417–423
219. Zanardi R, Smeraldi E (2006) A double-blind, randomised, controlled clinical trial of acetyl-L-carnitine vs. amisulpride in the treatment of dysthymia. Eur Neuropsychopharmacol 16:281–287
220. Berk M, Ng F, Dean O et al (2008) Glutathione: a novel treatment target in psychiatry. Trends Pharmacol Sci 29:346–351
221. Bilici M, Efe H, Köroğlu MA et al (2001) Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. J Affect Disord 64:43–51
222. Lafleur DL, Pittenger C, Kelmendi B et al (2006) N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Psychopharmacology (Berl) 184:254–256
223. Simpson JS, Crawford SG, Goldstein ET et al (2011) Systematic review of safety and tolerability of a complex micronutrient formula used in mental health. BMC Psychiatry 11:62
224. ClinicalTrials.gov (n.d.). Clinical trial of a nutritional supplement in adults with bipolar disorder. Investigators: Kaplan BJ, Goldstein E. Study registered in April 2005, updated to August 2011. Available at: http://www.clinicaltrials.gov/ct/show/NCT00109577?order=1. Accessed 1 May 2012