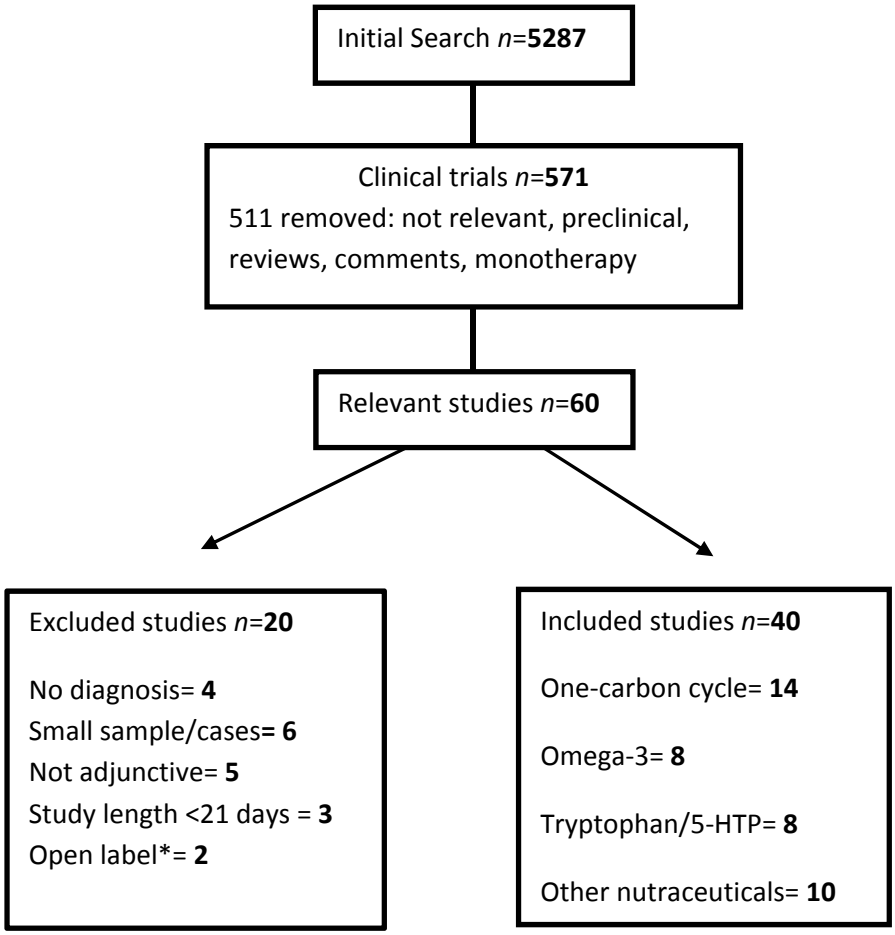
**FIGURE S1.** Systematic Review Search Flowchart




* Without prior medication 'non-response' established

## TABLE S1. One-Carbon Cycle Nutraceuticals

| Intervention | Study* | Year | Daily Dose | Design | Study Duration | N | Mean Age (years) | Gender (% Female) | Diagnosis | Antidepressant | Primary Outcome | Completers N (%) | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **S- Adenosyl Methionine (SAMe)** | Alpert (12) | 2004 | 1600mg (target dose) | OL<br>TR[a] | 6 weeks | 30 | 48 | 73 | DSM-IV MDD | Fluoxetine/paroxetine/citalopram ≥20mg/day; escitalopram≥10mg/day; sertraline≥50mg/day or venlafaxine≥75m/day | HAM-D 17 | 23 (77) | + |
| | Bambling (13) | 2015 | 1600mg versus 800mg | Dosage-blinded<br>OL<br>RA<br>TR[b] | 15 weeks | 36 | 49 | 61 | ICD–10 MDD | All SSRIs included | BDI | 26 (72) | +[c] |
| | De Berardis (14) | 2013 | 800mg | OL<br>TR[d]<br>SB | 8 weeks | 25 | 32 | 57 | DSM-IV MDD | SSRI, SNRI, agomelatine, mirtazapine or bupropion at adequate dose and at least 6 weeks duration | HAM-D | 24 (96) | + |
| | Papakostas (15) | 2010 | 1600mg (target dose) versus placebo | DB<br>RCT | 6 weeks | 73 | NA | 60 | DSM-IV MDD | SSRI or SNRI at adequate and stable dose for at least 4 weeks | HAM-D 17 | 55 (75) | ns (+)[e] |
| **Folic acid** | Coppen (16) | 2000 | 0.5mg versus placebo | DB<br>RCT | 10 weeks | 127 | 43 | 63[f] | DSM-III-R MDD | 20mg/day fluoxetine | HAM-D 17 | 109 (86) | +[g] |
| | Resler (17) | 2008 | 10mg versus placebo | DB<br>RCT | 6 weeks | 27 | 35 | 85 | DSM-IV MDD | 20mg/day fluoxetine | HAM-D 17 | 20 (74) | + |
| | Basoglu (18) | 2009 | 2.5mg versus escitalopram only | RA<br>OL | 6 weeks | 42 | 30 | 54 | DSM-IV MDD | 10mg/day escitalopram | MADRS | 28 (67) | ns |
| | Venkatasu-bramanian (19) | 2013 | 1.5mg versus 5mg | Dosage-blinded<br>OL<br>RA | 6 weeks | 42[h] | 33 | 100 | ICD–10 MDD | 20mg/day fluoxetine | HAM-D 17 | 30 (71) | + |
| | Bedson (20) | 2014 | 5mg versus placebo | DB<br>RCT | 12 weeks | 475 | 45 | 59 | ICD–10 MDD | All antidepressants included at adequate dose and duration | BDI-II | 440 (93) | ns |
| **Folic acid, B6 and B12** | Almeida (21) | 2014 | FA 2mg,<br>B12 0.5mg,<br>B6 25mg versus placebo | DB<br>RCT | 52 weeks | 153 | 63[i] | 56 | DSM-IV MDD | 20–40mg/day citalopram | MADRS | 128 (84) | ns (+)[j] |
| **Methylfolate (ME: methyl-folate; FO: folinic acid)** | Godfrey (22) | 1990 | ME 15mg versus placebo | DB<br>RCT | 6 months | 24[k] | 46 | 54 | DSM-III MDD | Undefined antidepressant treatment | HAM-D 17 | 24 (100) | + |
| | Alpert (23) | 2002 | FO 30mg (target dose) | OL<br>TR[a] | 8 weeks | 22 | 45 | 59 | DSM-IV MDD | SSRI or venlafaxine for at least 4 weeks duration | HAM-D 17 | 16 (73) | +[l] |
| | Papakostas (24) | 2012 | ME 15mg (target dose) versus | DB<br>RCT<br>SSRI- | Trial<br>1: 60 days<br>2: 60 days | Trial<br>1:148<br>2: 75 | Trial<br>1:48<br>2: 48 | Trial<br>1: 70<br>2: 71 | DSM-IV MDD | Fluoxetine/paroxetine/ citalopram≥20mg/day; escitalopram≥10mg/day; | HAM-D 17 | Trial<br>1:119 (80)<br>2: 61 (81) | Trial1<br>ns<br>Trial2 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | placebo[m] | resistant[n] | | | | | | sertraline≥50mg/day | | | + |
| **B12** | Syed (25) | 2013 | 1000mcg IMI versus antidepressant only | OL<br>RA<br>SB | 6 weeks | 73 | 37 | 48 | NA | TCA equivalent to imipramine 100mg to 200mg/day and SSRI equivalent to Fluoxetine 20–40mg/day | HAM-D 20 | 73 (100) | + |

+ Indicates a statistically significant reduction in depression rating scores in the treatment group compared with control group between baseline and endpoint or if the study is open label, treatment significantly reduced depression symptoms on the depression rating scale over the course of the trial. n.s. indicates no significant difference in depression rating scores between the treatment and control or if the study is open label, the treatment did not significantly reduce depression symptoms on the depression rating scale over the duration of the trial. * First author; BDI: Beck Depression Inventory, FO: folinic acid; HAM-D: Hamilton Depression Rating Scale; DB: double blind; FA: folic acid; IMI; Intramuscular Injection; ME: Methylfolate; NA; Not available; OL; Open Label; RA: randomized allocation; RCT; randomized placebo controlled trial, SB; Single blind; SNRI; Serotonin-Norepinephrine reuptake inhibitor, SSRI; Selective serotonin reuptake inhibitor, TCA; tricyclic antidepressant, TR; Treatment Resistant

[a] Defined as at least one failed antidepressant trial for current episode

[b] Defined as a history of suboptimal treatment response in the previous three episodes

[c] Significant reduction in symptoms from baseline to endpoint. However, no significant difference between 1600mg and 800mg daily doses in the reduction of depression symptoms.

[d] Defined as two failed antidepressants of different classes

[e] Superior response and remission rates for SAMe group versus placebo (a priori primary outcome) but a nonsignificant between-groups reduction in HAM-D scores

[f] Completers only

[g] For females only, result not found in males

[h] Females only

[i] Only participants over 50 years old were recruited

[j] Superior response and remission rates for FA, B12+B6 group versus placebo but nonsignificant reduction in MADRS scores for FA, B12+B6 group versus placebo

[k] Patients with depression and red cell folate levels below 200μg/l

[l] Significant decrease in HAM-D scores over course of trial but modest response and remission rates (31% and 19% respectively)

[m] Study comprised two sequential double-blind randomized controlled trials. Trial 1 comprised a 60-day study divided into two 30-day periods. Participants were randomly assigned to one of three groups: 1) *l*-methylfolate for 60 days (7.5 mg/day for 30 days, then 15 mg/day for 30 days); 2) placebo for 30 days followed by l-methylfolate (7.5 mg/day) for 30 days; or 3) placebo for 60 days. Trial 2 was identical to Trial 1 except the dose of *l*-methylfolate was 15 mg/day for both 30-day periods.

[n] Defined as one to two failed SSRI trials for the current episode

**TABLE S2. Omega-3**

| Intervention | Study* | Year | Daily Dose | Design | Study Duration | N | Mean Age (years) | Gender (% Female) | Diagnosis | Antidepressant | Primary Outcome | Completers N (%) | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EPA/DHA** | Su (26) | 2003 | 4.4 g EPA + 2.2 g DHA versus placebo | DB RCT | 8 weeks (plus 1 week placebo run-in) | 28 | 39 | 64 | DSM-IV MDD | All antidepressants included[a] | HAM-D 21 | 22 (79) | + |
| | Carney (27) | 2009 | 0.93g EPA+0.75g DHA versus placebo | DB RCT | 10 weeks weeks (plus 2 week placebo run-in) | 122 | 58 | 34 | DSM-IV MDD+CVD[b] | 50mg Sertraline | BDI-II | 115 (94) | ns |
| | Gertsik (28) | 2012 | 1.8g EPA+0.4g DHA versus placebo | DB RCT | 8 weeks (plus 1 week placebo run-in) | 42 | 41 | NA | DSM-IV MDD | 20–40mg Citalopram (titrated depending on response) | HAM-D 21 | 32 (76) | + |
| **EPA versus DHA** | Mozaffari-Khosravi (29) | 2013 | 1g EPA versus 1g DHA versus placebo | DB RCT | 12 weeks | 81 | 35 | 61 | DSM-IV MDD (mild-moderate depression) | All antidepressants included | HAM-D 17 | 61 (75) | +[c] |
| **Ethyl EPA** | Nemets (30) | 2002 | 2g E-EPA versus placebo | DB RCT | 4 weeks | 20 | 53 | 85 | DSM-IV MDD | All antidepressants included[d] | HAM-D 24 | 19 (95) | + |
| | Peet (31) | 2002 | 1g E-EPA versus 2g E-EPA versus 4g E-PA versus placebo | DB RCT | 12 weeks | 70 | 45 | 84 | NS | All antidepressants included | HAM-D 17 | 60 (86) | +[e] |
| | Jazayeri (32) | 2008 | 1g E-EPA+20mg Fluoxetine versus 1g E-EPA monotherapy versus 20mg Fluoxetine only | DB RCT Double dummy | 8 weeks | 60 | 35 | 55 | DSM-IV MDD | 20mg Fluoxetine | HAM-D 17 | 48 (80) | +[f] |
| | Bot (33) | 2010 | 1g E-EPA versus placebo | DB RCT | 12 weeks | 25 | 54 | 52 | DSM-IV MDD+diabetes[g] | All antidepressants included | MADRS | 23 (92) | ns |

+ Indicates a statistically significant reduction in depression rating scores in the treatment group compared with control group between baseline and endpoint or if the study is open label, treatment significantly reduced depression symptoms on the depression rating scale over the course of the trial. ns Indicates no significant difference in depression rating scores between the treatment and control or if the study is open label, the treatment did not significantly reduce depression symptoms on the depression rating scale over the duration of the trial. * First author; BDI-II: Beck Depression Inventory, HAM-D; Hamilton Depression Rating Scale, DB: double blind, DHA: docosahexaenoic acid, EPA: Eicosapentaenoic acid, E-EPA: Ethyl-Eicosapentaenoic acid, NS: Not Specified, RCT: randomized placebo controlled trial, SSRI: Selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant

[a] One patient in each group was not taking antidepressants (0.07% of the sample)

[b] All patients were diagnosed with coronary heart disease defined as at least 50% stenosis in at least one major coronary artery, a history of revascularization or hospitalization for an acute coronary syndrome

[c] EPA significantly reduced depression symptoms over both the placebo and DHA groups

[d] One patient was not taking antidepressants (5% of the sample)

[e] Significant reduction in depression symptoms found for the 1g E-EPA group only compared with placebo. Result not found for the 2g and 4g E-EPA groups

[f] Significant reduction in depression symptoms for the E-EPA+Fluoxetine group in comparison to E-EPA only and fluoxetine only
[g] All patients were diagnosed with comorbid diabetes mellitus (type 1 or 2)

## TABLE S3. Tryptophan

| Intervention | Study* | Year | Daily Dose | Design | Study Duration | N | Mean Age (years) | Gender (% Female) | Diagnosis | Antidepressant | Primary Outcome | Completers N (%) | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tryptophan** | Levitan (34) | 2000 | 4g (target dose) versus placebo | DB RCT | 8 weeks (plus 5 day placebo run in) | 39 | 44 | 70 | DSM-IV MDD | 20mg/day fluoxetine | HAM-D 29 | 30 (77) | ns |
| **L-Tryptophan** | Shaw (35) | 1975 | Clomipramine only versus clomipramine+6g L-Tryptophan versus clomipramine+desipramine versus desipramine+6g L-Tryptophan | DB RCT Triple dummy | 4 weeks | 54 | 56 | 85 | Unipolar affective disorder | Up to 175mg/day Clomipramine or 225mg/day desipramine | BDI | N/A | ns |
| | | | | | | | | | | | | | |
| | Thomson (36) | 1982 | 3g L-Tryptophan only versus amitriptyline only versus 3g L-Tryptophan+amitriptyline versus placebo only | DB RCT | 12 weeks (plus 1 week placebo run in) | 115 | 33 (mdn) | 78 | RDC Major affective disorder | 150mg/day amitriptyline | HAM-D 18 | 72 (63) | +[a] |
| **DL-Tryptophan** | Glassman (37) | 1969 | DL-Tryptophan (12, 15 or 18g depending on body weight) versus placebo | DB CT | 3 weeks | 20 | 59 | 70 | Depressive illness | 60mg/day Phenelzine | HAM-D (modified) | 20 (100) | + |
| | Ayuso Gutierrez (38) | 1971 | 6g DL-tryptophan versus placebo | DB RCT | 3 weeks | 30 | 43 | 83 | Endogenous depression | 500mg/day IMI (target dose) Nialamide | HAM-D | 29 (97) | + |
| | Walinder (39) | 1976 | 0.1g/kg of body weight DL-Tryptophan versus placebo | DB RCT | 3.5 weeks | 26 | 44 | 100 | Endogenous depression | 150mg/day Clomipramine | Cronholm-Ottosson Depression Scale | 24 (92) | + |
| | Walinder (40) | 1981 | 0.1/kg of body weight DL-Tryptophan versus placebo | DB RCT | 3 weeks | 26 | NA | 96 | Endogenous depression | 200mg Zimelidine | Cronholm-Ottosson Depression Scale | 25 (96) | ns |
| **L–5HTP** | Nardini (41) | 1983 | 300mg L–5HTP versus placebo | DB RCT | 4 weeks | 26 | 50 | 50 | Endogenous or reactive depression | 50mg Chlorimipramine | HAM-D | 24 (92) | + |

+ Indicates a statistically significant reduction in depression rating scores in the treatment group compared with control group between baseline and endpoint or if the study is open label, treatment significantly reduced depression symptoms on the depression rating scale over the course of the trial, ns Indicates no significant difference in depression rating scores between the treatment and control or if the study is open label, the treatment did not significantly reduce depression symptoms on the depression rating scale over the duration of the trial. * First author; BDI; Beck Depression Inventory; HAM-D; Hamilton Depression Rating Scale, DB; double blind, NA; Not available, RCT; randomized placebo controlled trial, CT; Controlled Trial

[a] All active treatment groups were more effective than placebo. The combination group (amitriptyline + L-tryptophan) was superior to the other active treatments alone (amitriptyline only and L-tryptophan only)

## TABLE S4. Other Nutraceuticals

| Intervention | Study* | Year | Daily Dose | Design | Study Duration | N | Mean Age (years) | Gender (% Female) | Diagnosis | Antidepressant | Primary Outcome | Completers N (%) | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Zinc** | Siwek (42) | 2009 | 25mg versus placebo | DB RCT | 12 weeks | 60 | 46 | 67 | DSM-IV MDD | 100 to 200mg/day imipramine | HAM-D 17 | 52 (87) | ns[a] |
| | Ranjbar (43) | 2013 | 25mg versus placebo | DB RCT | 12 weeks | 44 | 37 | 77 | DSM-IV MDD | 20 to 60mg/day citalopram or 20 to 60mg/day fluoxetine | BDI | 38 (86) | + |
| **Vitamin C** | Amr (44) | 2013 | 1g versus placebo | DB RCT | 6 months | 27[b] | 10 | 33 | DSM-IV MDD | 10 to 20mg/day fluoxetine | CDRS | 24 (89) | + |
| | Sahraian (45) | 2015 | 1g versus placebo | DB RCT | 8 weeks | 43 | 34 | 74 | DSM-IV MDD | 20mg/day citalopram | HAM-D 21 | 40 (93) | ns |
| **Vitamin $D_3$** | Khoraminya (46) | 2013 | 1500 IU versus placebo | DB RCT | 8 weeks | 42 | 39 | 85 | DSM-IV MDD | 20mg/day fluoxetine | HAM-D 24 | 40 (96) | + |
| | Zanetidou (47) | 2011 | 300000IU versus antidepressant only | OL CT | 4 weeks | 24[c] | 74[d] | 67 | DSM-IV MDD | All antidepressants included | HAM-D | 22 (92) | + |
| **Inositol** | Levine (48) | 1999 | 12g versus placebo | DB RCT | 4 weeks | 36 | 48 | 70 | DSM-IV MDD | SSRIs | HAM-D | 27 (75) | ns |
| | Nemets (49) | 1999 | 12g versus placebo | DB RCT | 4 weeks | 42 | 51 | 61 | DSM-IV MDD | SSRIs | HAM-D 24 | 34 (81) | ns |
| **Amino acids** | Ille (50) | 2007 | Individualized amino acid mixture versus placebo | DB RCT | 4 weeks | 40 | 46 | 80 | DSM-IV MDD | Mirtazapine (no dose specified) | HAM-D | 40 (100) | + |
| **Creatine** | Lyoo (51) | 2012 | 5g (target dose) versus placebo | DB RCT | 8 weeks | 52[e] | 47 | 100 | DSM-IV MDD | 20mg/day escitalopram | HAM-D 17 | 39 (75) | + |

+ Indicates a statistically significant reduction in depression rating scores in the treatment group compared with control group between baseline and endpoint or if the study is open label, treatment significantly reduced depression symptoms on the depression rating scale over the course of the trial, **ns** Indicates no significant difference in depression rating scores between the treatment and control or if the study is open label, the treatment did not significantly reduce depression symptoms on the depression rating scale over the duration of the trial. * First author; BDI; Beck Depression Inventory, HAM-D; Hamilton Depression Rating Scale, DB; double blind, NA; Not available, RCT; randomized placebo controlled trial, CT; Controlled Trial, SSRI; Selective serotonin reuptake inhibitor, CDRS; Children's Depression Rating Scale

[a] A significant treatment effect was found in a subgroup of patients who were treatment resistant (defined according to the Thase and Rush, 1997 model) compared with placebo

[b] Pediatric patients only

[c] Treatment group N=24; controls N=15

[d] Only patients over 65 years old were recruited

[e] Females only