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Review

REVIEW

# Mitochondrial Agents for Bipolar Disorder

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## Abstract

**Background:** Bipolar disorder is a chronic and often debilitating illness. Current treatment options (both pharmaco- and psychotherapy) have shown efficacy, but for many leave a shortfall in recovery. Advances in the understanding of the pathophysiology of bipolar disorder suggest that interventions that target mitochondrial dysfunction may provide a therapeutic benefit.

**Methods:** This review explores the current and growing theoretical rationale as well as existing preclinical and clinical data for those therapies aiming to target the mitochondrion in bipolar disorder. A Clinicaltrials.gov and ANZCTR search was conducted for complete and ongoing trials on mitochondrial agents used in psychiatric disorders. A PubMed search was also conducted for literature published between January 1981 and July 2017. Systematic reviews, randomized controlled trials, observational studies, case series, and animal studies with an emphasis on agents affecting mitochondrial function and its role in bipolar disorder were included. The search was augmented by manually searching the references of key papers and related literature. The results were presented as a narrative review.

**Results:** Mitochondrial agents offer new horizons in mood disorder treatment. While some negative effects have been reported, most compounds are overall well tolerated and have generally benign side-effect profiles.

**Conclusions:** The study of neuroinflammation, neurodegeneration, and mitochondrial function has contributed the understanding of bipolar disorder's pathophysiology. Agents targeting these pathways could be a potential therapeutic strategy. Future directions include identification of novel candidate mitochondrial modulators as well as rigorous and well-powered clinical trials.

**Keywords:** adjunctive, bipolar disorder, complimentary therapies, mitochondria

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## Introduction

Bipolar disorder (BD) is a complex illness with an approximate prevalence of 1% (Ferrari et al., 2016). It can cause marked disability and social impairment, particularly among people who experience continued subthreshold symptoms between acute phases, with depression being the greatest contributor (Judd et al., 2008).

Current pharmacological treatment offers limited efficacy overall, either in preventing relapses or recovery from acute episodes of depression (Perlis et al., 2006). The current treatment for the maintenance phase is mood stabilizers (Chen et al., 1999; Machado-Vieira et al., 2009; Oikawa and Sng, 2016). Antipsychotics and antidepressants are prescribed both in acute phases and maintenance phases, especially when subthreshold symptoms remain. While antipsychotics and mood stabilizers tend to effectively treat mania (Perlis et al., 2006), the treatment of bipolar depression is more challenging, as these agents may not improve depressive symptoms (Calabrese et al., 2007; Sachs et al., 2007), and treatment with antidepressants may induce phase switching, particularly with monotherapy (Post et al., 2006; Viktorin et al., 2014). An additional limitation to effective treatment options is the current lack of understanding of the underlying pathophysiology of bipolar depression (Sigitova et al., 2017). Therefore, several new biological hypotheses are emerging, including neuro-inflammation (Naaldijk et al., 2016), neurodegeneration (Myint and Kim, 2014), and, relevant to the current review, mitochondrial dysfunction (Kato and Kato, 2000; Kato, 2007, 2010).

Different lines of evidence implicate mitochondrial impairment in BD. A higher prevalence of mood disorders is reported in people with mitochondrial diseases compared to the general population (Fattal et al., 2007). Furthermore, morphological abnormalities and marginal distribution of mitochondria were reported both in postmortem prefrontal cortex samples and peripheral cells from living BD patients. These findings were controlled for lithium treatment (Cataldo et al., 2010). A plethora of molecular data also confirms abnormal energy metabolism in BD. Indeed, postmortem studies have reported higher lactate concentrations in the brain of people with BD, which suggests a shift from oxidative phosphorylation to glycolysis (Dager et al., 2004). This observation has been supported by similar studies using magnetic resonance spectroscopy (Stork and Renshaw, 2005) and cerebrospinal fluid studies (Regenold et al., 2009). Val66met, a brain-derived neurotrophic factor polymorphism that has been associated with BD, results in lower prefrontal cortex phosphocreatine (PCr) and creatine levels in BD patients (Frey et al., 2007).

Electron transport chain complex I is decreased in both levels and activity in BD patients (Andreazza et al., 2010). Moreover, BD patients downregulate nuclear transcripts for proteins of the entire electron transport chain when subject to glucose deprivation, while controls seem to have the opposite response (Naydenov et al., 2007). There is also robust evidence of increased lipid peroxidation and alterations in calcium metabolism in BD (Munakata et al., 2004; Kato, 2008). A decrease in the expression of genes regulating oxidative phosphorylation and proteasome degradation in BD patients in comparison to patients with schizophrenia (SZ) and healthy controls was also shown (Konradi et al., 2004). High energy requirements in the brain may also increase the production of reactive oxygen species (ROS), potentially damaging mitochondria themselves, resulting in an exacerbation of mitochondrial energy production failure (Hagen et al., 2002a).

Some already approved drugs for BD treatment affect mitochondrial function. Lithium and valproic acid may induce selective complex III and V phosphorylation and increase energy production (Corena-McLeod et al., 2013). Lithium treatment increased electron transport chain complex I expression and activity in postmortem brain studies (Sun et al., 2006a). Lithium has also been robustly associated with lower oxidative stress levels (Khairova et al., 2011; Banerjee et al., 2012; de Sousa et al., 2014) and a reversal of mitochondrial calcium alterations (Machado-Vieira et al., 2011). Atypical antipsychotics increase superoxide dismutase gene expression and have antiapoptotic properties (He et al., 2009).

As our understanding of the pathophysiology of BD increases, new compounds targeting mitochondrial function are of interest. The aim of this review is to give an update on potential interventions for BD that act via modulation of mitochondrial function (see Table 1). Where available, data from randomized controlled trials were preferred. However, where no clinical data exist, data from case reports or open-label studies were also discussed.

## Mitochodrial Agents

### N-Acetyl Cysteine

N-acetyl cysteine (NAC) is increasingly being used as an adjunctive therapy in psychiatry (Berk et al., 2013). Its use across psychiatric disorders is due to the number of mechanisms of action relevant to mental illness. In addition to providing rate-limiting cysteine for glutathione production, NAC has also been shown to be an antiinflammatory, enhance neurogenesis, decrease apoptosis, modulate glutamate pathways, and, importantly, alter mitochondrial activity (Samuni et al., 2013). In both mouse (R6/1) and rat (3-nitropropionic acid) models of Huntington's Disease, NAC has been shown to restore mitochondrial respiration (Wright et al., 2015) and complex activity (Sandhir et al., 2012). Restoration of mitochondrial respiration has also been shown in rat models of traumatic brain injury as well as improvements in mitochondrial complex activity and mitochondrial glutathione (Patel et al., 2014).

There is promising clinical evidence in support of adjunctive NAC in diverse psychiatric disorders (Deepmala et al., 2015). A systematic review and meta-analysis has shown that overall, adjunctive NAC treatment seems beneficial for both unipolar and bipolar depression (Fernandes et al., 2016).

To date, there have been 2 multi-site trials of NAC specifically exploring its use as an adjunctive treatment for BD. Several substudies have also been reported from these data. The initial study was conducted in participants with BD (n = 75) that were experiencing any symptoms (or euthymic). At 6 months post-baseline, participants that received 2000 mg/d NAC (in addition to standard treatment) reported improved measures of BD symptoms, functioning, and quality of life. This improvement persisted up to 4 weeks following NAC treatment cessation. Adverse effects did not significantly differ between the NAC and placebo groups (Berk et al., 2008).

Posthoc exploratory analyses were performed on a variety of data from this trial to assist in identifying who might benefit most from adjunctive NAC treatment in BD. This series of studies included the investigation of mania (or hypomania), bipolar II, major depressive episodes, cognition and comorbid systemic illness (Magalhães et al. 2011a, 2011b, 2013; Dean et al., 2012). When exploring major depressive episodes within the context of a BD sample, there were improvements following adjunctive

Table 1. Summary of Clinical Evidence

| Studies | | Findings | Conclusion | Limitations |
|---|---|---|---|---|
| NAC | | | | |
| Berk et al., 2008a | DBRPC of adjuntive treatment of depressive symptoms in 75 BD patients in maintenance phase with NAC (2 g/d for 24 weeks + 4-weeks washout) | *PO: improvement on the MADRS sores 16.6 to 6.6 (week 24)<br>Difference between placebo: -8.05<br>Benefits time-dependent<br>Response NAC vs placebo: 50% reduction in total MADRS score:<br>week 20 (46% vs 21%)<br>week 24 (51% vs 18%)<br>SO: Beneficial compared with placebo on symptoms, functioning, and quality of life | NAC is an effective and safe adjunctive treatment for depressive symptoms in BD | No effect on time to a mood episode (PO)<br>Improvements in MADRS were lost after washout |
| Berk et al., 2011 | An 8-week open label phase of DBRPCT on efficacy of NAC (2 g/d) as adjunctive treatment in BD on 149 patients with moderate depression | *PO: reduction on BDRS score 19.7 to 11.1 after 8 weeks of treatment (P < .001)<br>SO: reduction on MADRS scores, YMRS scores, SLICE-LIFE scores, CGI-BP (depression and overall) and improvements in GAF, SOFAS, Q-LES-Q | Robust decrement in depression scores with NAC treatment | No placebo group<br>Inclusion of BD I, II & NOS<br>Concomitant therapies |
| Berk et al., 2012 | A 24-week DBRPCT of adjunctive NAC treatment of maintenance phase of 149 BD patients who were previously screened for depression and received 2 g/d NAC for 8 weeks and were randomized to maintain NAC adjunctive treatment or switch to placebo | *PO: time to any intervention for mood symptoms was 199.9 d for the NAC group and 177.5 d for the placebo group<br>22 patients (37.3%) in the NAC group and 30 (48.4%) in the placebo group had a depressive episode, but the survival time for the NAC group was longer than for those in the placebo group (170.2 d vs 137.4 d)<br>7 patients (11.9%) in the NAC group and 2 (3.2%) in the placebo group had a manic episode during the maintenance phase phase (survival analysis was not conducted)<br>13 interventions for mood events in both groups<br>SO: No significant alterations in clinical and functioning measures | There were no significant differences between groups in recurrence or symptomatic outcomes<br>The improvements in depressive symptoms reached a plateau in the open-label phase and symptoms changed little from this very low base in randomized phase | Absence of restrictions on cormobid diagnosis<br>Concomitant therapies<br>Sample size<br>Length of the trial |
| CoQ10 | | | | |
| Forester et al., 2012 | An 8-week open label trial on CoQ10 (0.4-1.2 g/d) effects on CK activity and mood (measured with PMRS and MADRS, respectively) as adjunctive treatment of 10 BD patients ≥55 years old in depression phase + 8 healthy controls | *PO: Kfor of CK were 0.19 vs 0.2 as baseline in BD vs controls and 0.03 for BD and controls after 8 weeks<br>SO: decrease in MADRS scores | No significance difference between group in Kfor of CK<br>Significant improvements in depression symptoms | Sample size<br>No placebo group<br>Concomitant therapies |

Table 1. Continued

| Studies | | Findings | Conclusion | Limitations |
|---|---|---|---|---|
| **NAC** | | | | |
| ALA | | | | |
| Brennan et al., 2013 | A 12-week PCL of adjunctive treatment of 40 BD patients in depression phase with ALA (0.6–1.8 g/d) and ALC (1-3 g/d) | *PO: No significant changes were found between groups on MADRS scores<br>In 20 patients (10 ALC/ALA and 10 placebo) phosphocreatine levels were measured by PMRS analyses: no differences found at baseline, no significant association between change in primary $^{31}$P-MRS measures and MADRS scores | ALA and ALC did not show antidepressant effects or affect mitochondrial function | Length of the trial<br>Inclusion of BD I, II & NOS<br>Concomitant therapies<br>Low oral bioavailability of ALC and ALA |
| SAMe | | | | |
| Murphy et al., 2014 | A 4-week DBRCT of adjunctive treatment with SAMe (1.6 g/d) in 28 BD patients with depression episode (+2 weeks of no medications) | *PO: no significant differences were observed in MADRS (0.04 vs 1), HAM-D (-0.56 vs 1) between SAMe and placebo group<br>SO: no difference in YMRS (1.03 vs 0.32) | No improvements in depressed patients beyond those observed in the placebo-treated group | Low oral bioavailability |
| Lipinski et al., 1984 | A 14-d open trial with SAMe (200 mg/d i.v.) with 6 BD in depressive phase and 3 MDD | 8 patients showed reduction in HAM-D scores ≥8 points (much improvement)<br>2 patients developed mania or hypomania | Antidepressant effect | Preliminary data |
| CM | | | | |
| Roitman et al., 2007 | A 4-week open label trial with CM (3-5 g/d) adjunctive treatment in 2 BD + 8 MDD patients | Improved HAM-D, CGI, and HAM-A scores for 8 MDD patients<br>Switch to elevated mood in both BD patients | Beneficial effect of creatine augmentation in unipolar depression, but possible precipitation of manic switch in bipolar depression<br>Beneficial effect of creatine augmentation in unipolar depression, but possible precipitation of a manic switch in bipolar depression<br>Beneficial effects on unipolar depression<br>Possible manic switch in BD | Preliminary data<br>Small sample |
| Melatonin | | | | |
| Romo-Nava et al., 2014 | An 8-week RDBPGPCCT of melatonin (5 mg/d) adjunctive treatment (+2GAP) of 20 BD + 24 SZ | *PO: melatonin group vs placebo: mean changes in DBP: 5.5 mmHg vs 5.7 mmHg; fat mass: 2.7 vs 0.2 kg; triglycerides: 50.1 vs 20 mg/dL (only in BD patients, not SZ)<br>SO measures:<br>Similar improvements in HAM-D and YMRS scores in the BD placebo and melatonin groups of BD placebo or melatonin groups | Beneficial metabolic effect with melatonin-treated patients suggests that melatonin may help to reestablish a damaged circadian rhythm in BD | |

Table 1. Continued

| Studies | | Findings | Conclusion | Limitations |
|---|---|---|---|---|
| NAC | | | | |
| Bersani and Garavini, 2000 | A 4-week open label trial of melatonin adjunctive treatment of 11 BD patients in manic phase with insomnia | All patients had longer hours of sleep and severity of mania Significant decrease in BFRS scores | Melatonin improved mania scale scores by the normalization of sleep/wake cycle | Open study<br>Small sample<br>Measurement of sleep duration subjective—self-rating sleep questionnaire |
| Pyrimidines | | | | |
| Kondo et al., 2011 | A 6-week open label trial of adjunctive treatment with uridine (1 g/d) of 7 BD teenagers in depressive phase | Improvement in the CDRS-R: 65.6 at baseline vs 27.2 after 6 weeks (54% reduction) | Uridine was efficacious and well tolerated, showing a potential role in BD treatment | Concomitant therapies<br>Inclusion of BD I, II & NOS |
| Jensen et al., 2008 | A 6-week trial of adjunctive treatment of 11 BD patients with depression with TAU (18 g/d) | 6 patients responded to TAU, 5 did not<br>TAU responders showed pH changes from baseline<br>% changes and time effects of TAU on MADRS may indicate improvement in early symptoms | TAU treatment may have clinical and biochemical effects—decrease symptoms of depression and improve mitochondrial functioning | Small and heterogeneous population<br>Gender disproportion<br>No restrictions on medications |
| Yoon et al., 2009 | A 12-week DBRPCT of cytidine adjunctive treatment (with valproate) of 35 BD patients in depressive phase | Improvement in depressive symptoms<br>Reduction in cerebral glutamate/glutamine measured with PMRS<br>Glutamate/glutamine alterations and reduction in depressive symptoms correlated in cytidine group and not in placebo group | Cytidine augmentation of valproate associated with earlier response and reductions in cerebral glutamate/glutamine levels | |
| Vitamin C | | | | |
| Naylor and Smith, 1981 | A 2-d RPT of treatment of 23 BD (11 manic and 12 depressed) with 3 g/d of vitamin C or placebo | Lowest scores on the vitamin C-treated day were significantly lower ($P < .005$) than those on placebo-treated day (similar results even in patients divided into manic and depressed groups) | | Small sample<br>Short period of time<br>No control group |
| Kay et al., 1984 | A 28-d DBPCT with 61 BD female patients:<br>29 manic (13 were medicated with 800 g/d lithium and 16 received 4 g vitamin C+4 g EDTA)<br>32 depressed (14 were medicated with 150 mg amitriptiline and18 received 4 g vitamin C + 4 g EDTA) | Manic participants responded better to lithium than to vitamin C (43.3 vs 70.6) in the Beigel rating scale<br>There was no significant difference in depression symptoms between amitriptyline or vitamin C in the depressed group on HAM-D (8.4 vs 10.7) and BDI (16.6 vs 19.8) ratings | Vitamin C could be important in the co-treatment of bipolar depression, but the results do not support for mania | Small sample<br>Withdrawn patients |
| Vitamin D | | | | |
| Sikoglu et al., 2015 | An 8-week open label trial of adjunctive treatment with vitamin D (2000 IU) of 16 BD patients (6-17 y old) in manic phase | Decrease in YMRS scores<br>Decrease in CDRS scores<br>Significant increase in anterior cingulate cortex (ACC) glutamate, and γ-aminobutyric acid measured with PMRS | 43% improvement in manic symptoms | Open label<br>Small sample<br>Medication effects as a confounding factor |

Table 1. Continued

| Studies | | Findings | Conclusion | Limitations |
|---|---|---|---|---|
| **NAC** | | | | |
| Vitamin B9 (folic acid) | | | | |
| Behzadi et al., 2009 | A 3-week DBPRCT of adjunctive treatment of folic acid (+valproate) of 88 BD manic patients | Statistically significant difference in YMRS scores between BD group and control groups (7.1 ± 0.9 vs 10.1 ± 1.1) | Folic acid use as augmentation to valproate showed better response in BD patients in treatment of acute mania | Short follow-up |
| Coppen et al., 1986 | A 52-week DBPRCT of adjunctive treatment of 200 μg folic acid (+lithium) of 75 BD (n = 17), MDD, and schizoaffective patients | 21 patients with plasma folate concentration ≤12.9 ng/mL had a higher Beck score (6.6 + 1.7) than the 18 patients with plasma folate concentration >13.0 ng/mL (3.5 + 0.8) | Lower plasma folate concentrations can be correlated with higher affective morbidity<br>Daily supplement of folic acid could be helpful in long-term lithium prophylaxis | |
| Nierenberg et al., 2017 | A 6-week open label of adjunctive treatment with L-methylfolate (15 mg/d) of 10 BD patients in depressive phase | 55% improvement in depression symptom in MADRS and small mean decrease in YMRS | Potential as BD adjunctive treatment | |
| Choline | | | | |
| Stoll et al., 1996 | Collection of 6 case reports of choline augmentation of lithium in rapid-cycling BD patients | 5 patients had reduction of manic symptoms<br>2 patients had improvement on depressive symptoms<br>Choline responders exhibited a basal ganglia rise in concentration of choline-containing compounds | Choline was well tolerated in all cases and in combination with lithium could be an effective therapy | |
| Lyoo et al., 2003b | A 12-week DBT of adjunctive treatment of choline (+lithium) of 8 rapid-cycling BD patients | No significant differences in change-from-baseline measures of CGI, YMRS, or HAM-D<br>Choline-treated group showed decreased brain purine levels compared with placebo | Adjuvant treatment with choline resulted in lower purine levels and increased membrane phospholipid synthesis | |

Abbreviations: ALA, α-lipoic acid; ALC, acetyl-L-carnitine; BDI, Beck Depression Inventory; BD, bipolar disorder; BDRS, Bipolar Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; CDRS-R, Children's Depression Rating Scale-Revised; CGI-BP, Clinical Global Impressions-Bipolar Disorder; CK, creatine kinase; CoQ10, coenzyme Q10; CM, creatine monohydrate; DBP, diastolic blood pressure; DBRPCT, double-blind randomized placebo-controlled trial; EDTA, ethylene diamine tetra acetic acid; GAF, Global Assessment of Functioning; 2GAP, second generation antipsychotics; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Rating Scale for Depression; Kfor, forward rate constant; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depression disorder; NAC, N-acetyl cysteine; NOS, not otherwise especified; PCL, placebo control trial; PMRS, phosphorus magnetic resonance spectroscopy; PMRS, proton magnetic resonance spectroscopy; PO, primary outcomes; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; RDBPGPCCT, randomized, double-blind, parallel-group, placebo-controlled clinical trial; SAMe, S-adenosylmethionine; SLICE-LIFE, Streamed Longitudinal Interval Clinical Evaluation for the Longitudinal Interview Follow-Up Evaluation; SO, secondary outcomes; SOFAS, Social and Occupational Assessment Scale; SZ, schizophrenia; TAU, triacetyluridine; YMRS, Young Mania Rating Scale.

NAC compared with placebo (Magalhães et al., 2011b). The investigation of those experiencing mania indicated within-group improvements in the NAC group (Magalhães et al., 2013). Similarly, when exploring a subgroup of participants (n = 14) with bipolar II (divided in 2 groups of 7 patients each randomized to placebo or NAC), NAC was found to improve symptoms in 6/7 participants, compared with 2/7 in the placebo group (Magalhães et al., 2011a). NAC was also shown to improve functional outcomes for people experiencing cardiovascular or endocrine comorbidities when compared to those who did not (Magalhães et al., 2012). Finally, a paper on posthoc analyses has reported no change in cognition in a small subset of participants following NAC (Dean et al., 2012).

The next study included a maintenance design with an initial open-label phase. Participants were given 2000 mg/d of NAC (n = 149) for a total of 8 weeks and were then randomized to continuation of adjunctive NAC treatment or a placebo. The open-label phase showed significant improvements in participants experiencing bipolar depression (Berk et al., 2011). However, in the maintenance (randomized) phase, participants in both arms generally stayed well, which resulted in no significant treatment effects (Berk et al., 2012).

We further searched ANZCTR and Clinicaltrials.gov to ascertain if there are upcoming studies in this area. A protocol has been published describing a study of NAC and a combination of other agents that enhance mitochondrial function, compared with placebo, over 16 weeks of treatment (Dean et al., 2015).

Overall, NAC is a potentially useful adjunctive therapy for BD and, in particular, bipolar depression during the acute phase. NAC has been shown to enhance mitochondrial function in preclinical models. However, no clinical studies that have investigated NAC for BD have evaluated outcomes related to mitochondrial function. Further research is required to explore the interactions of NAC clinical efficacy and changes in relevant pathways, including pathways relevant to mitochondrial function.

## Coenzyme Q10

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a powerful lipid-soluble antioxidant that reduces the flow of electrons on the ROS-producing regions of Complex I, II, and III of the mitochondria (Lenaz et al., 2002; Nierenberg et al., 2013). CoQ10 reduces ROS by neutralizing the free radical alpha-tocopheroxyl to alpha-tocopherol (vitamin E) and plays a role in the biosynthesis of adenosine triphosphate (ATP) (Morris et al., 2013; Nierenberg et al., 2013). The genes associated with these complexes and the transportation of electrons across them are expressed differently in BD compared with healthy controls (Sun et al., 2006b). Supplementary CoQ10 has poor oral bioavailability; however, it does cross the blood-brain barrier (Matthews et al., 1998).

Morris et al. (2013) discussed the reduction in CoQ10 levels in psychiatric and mitochondrial disorders such as depression, chronic fatigue syndrome, fibromyalgia, and Parkinson's disease and postulated that CoQ10 supplementation could be a treatment for these disorders. However, a meta-analysis of CoQ10 supplementation compared with placebo showed no significant benefits for participants with Parkinson's disease (Negida et al., 2016).

There have been several studies proposing the use of CoQ10 supplementation as a mitochondrial enhancing agent in general and for BD in particular (Morris et al., 2013; Nierenberg et al., 2013). Despite this, there have been only 2 studies directly looking at CoQ10 supplementation and BD. One study explored CoQ10 in combination with other mitochondrial agents (such as NAC and b-group vitamins) as an adjunctive treatment for bipolar depression (Dean et al., 2015). This study has been completed but results are still pending.

Forester et al. (2012) investigated an 8-week intervention of CoQ10 in a sample of 10 outpatients aged 55 years and older with a DSM-IV diagnosis of bipolar depression in an 8-week study. Participants were administered CoQ10 and compared with 8 healthy controls who did not receive CoQ10 supplementation. The maximum dose of CoQ10 was 1200 mg/d, starting at 400 mg/d and titrated up by 400 mg/d every 2 weeks. Participants on CoQ10 showed modest but significant improvements in their depression symptoms (measured on the Montgomery–Åsberg Depression Rating Scale MADRS) over the 8-week study. Furthermore, this study also investigated mitochondrial function via phosphorus magnetic resonance spectroscopy and reported no significant differences between groups for creatine kinase (a mitochondrial protein). This small study is limited by the sample size and lack of placebo control but highlights the potential of CoQ10 as an antidepressant and treatment for BD.

## Alpha-Lipoic Acid

Alpha-lipoic acid (ALA), also known as thioctic acid, is a pleiotropic substance (Gomes and Negrato, 2014). ALA is a strong antioxidant (Suzuki et al., 1991; Moini et al., 2002). It increases levels of glutathione (Han et al., 1997; Yamada et al., 2011; Kleinkauf-Rocha et al., 2013), raises hepatocyte ascorbate levels (Lykkesfeldt et al., 1998; Michels et al., 2003), downregulates nuclear factor kappa-light-chain-enhancer of activated B cells (DeMarco et al., 2004), and is a metal chelator (Ou et al., 1995; Suh et al., 2005), an antiviral in glial cells (Scumpia et al., 2014), and a glucose uptake promoter (Estrada et al., 1996; Henriksen et al., 1997; Saengsirisuwan et al., 2004), increasing GLUT4 levels and insulin action (Hughes et al., 1993). Relevant to the current review, ALA also has a role as a mitochondrial agent. It can be endogenously synthesized in the mitochondria where it acts as a coenzyme for the formation of pyruvate dehydrogenase and α-ketoglutarate—both essential components of the Krebs cycle. Because pyruvate dehydrogenase converts pyruvate to acetyl CoA, ALA decreases lactate levels, thus inhibiting glycolysis (Gomes and Negrato, 2014). It also modulates the key regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PPAR-GC-1α) (Liu, 2008). PPAR-GC-1α stimulation has been linked to neuroprotection and its suppression to mitochondrial dysfunction and neurodegeneration (Cui et al., 2006; St-Pierre et al., 2006). ALA also affects the mitochondrial pathway of apoptosis, prompting research in oncology as an agent with antimetastatic potential (Dörsam and Fahrer, 2016). This provides a rationale for its action in mood and cognitive disorders.

In a corticosterone-induced model of depression in mice, ALA showed antidepressant properties and reversed brain-derived neurotrophic factor reduction in the hippocampus and striatum (de Sousa et al., 2015). In a d-amphetamine-induced model of mania, ALA was able to both prevent and reverse symptoms with comparable efficiency to lithium (Macêdo et al., 2012).

Only one clinical trial has explored ALA as an adjunctive treatment for bipolar depression. The trial tested a combination of ALA (600–1800 mg/d) and acetyl-L-carnitine (ALC) (1000–3000 mg/d) or placebo for 12 weeks in 40 participants with bipolar depression. Previous treatment (stable for at least 4 weeks) was continued. The primary outcome was depression, measured on

the MADRS. No significant changes were found between groups (Brennan et al., 2013). As the authors note, the shorter duration of the study (12 weeks) compared with a positive RCT of a mitochondrial agent (NAC) in BD (24 weeks) (Berk et al., 2008), the inclusion of bipolar I and II types, concomitant medication use, and possible low oral bioavailability of the agents are all potential confounders that should be addressed.

More research is required to determine the efficacy of ALA in BD. Moreover, there is one study (described earlier) in bipolar depression that is currently being completed that includes a combination of agents including ALA, ALC, and NAC (ACTRN12612000830897).

### ALC

In addition to the role of ALC in mitochondrial β-oxidation and energy production (Hoppel, 2003), ALC has antioxidant properties (Gülçin, 2006; Mescka et al., 2011). Additionally, ALC has been proposed to mediate the transfer of acetyl groups for acetylcholine synthesis, modulate nerve growth factors and gene expression (Nałecz and Nałecz, 1996; Binienda, 2003; Nacz et al., 2004), and counter glutamate-induced excitotoxicity (Zanelli et al., 2005).

Data from animal models provide further evidence for ALC's therapeutic potential due to its role as an antioxidant and in improving mitochondrial energy production (Rao et al., 1997; Aureli et al., 1998; Hagen et al., 2002b; Al-Majed et al., 2006), its neuroprotective action in trauma (Karalija et al., 2014) and ischemia (Rosenthal et al., 1992; Barhwal et al., 2007), its antidepressant effect in the forced swim test (FST) (Wang et al., 2015), and its ability to reverse memory loss in older rats (Liu et al., 2002).

Two patients with geriatric depression treated with ALC showed increases in PCr and β-nucleoside triphosphate (β-NTP) levels (Pettegrew et al., 2002). PCr serves as a reservoir for high-energy phosphates, and β-NTP is acknowledged as an index of brain levels of ATP. Thus, these results provide support for a link between the antidepressant action of ALC and improved energy production within the brain.

However, the only RCT in BD reported no effect when administered in combination with ALA (Brennan et al., 2013) (see above). Furthermore, the change in PCr and β-NTP, previously found in geriatric depression patients (Pettegrew et al., 2002), was not observed (Brennan et al., 2013). Two case reports of ALC-associated relapse in BD also suggest some caution with clinical use. The first case-reports detail a psychotic episode in a known BD type I patient, 5 days after starting treatment with nutritional supplements including vitamin C, vitamin E, and ALC (500 mg/d) (Evcimen et al., 2007). Manic symptoms associated with self-prescribed ALC treatment (2000 mg/d) in a man with BD type I resolved 3 days after cessation of ALC (Goodison et al., 2016).

### S-Adenosylmethionine

S-Adenosylmethionine (SAMe) results from the combination of ATP and methionine and plays a crucial role as a methyl donor in reactions involving methyltrasnferases (Bottiglieri, 2002). SAMe is also a precursor molecule for glutathione production, which plays an essential role in reducing oxidative stress. In the brain, SAMe repairs and degrades proteins and activates thyroxine hydroxylase through methylation, which is critical in the synthesis and regulation of monoamines (i.e., dopamine, serotonin), which are known to be dysregulated in BD (Bottiglieri et al., 2000, 2002). Recently, an RCT of SAMe as an add-on to an approved mood stabilizer in 20 participants with BD (type I and II) was conducted. To enroll, subjects were required to have not responded previously to either 2 antidepressants (of different classes) or to 2 different mood stabilizers. No significant differences were observed in MADRS, Hamilton Rating Scale for Depression (HAM-D), or Young Mania Rating Scale (YMRS) between the SAMe and placebo groups. No switches to mania were reported (Murphy et al., 2014). Carney et al. (1989) reported 3 open label trials and 1 placebo-controlled trial after a drug-free period of at least 7 days. There were 14 unipolar depression and 11 BD participants. Nine of the 11 BD participants switched to hypomania, mania, or "elevated mood." The other 2 participants did not respond to treatment (Carney et al., 1989). In an open-label trial of i.v. SAMe monotherapy for depression, 7 of 9 patients improved or had depression remission. There were 2 case reports of mood switch in BD patients, 1 of mania, and 1 of hypomania (Lipinski et al., 1984). Due to the potential for manic switching, SAMe for BD should be investigated with caution. In unipolar depression, a meta-analysis in 2002 showed that SAMe is superior to placebo improving HAM-D scores (Hardy et al., 2003). A recent systematic review collected clinical information from 115 clinical trials and 17 preclinical studies on the effect of SAMe on several neuropsychiatric conditions. Positive but limited evidence was found for the use of SAMe in major depressive disorder (MDD) as both a monotherapy and adjunctive therapy (Sharma et al., 2017). Recently, 2 studies have demonstrated benefits of SAMe as an augmentation antidepressant therapy. In a 6-week, double blind, placebo RCT with serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors non-responders, participants undergoing SAMe augmentation had lower HAM-D score and higher remission rates (final HAM-D score <8) than placebo (Papakostas et al., 2010).

### Creatine Monohydrate

Creatine is the precursor of PCr. Long-term decrease of PCr decreases ATP production, attributable to mitochondrial dysfunction (Erecińska and Silver, 1989). Oral supplementation of creatine monohydrate increases creatine and brain concentrations of PCr (Dechent et al., 1999; Lyoo et al., 2003a). In BD, decreased PCr concentrations have been reported (Stork and Renshaw, 2005). Furthermore, creatine has been shown to have antioxidant properties in animal models of oxidative stress (Sullivan et al., 2000; Tarnopolsky and Beal, 2001; Lawler et al., 2002)

A 4-week open-label trial with 10 participants experiencing treatment-resistant depression (8 unipolar and 2 bipolar) showed improved depression scores with 3 to 5 g/d creatine monohydrate augmentation, provoking switch to elevated mood in both BD patients (Roitman et al., 2007). Two trials focusing on a combination of cytidine and creatine in bipolar depression are currently being conducted (NCT01543139; NCT02625779). A 6-week, double blind, placebo RCT to evaluate the efficacy of creatine monohydrate as an adjunctive therapy for BD type I depression (NCT01655030) is also currently recruiting.

### Melatonin

Melatonin regulates several homeostatic processes such as circadian rhythm maintenance, growth hormone stimulation, and insulin secretion (Paredes et al., 2014; Simões et al., 2016; Zhang et al., 2016). Relevant to mitochondrial physiology, melatonin improves oxidative phosphorylation, increasing the activity of the I and IV dose-dependent complexes and membrane fluidity and closes the mitochondrial permeability transition pore

(a protein complex spanning the inner and outer mitochondrial membranes), preventing ATP depletion and necrotic cell death (Acuña-Castroviejo et al., 2001, 2007; Martín et al., 2002; Leon et al., 2005). Moreover, melatonin and some of its metabolites play an important antiinflammatory and antioxidant role through scavenging oxygen and nitrogen-based ROS (López-Burillo et al., 2003; Korkmaz et al., 2009). Melatonin directly boosts mRNA expression of genes implicated in the production of glutathione peroxidase and superoxide dismutase, 2 antioxidant enzymes (Rodriguez et al., 2004; Acuña-Castroviejo et al., 2007; Anderson and Maes, 2014). Furthermore, peripheral melatonin, produced outside the brain, is decreased in BD compared with healthy controls, suggesting supplemental melatonin may be a relevant intervention in this population (Anderson and Maes, 2014).

In an 8-week, double blind, placebo control trial, 44 participants (24 participants with SZ and 20 with BD) treated with second-generation antipsychotics received low dosages of melatonin (5 mg/d) and placebo. The melatonin group showed lower diastolic blood pressure and less weight gain, these results being greater in the BD group (Romo-Nava et al., 2014). In an open-label trial, melatonin improved mania scale scores and sleeping patterns (Bersani and Garavini, 2000) but had no significant effects on mood or sleep in a double-blind, placebo-controlled trial using the same dose with 5 rapid-cycling DSM-III-R BD patients (Leibenluft et al., 1997).

McElroy et al. (2011) tested ramelteon (a highly selective melatonin MT1/MT2 receptor agonist) as an adjunctive treatment in 21 outpatients with bipolar I disorder with mild-to-moderate manic symptoms and sleep disturbance in an 8-week, double-blind, fixed-dose (8 mg/d) study. A global improvement in a global rating of depressive symptoms was reported; however, no significant differences in ratings of insomnia, mania, and global severity of illness were observed. Norris et al. (2013) conducted a double-blind, randomized, placebo-controlled trial of adjunctive ramelteon in euthymic bipolar patients with sleep disturbances and reported that participants receiving ramelteon were significantly less likely to relapse compared with placebo. Recently, a RCT comparing placebo with sublingual ramelteon in different dosages (0.1 mg, 0.4 mg, 0.8 mg, once daily) as adjunctive maintenance therapy in stable BD patients did not show significant differences between any dose of ramelteon and placebo (Mahableshwarkar et al., 2017). The study was terminated before the expected sample size due to meeting the futility criteria. All studies showed ramelteon was well tolerated and associated with no serious adverse events.

Agomelatine (an agonist of melatonin 1 and 2 receptors and antagonist of serotonin 2C receptors drug) has also been investigated as an adjunctive treatment for bipolar depression. In an open-label trial with 21 type I BD patients in a severe depressive episode (14 treated with lithium and 7 with valpromide), agomelatine was added at 25 mg/d for at least 6 weeks and, if participants opted-in, up to 1 year. At week 6, 81% of patients improved >50% in HAM-D score from baseline and almost 50% in the first study week. Three patients switched to mania or hypomania from the sixth week until the complete year follow-up (Calabrese et al., 2007). In a similar study, 28 type II BD patients in a severe depressive episode (11 treated with lithium and 17 with valproate) were treated with agomelatine at fixed dosages of 25 mg/d from at least 6 weeks to a possible 30-week extension. At 6 weeks, 64% of patients improved >50% in HAM-D score from baseline and 86% responded at 36 weeks. There were 4 drop-outs in total due to polarity change (1 manic and 3 hypomanic episodes) (Fornaro et al., 2013). Recently, 344 type I BD patients undergoing a current major depressive episode that were treated with lithium or valproic acid for at least 6 weeks were randomized to treatment with agomelatine or placebo (n = 172 each group) in a double-blind study (Yatham et al., 2016). No significant differences between both groups in MADRS total score or response or remission rates from baseline to endpoint were found. The number of manic or hypomanic symptoms was comparable between both groups at each assessment time. As a number of sites had placebo response rates of 100%, when these were excluded in a posthoc analysis, a signal favoring agomelatine over placebo emerged. While the meta-analyses in unipolar depression confirm the antidepressant effects of agomelatine (Singh et al., 2012; Taylor et al., 2014), melatonin supplementation did not significantly improve treatment or prophylaxis of unipolar depression (Hansen et al., 2014).

## Pyrimidines

The pyrimidine nucleosides such as uridine, triacetyluridine, and cytidine have effects on mitochondrial function, glutamatergic transmission, catecholamine synthesis, and cerebral phospholipid metabolism, which has been linked to the pathophysiology of BD (Yoon et al., 2009; Kondo et al., 2011). Uridine (1000 mg/d) was studied in a 6 weeks open-label trial of 7 teenagers with bipolar depression. Children's Depression Rating Scale-Revised and the Clinical Global Impressions scale were used to measure the treatment results. Uridine was well tolerated and depressive symptoms decreased (Kondo et al., 2011).

In another 6-week study (n = 20), 18 g/d day of triacetyluridine (TAU), a uridine prodrug, or placebo was given to patients with bipolar depression. BD patients who had a reduction in MADRS scores ≥50% showed a greater difference in pH changes (assessed by phosphorus magnetic resonance spectroscopic imaging (PMRSI)) compared with TAU nonresponders, suggesting that TAU treatment can have benefits in depressive symptoms and in mitochondrial function (Jensen et al., 2008). Cytidine, available from dietary sources and converted in uridine in the human body, was investigated in a 12-week, randomized, placebo trial with 35 patients with bipolar depression. Participants were randomly given valproate plus placebo or valproate plus cytidine. At 2, 4, and 12 weeks, the cerebral levels of glutamate/glutamine were measured using PMRSI. The results showed that cytidine supplementation resulted in earlier improvement in symptoms of depression and greater reduction in glutamate/glutamine levels. These data suggest that the observed therapeutic effect of cytidine may be mediated via a decrease in cerebral glutamate/glutamine levels (Yoon et al., 2009).

## Choline

Choline is a constituent of the neurotransmitter acetylcholine, a major methyl-donor, and needed for structural integrity and intracellular signaling within cell membranes. In an open-label trial, Stoll et al. (1996) studied the effects of lithium augmentation with choline in 6 rapid-cycling BD outpatients. Five participants experienced a reduction in manic symptoms and 4 had a reduction in all mood symptoms during choline therapy. The impact on depression was variable. Lyoo et al. (2003b) studied 8 lithium-treated, rapid-cycling BD I and II patients randomized to receive either choline or placebo, and reported significantly decreased brain purine levels, a marker of energy metabolism.

## Vitamin A

Both deficient and excessive levels of vitamin A disrupt many human systems, including the central nervous system (CNS)

(Chapman, 2012). Vitamin A is required for vision, gene transcription, immune system, and skin cell differentiation (Haybaeck et al., 2015). The role of vitamin A in gene expression and its role in redox activation suggest a possible role as a mitochondrial agent in the treatment of BD. Vitamin A also plays a very important role as a co-factor in redox activation, binding to protein kinase C (Hoyos et al., 2012; Hammerling, 2016). Retinoid receptors are concentrated in the striatum, hippocampus, frontal cortex, and hypothalamus, all key brain areas involved in depression (Bremner et al., 2012). Being involved in neuroplasticity in the hippocampus, vitamin A deficiency can also affect memory, appetite, and growth (Haybaeck et al., 2015; Stoney and McCaffery, 2016). Haybaeck et al. (2015) found the brains of patients with SZ, BD, or MDD to have significantly increased expression of vitamin A-inducible or induced gene 1, pointing to altered signaling pathways. Another study found mRNA levels of key elements of vitamin A signaling were significantly reduced in the postmortem dorsolateral prefrontal cortex/anterior cingulate cortex from elderly depressed patients (Qi et al., 2015). A similar signal was detected in a chronic unpredictable mild stress model in rats (Qi et al., 2015). There is evidence of a link between isotretinoin use and depression and suicide (Bremner et al., 2012; Hu et al., 2016), clinical exacerbation of BD, and possibly to psychosis (Ludot et al., 2015). Vitamin A therapy at high doses is also associated with cognitive decline (de Oliveira et al., 2009; 2015) and increased levels of oxidative stress markers in both human and animals (de Oliveira et al., 2009).

### Vitamin C

Vitamin C is an antioxidant capable of scavenging free radicals and other ROS formed in cell metabolism. In addition to its role as an antioxidant, vitamin C is a co-substrate of many important oxidoreductases and may regulate gene transcription (Arrigoni and de Tullio, 2002). Because of these characteristics, vitamin C has been tested as a possible adjunctive therapy in psychiatric disorders. A double-blind, placebo RCT in high school students showed lower levels of anxiety after 14 days of vitamin C supplementation compared with placebo (de Oliveira et al., 2015). Positive results were also reported in a 6-month, double-blind, randomized control pilot trial with 1000 mg/d vitamin C as an adjunct to 10 to 20 mg/d fluoxetine in children (n = 24) diagnosed with MDD (Amr et al., 2013). However, the only RCT testing vitamin C as an adjuvant (1000 mg/d) in the treatment of adults (n = 43) with MDD (added to 60 mg/d citalopram) showed no statistically significant results (Sahraian et al., 2015).

In BD, vitamin C was proposed as a treatment in a double-blind, placebo control cross-over trial, where 23 BD participants receiving 3 g/d of vitamin C reported improvement in depressive symptoms (Naylor and Smith, 1981). Kay et al. (1984) conducted a 28-day, double-blind, randomized active-control study with 61 BD inpatients (29 with manic symptoms and 32 with depressive symptoms). The depressed participants received either 150 mg/d amitriptyline (n = 14) or 4 g/d vitamin C plus 4 g/d ethylene diamine tetra acetic acid (EDTA) (n = 18). The manic participants were also divided into 2 groups—13 were medicated with 800 g/d lithium and 16 received only vitamin C plus EDTA. Manic participants responded better to lithium than to vitamin C. There was no significant difference in depression symptoms between amitriptyline or vitamin C in the depressed group on HAM-D and Beck Depression Inventory (BDI) ratings.

### Vitamin D

Vitamin D is a fat-soluble antioxidant involved in the regulation of calcium and phosphate metabolism. Moreover, vitamin D is implicated in the production of melatonin and in seasonal affective disorder (Gloth et al., 1999). The association between low levels of vitamin D and mood disorders (MDD, BD, and dysthymia) has been established (Anglin et al., 2013; Belzeaux et al., 2015), and it was also identified as a risk factor for development of postpartum depression in pregnant women (Robinson et al., 2014). Furthermore, vitamin D influences monoamine metabolism by modulating the hypothalamic-pituitary-adrenal axis through vitamin D receptors (VDRs) (Puchacz et al., 1996; Prüfer et al., 1999; Eyles et al., 2005). VDRs also affect nuclear transcription, regulate the expression of the dopamine receptor gene (Trinko et al., 2016), and may also be involved in the regulation of mitochondrial function and lipid metabolism (Silvagno and Pescarmona, 2017). VDR is now known to translocate into mitochondria, which raises the possibility of vitamin D having a direct impact on cellular bioenergetics by altering mitochondrial function and VDR to work as a modulator of energy balance in humans (Silvagno and Pescarmona, 2017). Studies on cancer cells (Consiglio et al., 2014), keratinocytes (Consiglio et al., 2015), adipocytes (Ricciardi et al., 2015), and VDR-null mutant mice (Wong et al., 2011) found that VDR can influence the transcription of proteins of the mitochondria respiratory chain, inhibiting it and redirecting Krebs cycle intermediates toward biosynthesis (Consiglio et al., 2014). However, establishing the treatment effect of vitamin D supplementation has been somewhat problematic as studies are likely too heterogeneous (including depression, seasonal affective disorder, obesity, postmenstrual tension, and hospitalized patients). Therefore, varying the selection criteria wields both positive and negative meta-analysis results: A meta-analysis of 15 RCTs (with samples between 15 and 2117) was favorable for vitamin D supplementation (≥800 I.U. daily) (Spedding, 2014), while another meta-analysis using 6 RCTs (n = 1203, 71 depressed) showed no significant effect of vitamin D supplementation on postintervention depression scores (Li et al., 2014). A more recent double-blind RCT of 40 MDD patients on vitamin D monotherapy (50 kIU/d for 8 weeks) showed beneficial effects on the depressive symptoms measured by the BDI on indicators of glucose homeostasis and on oxidative stress levels (Sepehrmanesh et al., 2016). Regarding BD, an 8-week open-label trial tested the effect of adjunctive vitamin D supplementation in mania in young bipolar spectrum disorder patients (aged 6–17 years old). There was a significant decrease in YMRS scores and improvement in levels of glutamate and γ-aminobutyric acid (GABA) measured in the anterior cingulate cortex (Sikoglu et al., 2015).

### Vitamin E

Vitamin E or tocopherol is a fat-soluble antioxidant, which has a stabilizing function in the mitochondrial membrane attributed to radical scavenging and lipid peroxidation reduction (Kagan et al., 1990; Pham-Huy et al., 2008). Studies have suggested that vitamin E may be more effective when combined with CoQ10 or vitamin C (Kontush and Schrkatolina, 2004; Dhitavat et al., 2005). To our knowledge, the efficacy of vitamin E in BD or MDD has not been examined. Some animal studies found positive results—chronic administration of high doses of vitamin E improved lifespan, neurological performance, and brain mitochondrial function in aging mice (Navarro et al., 2005). Likewise, studies in Alzheimer's disease are also promising.

A multi-center RCT studied the effect of vitamin E supplementation in 613 participants with mild-to-moderate Alzheimer's disease, medicated with memantine, and reported slower functional decline and decreased caregiver burden (Dysken et al., 2014). A cross-sectional and prospective study of 104 patients with Alzheimer's disease showed reduced prevalence and incidence of Alzheimer's on those consuming vitamin E plus C supplementation (Zandi et al., 2004). A clinical trial with combined therapy with vitamin C for MDD in elderly patients is now in the recruiting phase (NCT02793648).

## Vitamin B Complex

The vitamin B complex contains water-soluble vitamins B1, B2, B3, B5, B6, B7, B9, and B12. They play an important role in a variety of critical brain pathways and participate in mitochondrial energy production and cellular function (Dean et al., 2012). Vitamin B complex is known to influence cognitive performance and mood. Its influence in CNS function has been suggested to occur in 2 interrelated ways: direct via of hypomethylation and indirectly by homocysteine levels resulting in structural changes in the brain (Calvaresi and Bryan, 2001). They often work in synergy and thereby are best administered as a complex (Dean et al., 2012).

### *Vitamin B9*

Vitamin B9, or folate, is involved in the synthesis, repair, and methylation of DNA and in the formation of monoamine neurotransmitters, thus being important in the pathogenesis of affective disorders (Mattson and Shea, 2003; Folstein et al., 2007; Miller, 2008; Sharpley et al., 2014). Together with vitamin B12, vitamin B9 plays an essential role in mitochondrial energy production through 1-carbon transfer pathways (Dean et al., 2015). Folate deficiency has been associated with several neuropsychiatric disorders, especially in inpatients (Hall et al., 1997; Dean et al., 2015) such as depression, BD, and cognitive dysfunction (Bell et al., 1990; Godfrey et al., 1990; Hasanah et al., 1997; Selhub et al., 2000; Bryan et al., 2002; Reynolds, 2002; Gilbody et al., 2007). Furthermore, in long-term lithium-treated patients, low serum folate levels were associated with higher affective morbidity (Coppen and Abou-Saleh, 1982). Schou et al. (1986) also found low levels of folate in untreated BD patients (25% lower than controls) and their normalization after 6 months of lithium. Behzadi et al. (2009) conducted a preliminary RCT with 88 BD type I manic patients treated with sodium valproate and adjuvant folic acid (synthetic form of folate). After 3 weeks, a statistically significant difference in the YMRS was found. Another double-blind RCT of 75 lithium-treated BD patients on a daily supplementation of 200 μg folic acid for 52 weeks showed a significant reduction in affective morbidity (Coppen et al., 1986). L-methylfolate was also recently studied in the first open-label trial for bipolar depression. Ten patients with BD type I on standard treatment for bipolar depression (but with no antidepressant) received 15 mg of folate daily for 6 weeks. A 55% improvement in depression symptom ratings (MADRS) and a small mean decrease in YMRS was found, suggesting its potential as BD adjunctive treatment (Nierenberg et al., 2017). L-methylfolate has potential as an adjunctive treatment for unipolar depression. Two multicenter sequential parallel comparison design trials were conducted with MDD patients (n = 148 and n = 75) with partial or no response to serotonin reuptake inhibitors. L-methylfolate supplementation was given for 30 days at the dosing of 7.5 mg/d and augmented later to 15 mg/d in the following month in trial one. In trial two, 15 mg/d of L-methylfolate was given for 60 days. The second trial had positive results on primary outcomes—degree of improvement in depressive symptom score and response rate (Papakostas et al., 2012). Folic acid was also found to improve the therapeutic effect of fluoxetine in depressed patients in another 2 placebo-controlled RCTs. Studies with samples of 127 and 42 patients with MDD, respectively, were treated with folic acid plus 20 mg of fluoxetine and showed greater improvement in the HAM-D and in the BDI (Coppen and Bailey, 2000; Venkatasubramanian et al., 2013). Moreover, long-term treatment of post-stroke survivors (n = 273) with folic acid, B6, and B12 was associated with a reduction in the risk for MDD (Almeida et al., 2010). The effect of vitamin B9 as a possible early intervention was studied in a double-blind, placebo RCT in healthy teenagers (n = 112) with increased familial risk of depression and BD. Folic acid did not reduce the incidence of a mood disorder diagnosis but may have delayed the first mood episode and its clinical presentation tended to be milder (Sharpley et al., 2014).

### *Vitamin B1*

Vitamin B1, or thiamine, functions as a cofactor essential for the oxidative decarboxylation of the Krebs cycle (Depeint et al., 2006). Vitamin B1 deficiency is associated with neurological problems, including cognitive deficits and encephalopathy (Depeint et al., 2006; Gibson et al., 2016). Healthy elderly women with marginal vitamin B1 deficiency experienced with thiamin supplementation a significant increase of appetite, body weight, energy, and activity, and decreased fatigue, improvement of sleep patterns, and of general well-being (Smidt et al., 1991).

### *Vitamin B3*

Vitamin B3, or niacin, is a precursor for NADH and nicotinamide adenine dinucleotide phosphate, which is involved in more than 500 enzymatic reactions pertaining to mitochondrial respiration (oxidative phosphorylation), glycolysis, and lipid oxidation (Depeint et al., 2006). The potential of NADH as an antidepressant was first tested in the FST model in Wistar rats, yielding a similar effect to fluoxetine (Rex et al., 2004). Vitamin B3 supplementation was also shown to prevent development and progression of mitochondrial myopathy in mice (Khan et al., 2014). More relevant to BD, evidence of mood elevation was reported in a 54-year-old man with no previous mental illness, who had a manic episode after commencing vitamin B3 for his dyslipidemia (Loebl and Raskin, 2013).

### *Vitamin B6*

Vitamin B6 refers to 3 primary forms: pyridoxine, pyridoxal phosphate, and pyridoxamine. The last 2 serve as coenzymes for protein metabolism, conversion of tryptophan to niacin, and neurotransmitter function. Some of the protective effect of vitamin B6 may occur via modification of mitochondrial function by preventing the oxygen radical generation and lipid peroxidation (Kannan and Jain, 2004). Higher dietary intake of vitamin B6 and folate was associated with lower prevalence of depression symptoms (measured with the Center for Epidemiologic Studies Depression Scale) in a large cross-sectional study of 6517 community adolescents (aged 12 to 15) (Murakami et al., 2010). Another study in 38 healthy older men on 20 mg of vitamin B6 supplementation showed cognitive benefits such as improved memory but failed to improve mood (Deijen et al., 1992). A double-blind RCT in 211 healthy women showed similar results (Bryan et al., 2002). Another 4-week, double-blind RCT with 14 geriatric depressed inpatients tested the augmentation of tricyclic antidepressant treatment with vitamins B1, B2, and

B6 (10 mg/d). The active vitamin group demonstrated greater improvement in scores on ratings of depression and cognitive function (Bell et al., 1992). A 24-week, open-label clinical trial with 10 participants with SZ patients that were already receiving antipsychotics were given 1200–2400 mg/d of pyridoxamine. The patients had high levels of plasma pentosidine, a carbonyl stress biomarker. The results were measured with the Positive and Negative Syndrome Scale score and the Brief Psychiatric Rating Scale. Treatment augmentation with pyridoxamine showed partial results in participants with enhanced carbonyl stress; however, only 3 patients had reduction of psychopathology. Four patients showed improvement on iatrogenic parkinsonism. However, 2 patients had Wernicke's encephalopathy-like adverse drug reactions, reversed by thiamine supplementation (Itokawa et al., 2018).

#### *Vitamin B2*

Vitamin B2 is a precursor of flavin adenine dinucleotide and flavin mononucleotide and is required for electron transport chain in complexes I and II. They work synergistically with other B vitamins for mitochondrial respiration (Depeint et al., 2006). Henriques et al. (2016) showed that vitamin B2 supplementation could functionally compensate for mitochondrial ß-oxidation enzymes. Four nonrandomized trials have been reported effectively treating mitochondrial diseases with complex I and/or complex II (Bernsen et al., 1993; Bugiani et al., 2006; Gerards et al., 2011) and III and IV (Ghezzi et al., 2010) deficiency.

#### *Vitamin B5*

Vitamin B5 is the precursor of CoA, important in the Krebs cycle and fatty acid oxidation. In vitro and in vivo studies suggest that vitamin B5 can restore ATP synthesis levels as well as the activity of antioxidant enzymes and can prevent the collapse of mitochondrial membrane potential (Depeint et al., 2006). There are established associations between vitamin B5 deficiency and neurodegenerative diseases, dermatitis, hypoglycemia, convulsions, and encephalopathy with liver failure (Depeint et al., 2006).

#### *Vitamin B7*

Vitamin B7 is a coenzyme for 5 mitochondrial carboxylases and is essential for growth, development, and normal mitochondrial and cellular functions, including fatty acid oxidation and gluconeogenesis. Reductions in vitamin B7 result in the loss of mitochondrial complex IV, which leads to increased production of oxidative species by the mitochondria (Depeint et al., 2006). Several clinical disorders are associated with B7 deficiency, such as cutaneous conditions (skin rashes, alopecia, and conjunctivitis), neurological conditions (depression, seizures, paresthesia), and diabetes (Depeint et al., 2006).

#### *Vitamin B12*

Vitamin B12, or cobalamin, is a cofactor for methionine synthesis, required for DNA and myelin synthesis and maintenance of neuronal integrity as well as neurotransmitter regulation. Vitamin B12 deficiency is a common but often under-recognized condition causing neurologic, cognitive, psychiatric, and mood symptoms (Lindenbaum et al., 1988; Issac et al., 2015). Further, deficiencies of B12, folate, or B6 can lead to macrocytic or pernicious anemia with symptoms of fatigue, psychomotor, cognitive, and mood deficits (Selhub et al., 2009). In an RCT in elderly participants with depressive symptoms, long-term daily supplementation with folic acid and vitamin B12 improved cognitive functioning, particularly immediate and delayed memory performance (Walker et al., 2012). More relevant to BD, there is a case-report of an acute onset of mania in a 94-year-old man with no previous mental illness and profound cobalamin deficiency who responded to cobalamin therapy (Jacobs et al., 1990). In a double-blind RCT of vitamin B12 supplementation in winter seasonal affective disorder, no significant differences were found (Oren et al., 1994). No benefit for B12 replacement was found in cognitive symptoms in dementia (van Dyck et al., 2009) or depressive symptoms in an elderly man (Ford et al., 2008).

### Other Potential BD Agents

#### *Taurine*

Taurine is a free amino acid that has important functions as a neuromodulator and antioxidant. It protects against glutamate-induced neurotoxicity and has been hypothesized to prevent membrane depolarization and mitochondrial energy failure (Timbrell et al., 1995; Ye et al., 2013). Recently, taurine has been reported to reduce oxidative stress and maintain mitochondrial function in cortical neurons (Xu et al., 2015). Moreover, taurine acts as an agonist for glycine and γ-aminobutyric acid receptors (Albrecht and Schousboe, 2005). In the FST model in rats, taurine supplementation has antidepressant-like effects (Toyoda and Iio, 2013). In a double-blind RCT in people with first-episode psychosis, taurine improved symptoms of depression and reduced psychotic symptoms as well as improved measures of functioning but failed to impact cognition (O'Donnell et al., 2016). While a double-blind RCT in BD adolescents with a manic episode was conducted (CT00391001), the study was terminated and no results have been published. Another double-blind RCT was carried out but despite its completion, no results have been revealed at this time (NCT00217165).

#### *Bezafibrate*

An agonist of the PPAR usually prescribed as an hypolipidemic drug, bezafibrate can restore fatty acid oxidation activity in cells from carnitine palmitoyltransferase-2 and very-long-chain acyl-CoA dehydrogenase deficiencies in in vitro conditions (Bastin et al., 2008). Data suggest that the PPAR signaling pathway is directly implicated in mitochondrial physiology. Exposure to bezafibrate increased the transcription of HADHA and HADHB genes (responsible the encoding of alpha and beta subunit of the mitochondrial trifunctional protein) (Aoyama et al., 1998), immune-detectable alpha and beta subunit proteins, activities of long-chain 3-hydroxyacylCoA dehydrogenase and long-chain 3-ketoacylCoA thiolase, and stimulated fatty acid oxidation capacities in human fibroblasts (Djouadi et al., 2016). To the best of our knowledge, no clinical data are available in the literature regarding the role of benzafibrate in psychiatry. However, an 8-week, open-label pilot trial of bezafibrate 400 mg/d added to lithium in 20 participants with bipolar depression is being conducted to assess its safety, tolerability, and antidepressant efficacy (NCT02481245).

## Conclusion

The study of neuroinflammation, neurodegeneration, and mitochondrial function has contributed to the understanding of BD's pathophysiology and led to the exploration of agents targeting these pathways. While some negative effects have been reported, compounds tested to date have been well-tolerated in the existing clinical data. Future directions include combinations of compounds targeting multiple mitochondrial pathways with potentially synergistic effects. Additionally, combinations with antioxidant or antiinflammatory agents could be feasible next steps to achieve better outcomes due to the role of inflammation

and oxidative stress in generation and maintenance of mitochondrial dysfunction (Rodriguez et al., 2007; Tarnopolsky, 2008). Identification of novel candidate mitochondrial modulators as well as rigorous and well-powered clinical trials are needed to explore this potential therapeutic strategy.

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## References

Acuña-Castroviejo D, Martín M, Macías M, Escames G, León J, Khaldy H, Reiter RJ (2001) Melatonin, mitochondria, and cellular bioenergetics. J Pineal Res 30:65–74.

Acuña-Castroviejo D, Escames G, Rodriguez MI, Lopez LC (2007) Melatonin role in the mitochondrial function. Front Biosci 12:947–963.

Albrecht J, Schousboe A (2005) Taurine interaction with neurotransmitter receptors in the CNS: an update. Neurochem Res 30:1615–1621.

Al-Majed AA, Sayed-Ahmed MM, Al-Omar FA, Al-Yahya AA, Aleisa AM, Al-Shabanah OA (2006) Carnitine esters prevent oxidative stress damage and energy depletion following transient forebrain ischaemia in the rat hippocampus. Clin Exp Pharmacol Physiol 33:725–733.

Almeida OP, Marsh K, Alfonso H, Flicker L, Davis TM, Hankey GJ (2010) B-vitamins reduce the long-term risk of depression after stroke: the VITATOPS-DEP trial. Ann Neurol 68:503–510.

Amr M, El-Mogy A, Shams T, Vieira K, Lakhan SE (2013) Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Nutr J 12:31.

Anderson G, Maes M (2014) Local melatonin regulates inflammation resolution: a common factor in neurodegenerative, psychiatric and systemic inflammatory disorders. CNS Neurol Disord Drug Targets 13:817–827.

Andreazza AC, Shao L, Wang JF, Young LT (2010) Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry 67:360–368.

Anglin RE, Samaan Z, Walter SD, McDonald SD (2013) Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry 202:100–107.

Aoyama T, Peters JM, Iritani N, Nakajima T, Furihata K, Hashimoto T, Gonzalez FJ (1998) Altered constitutive expression of fatty acid-metabolizing enzymes in mice lacking the peroxisome proliferator-activated receptor alpha (pparalpha). J Biol Chem 273:5678–5684.

Arrigoni O, De Tullio MC (2002) Ascorbic acid: much more than just an antioxidant. Biochim Biophys Acta 1569:1–9.

Aureli T, Di Cocco ME, Puccetti C, Ricciolini R, Scalibastri M, Miccheli A, Manetti C, Conti F (1998) Acetyl-L-carnitine modulates glucose metabolism and stimulates glycogen synthesis in rat brain. Brain Res 796:75–81.

Banerjee U, Dasgupta A, Rout JK, Singh OP (2012) Effects of lithium therapy on Na+-K+-atpase activity and lipid peroxidation in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 37:56–61.

Barhwal K, Singh SB, Hota SK, Jayalakshmi K, Ilavazhagan G (2007) Acetyl-L-carnitine ameliorates hypobaric hypoxic impairment and spatial memory deficits in rats. Eur J Pharmacol 570:97–107.

Bastin J, Aubey F, Rötig A, Munnich A, Djouadi F (2008) Activation of peroxisome proliferator-activated receptor pathway stimulates the mitochondrial respiratory chain and can correct deficiencies in patients' cells lacking its components. J Clin Endocrinol Metab 93:1433–1441.

Behzadi AH, Omrani Z, Chalian M, Asadi S, Ghadiri M (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.

Bell IR, Edman JS, Marby DW, Satlin A, Dreier T, Liptzin B, Cole JO (1990) Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. Biol Psychiatry 27:125–137.

Bell IR, Edman JS, Morrow FD, Marby DW, Perrone G, Kayne HL, Greenwald M, Cole JO (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.

Belzeaux R, Boyer L, Ibrahim EC, Féron F, Leboyer M, Fond G (2015) Mood disorders are associated with a more severe hypovitaminosis D than schizophrenia. Psychiatry Res 229:613–616.

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468–475.

Berk M, Dean O, Cotton SM, Gama CS, Kapczinski F, Fernandes BS, Kohlmann K, Jeavons S, Hewitt K, Allwang C, Cobb H, Bush AI, Schapkaitz I, Dodd S, Malhi GS (2011) The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. J Affect Disord 135:389–394.

Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, Kohlmann K, Jeavons S, Hewitt K, Moss K, Allwang C, Schapkaitz I, Cobb H, Bush AI, Dodd S, Malhi GS (2012) Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC Med 10:91.

Berk M, Malhi GS, Gray LJ, Dean OM (2013) The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci 34:167–177.

Bernsen PL, Gabreëls FJ, Ruitenbeek W, Hamburger HL (1993) Treatment of complex I deficiency with riboflavin. J Neurol Sci 118:181–187.

Bersani G, Garavini A (2000) Melatonin add-on in manic patients with treatment resistant insomnia. Prog Neuropsychopharmacol Biol Psychiatry 24:185–191.

Binienda ZK (2003) Neuroprotective effects of L-carnitine in induced mitochondrial dysfunction. Ann N Y Acad Sci 993:289–295; discussion 345.

Bottiglieri T (2002) S-adenosyl-L-methionine (same): from the bench to the bedside–molecular basis of a pleiotrophic molecule. Am J Clin Nutr 76:1151S–1157S.

Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH (2000) Homocysteine, folate, methylation, and monoamine metabolism in depression. J Neurol Neurosurg Psychiatry 69:228–232.

Bremner JD, Shearer KD, McCaffery PJ (2012) Retinoic acid and affective disorders: the evidence for an association. J Clin Psychiatry 73:37–50.

Brennan BP, Jensen JE, Hudson JI, Coit CE, Beaulieu A, Pope HG Jr, Renshaw PF, Cohen BM (2013) A placebo-controlled trial of acetyl-L-carnitine and α-lipoic acid in the treatment of bipolar depression. J Clin Psychopharmacol 33:627–635.

Bryan J, Calvaresi E, Hughes D (2002) Short-term folate, vitamin B-12 or vitamin B-6 supplementation slightly affects memory performance but not mood in women of various ages. J Nutr 132:1345–1356.

Bugiani M, Lamantea E, Invernizzi F, Moroni I, Bizzi A, Zeviani M, Uziel G (2006) Effects of riboflavin in children with complex II deficiency. Brain Dev 28:576–581.

Calabrese JR, Guelfi JD, Perdrizet-Chevallier C, Agomelatine Bipolar Study Group (2007) Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. Bipolar Disord 9:628–635.

Calton EK, Keane KN, Soares MJ (2015) The potential regulatory role of vitamin D in the bioenergetics of inflammation. Curr Opin Clin Nutr Metab Care 18:367–373.

Calvaresi E, Bryan J (2001) B vitamins, cognition, and aging: a review. J Gerontol Psychol Sci Am 56:327–339.

Carney MW, Chary TK, Bottiglieri T, Reynolds EH (1989) The switch mechanism and the bipolar/unipolar dichotomy. Br J Psychiatry 154:48–51.

Cass WA, Smith MP, Peters LE (2006) Calcitriol protects against the dopamine- and serotonin-depleting effects of neurotoxic doses of methamphetamine. Ann N Y Acad Sci 1074:261–271.

Castro-Marrero J, Cordero MD, Segundo MJ, Sáez-Francàs N, Calvo N, Román-Malo L, Aliste L, Fernández de Sevilla T, Alegre J (2015) Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? Antioxid Redox Signal 22:679–685.

Cataldo AM, McPhie DL, Lange NT, Punzell S, Elmiligy S, Ye NZ, Froimowitz MP, Hassinger LC, Menesale EB, Sargent LW, Logan DJ, Carpenter AE, Cohen BM (2010) Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. Am J Pathol 177:575–585.

Chapman MS (2012) Vitamin a: history, current uses, and controversies. Semin Cutan Med Surg 31:11–16.

Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, Manji HK (1999) The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. J Neurochem 72:879–882.

Consiglio M, Destefanis M, Morena D, Foglizzo V, Forneris M, Pescarmona G, Silvagno F (2014) The vitamin D receptor inhibits the respiratory chain, contributing to the metabolic switch that is essential for cancer cell proliferation. Plos One 9:e115816.

Consiglio M, Viano M, Casarin S, Castagnoli C, Pescarmona G, Silvagno F (2015) Mitochondrial and lipogenic effects of vitamin D on differentiating and proliferating human keratinocytes. Exp Dermatol 24:748–753.

Coppen A, Abou-Saleh MT (1982) Plasma folate and affective morbidity during long-term lithium therapy. Br J Psychiatry 141:87–89.

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.

Coppen A, Chaudhry S, Swade C (1986) Folic acid enhances lithium prophylaxis. J Affect Disord 10:9–13.

Corena-McLeod M, Walss-Bass C, Oliveros A, Gordillo Villegas A, Ceballos C, Charlesworth CM, Madden B, Linser PJ, Van Ekeris L, Smith K, Richelson E (2013) New model of action for mood stabilizers: phosphoproteome from rat pre-frontal cortex synaptoneurosomal preparations. PLoS One 8:e52147.

Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, Krainc D (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127:59–69.

Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, Dunner DL, Renshaw PF (2004) Brain metabolic alterations in medication-free patients with bipolar disorder. Arch Gen Psychiatry 61:450–458.

Dean OM, Bush AI, Copolov DL, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2012) Effects of N-acetyl cysteine on cognitive function in bipolar disorder. Psychiatry Clin Neurosci 66:514–517.

Dean OM, Turner A, Malhi GS, Ng C, Cotton SM, Dodd S, Sarris J, Samuni Y, Tanious M, Dowling N, Waterdrinker A, Smith D, Berk M (2015) Design and rationale of a 16-week adjunctive randomized placebo-controlled trial of mitochondrial agents for the treatment of bipolar depression. Rev Bras Psiquiatr 37:3–12.

Dechent P, Pouwels PJ, Wilken B, Hanefeld F, Frahm J (1999) Increase of total creatine in human brain after oral supplementation of creatine-monohydrate. Am J Physiol 277:R698–R704.

Deepmala, Slattery J, Kumar N, Delhey L, Berk M, Dean O, Spielholz C, Frye R (2015) Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neurosci Biobehav Rev 55:294–321.

Deijen JB, van der Beek EJ, Orlebeke JF, van den Berg H (1992) Vitamin B-6 supplementation in elderly men: effects on mood, memory, performance and mental effort. Psychopharmacology (Berl) 109:489–496.

Demarco VG, Scumpia PO, Bosanquet JP, Skimming JW (2004) Alpha-lipoic acid inhibits endotoxin-stimulated expression of inos and nitric oxide independent of the heat shock response in RAW 264.7 cells. Free Radic Res 38:675–682.

Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ (2006) Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chem Biol Interact 163:94–112.

de Oliveira IJ, de Souza VV, Motta V, Da-Silva SL (2015) Effects of oral vitamin C supplementation on anxiety in students: a double-blind, randomized, placebo-controlled trial. Pak J Biol Sci 18:11–18.

de Oliveira MR, Oliveira MW, Behr GA, Hoff ML, da Rocha RF, Moreira JC (2009) Evaluation of the effects of vitamin A supplementation on adult rat substantia nigra and striatum

redox and bioenergetic states: mitochondrial impairment, increased 3-nitrotyrosine and alpha-synuclein, but decreased D2 receptor contents. Prog Neuropsychopharmacol Biol Psychiatry 33:353–362.

de Sousa CNS, Meneses LN, Vasconcelos GS, Silva MCC, da Silva JC, Macêdo D, de Lucena DF, Vasconcelos SMM (2015) Reversal of corticosterone-induced BDNF alterations by the natural antioxidant alpha-lipoic acid alone and combined with desvenlafaxine: emphasis on the neurotrophic hypothesis of depression. Psychiatry Res 230:211–219.

de Sousa RT, Zarate CA Jr, Zanetti MV, Costa AC, Talib LL, Gattaz WF, Machado-Vieira R (2014) Oxidative stress in early stage bipolar disorder and the association with response to lithium. J Psychiatr Res 50:36–41.

Dhitavat S, Ortiz D, Rogers E, Rivera E, Shea TB (2005) Folate, vitamin E, and acetyl-L-carnitine provide synergistic protection against oxidative stress resulting from exposure of human neuroblastoma cells to amyloid-beta. Brain Res 1061:114–117.

Djouadi F, Habarou F, Le Bachelier C, Ferdinandusse S, Schlemmer D, Benoist JF, Boutron A, Andresen BS, Visser G, de Lonlay P, Olpin S, Fukao T, Yamaguchi S, Strauss AW, Wanders RJ, Bastin J (2016) Mitochondrial trifunctional protein deficiency in human cultured fibroblasts: effects of bezafibrate. J Inherit Metab Dis 39:47–58.

Dörsam B, Fahrer J (2016) The disulfide compound α-lipoic acid and its derivatives: a novel class of anticancer agents targeting mitochondria. Cancer Lett 371:12–19.

Dysken MW, et al (2014) Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. Jama 311:33–44.

Erecińska M, Silver IA (1989) ATP and brain function. J Cereb Blood Flow Metab 9:2–19.

Estrada DE, Ewart HS, Tsakiridis T, Volchuk A, Ramlal T, Tritschler H, Klip A (1996) Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. Diabetes 45:1798–1804.

Evcimen H, Mania I, Mathews M, Basil B (2007) Psychosis precipitated by acetyl-l-carnitine in a patient with bipolar disorder. Prim Care Companion J Clin Psychiatry 9:71–72.

Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ (2005) Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat 29:21–30.

Fattal O, Link J, Quinn K, Cohen BH, Franco K (2007) Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. CNS Spectr 12:429–438.

Fernandes BS, Dean OM, Dodd S, Malhi GS, Berk M (2016) N-acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. J Clin Psychiatry 77:e457–e466.

Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, Whiteford HA (2016) The prevalence and burden of bipolar disorder: findings from the global burden of disease study 2013. Bipolar Disord 18:440–450.

Folstein M, Liu T, Peter I, Buell J, Buel J, Arsenault L, Scott T, Qiu WW (2007) The homocysteine hypothesis of depression. Am J Psychiatry 164:861–867.

Ford AH, Flicker L, Thomas J, Norman P, Jamrozik K, Almeida OP (2008) Vitamins B12, B6, and folic acid for onset of depressive symptoms in older men: results from a 2-year placebo-controlled randomized trial. J Clin Psychiatry 69:1203–1209.

Forester BP, Zuo CS, Ravichandran C, Harper DG, Du F, Kim S, Cohen BM, Renshaw PF (2012) Coenzyme Q10 effects on creatine kinase activity and mood in geriatric bipolar depression. J Geriatr Psychiatry Neurol 25:43–50.

Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M, Colicchio S, Cattaneo CI, D'Angelo E, Fornaro P (2013) Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatr Dis Treat 9:243–251.

Frey BN, Walss-Bass C, Stanley JA, Nery FG, Matsuo K, Nicoletti MA, Hatch JP, Bowden CL, Escamilla MA, Soares JC (2007) Brain-derived neurotrophic factor val66met polymorphism affects prefrontal energy metabolism in bipolar disorder. Neuroreport 18:1567–1570.

Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, Cotman C, Cottrell B, Montine TJ, Thomas RG, Aisen P, Alzheimer's Disease Cooperative Study (2012) Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol 69:836–841.

Gerards M, van den Bosch BJ, Danhauser K, Serre V, van Weeghel M, Wanders RJ, Nicolaes GA, Sluiter W, Schoonderwoerd K, Scholte HR, Prokisch H, Rötig A, de Coo IF, Smeets HJ (2011) Riboflavin-responsive oxidative phosphorylation complex I deficiency caused by defective ACAD9: new function for an old gene. Brain 134:210–219.

Ghezzi D, Sevrioukova I, Invernizzi F, Lamperti C, Mora M, D'Adamo P, Novara F, Zuffardi O, Uziel G, Zeviani M (2010) Severe X-linked mitochondrial encephalomyopathy associated with a mutation in apoptosis-inducing factor. Am J Hum Genet 86:639–649.

Gibson GE, Hirsch JA, Fonzetti P, Jordan BD, Cirio RT, Elder J (2016) Vitamin B1 (thiamine) and dementia. Ann N Y Acad Sci 1367:21–30.

Gilbody S, Lightfoot T, Sheldon T (2007) Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity. J Epidemiol Community Health 61:631–637.

Gloth FM 3rd, Alam W, Hollis B (1999) Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nutr Health Aging 3:5–7.

Godfrey PS, Toone BK, Carney MW, Flynn TG, Bottiglieri T, Laundy M, Chanarin I, Reynolds EH (1990) Enhancement of recovery from psychiatric illness by methylfolate. Lancet 336:392–395.

Gomes MB, Negrato CA (2014) Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. Diabetol Metab Syndr 6:80.

Goodison G, Overeem K, de Monte V, Siskind D (2017) Mania associated with self-prescribed acetyl-l-carnitine in a man with bipolar I disorder. Australas Psychiatry 25:13–14.

Gülçin İ (2006) Antioxidant and antiradical activities of l-carnitine. Life Sci 78:803–811.

Hagen TM, Liu J, Lykkesfeldt J, Wehr CM, Ingersoll RT, Vinarsky V, Bartholomew JC, Ames BN (2002a) Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. Proc Natl Acad Sci U S A 99:1870–1875.

Hagen TM, Liu J, Lykkesfeldt J, Wehr CM, Ingersoll RT, Vinarsky V, Bartholomew JC, Ames BN (2002b) Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. Proc Natl Acad Sci U S A 99:1870–1875.

Hager K, Marahrens A, Kenklies M, Riederer P, Münch G (2001) Alpha-lipoic acid as a new treatment option for Alzheimer type dementia. Arch Gerontol Geriatr 32:275–282.

Hager K, Kenklies M, McAfoose J, Engel J, Münch G (2007) Alpha-lipoic acid as a new treatment option for Alzheimer's

disease—a 48 months follow-up analysis. J Neural Transm Suppl 72:189–193.

Hall NC, Carney JM, Plante OJ, Cheng M, Butterfield DA (1997) Effect of 2-cyclohexene-1-one-induced glutathione diminution on ischemia/reperfusion-induced alterations in the physical state of brain synaptosomal membrane proteins and lipids. Neuroscience 77:283–290.

Hammerling U (2016) Vitamin A as PKC co-factor and regulator of mitochondrial energetics. Subcell Biochem 81:201–230.

Han D, Handelman G, Marcocci L, Sen CK, Roy S, Kobuchi H, Tritschler HJ, Flohé L, Packer L (1997) Lipoic acid increases de novo synthesis of cellular glutathione by improving cystine utilization. Biofactors 6:321–338.

Hansen MV, Danielsen AK, Hageman I, Rosenberg J, Gögenur I (2014) The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: a systematic review and meta-analysis. Eur Neuropsychopharmacol 24:1719–1728.

Hardy M, Coulter I, Morton S, Favreau J, Venuturupalli S, Chiappelli F, Rossi F, Orshansky G, Jungvig L, Roth E, Suttorp M, Shekelle P (2003) S-Adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease: summary. Pain 158:802–810.

Hasanah CI, Khan UA, Musalmah M, Razali SM (1997) Reduced red-cell folate in mania. J Affect Disord 46:95–99.

Haybaeck J, Postruznik M, Miller CL, Dulay JR, Llenos IC, Weis S (2015) Increased expression of retinoic acid-induced gene 1 in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. Neuropsychiatr Dis Treat 11:279–289.

He J, Kong J, Tan QR, Li XM (2009) Neuroprotective effect of atypical antipsychotics in cognitive and non-cognitive behavioral impairment in animal models. Cell Adh Migr 3:129–137.

Henriksen EJ, Jacob S, Streeper RS, Fogt DL, Hokama JY, Tritschler HJ (1997) Stimulation by alpha-lipoic acid of glucose transport activity in skeletal muscle of lean and obese Zucker rats. Life Sci 61:805–812.

Henriques BJ, Lucas TG, Gomes CM (2016) Therapeutic approaches using riboflavin in mitochondrial energy metabolism disorders. Curr Drug Targets 17:1527–1534.

Hoppel C (2003) The role of carnitine in normal and altered fatty acid metabolism. Am J Kidney Dis 41:S4–12.

Hoyos B, Acin-Perez R, Fischman DA, Manfredi G, Hammerling U (2012) Hiding in plain sight: uncovering a new function of vitamin A in redox signaling. Biochim Biophys Acta 1821:241–247.

Hu P, Wang Y, Liu J, Meng FT, Qi XR, Chen L, van Dam AM, Joëls M, Lucassen PJ, Zhou JN (2016) Chronic retinoic acid treatment suppresses adult hippocampal neurogenesis, in close correlation with depressive-like behavior. Hippocampus 26:911–923.

Hughes VA, Fiatarone MA, Fielding RA, Kahn BB, Ferrara CM, Shepherd P, Fisher EC, Wolfe RR, Elahi D, Evans WJ (1993) Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. Am J Physiol 264:E855–E862.

Issac TG, Soundarya S, Christopher R, Chandra SR (2015) Vitamin B12 deficiency: an important reversible co-morbidity in neuropsychiatric manifestations. Indian J Psychol Med 37:26–29.

Itokawa M, Miyashita M, Arai M, Dan T, Takahashi K, Tokunaga T, Ishimoto K, Toriumi K, Ichikawa T, Horiuchi Y, Kobori A, Usami S, Yoshikawa T, Amano N, Washizuka S, Okazaki Y, Miyata T (2018) Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress. Psychiatry Clin Neurosci 72:35–44.

Jacobs LG, Bloom HG, Behrman FZ (1990) Mania and a gait disorder due to cobalamin deficiency. J Am Geriatr Soc 38:473–474.

Jensen JE, Daniels M, Haws C, Bolo NR, Lyoo IK, Yoon SJ, Cohen BM, Stoll AL, Rusche JR, Renshaw PF (2008) Triacetyluridine (TAU) decreases depressive symptoms and increases brain ph in bipolar patients. Exp Clin Psychopharmacol 16:199–206.

Judd LL, Schettler PJ, Akiskal HS, Coryell W, Leon AC, Maser JD, Solomon DA (2008) Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry 65:386–394.

Kagan V, Serbinova E, Packer L (1990) Antioxidant effects of ubiquinones in microsomes and mitochondria are mediated by tocopherol recycling. Biochem Biophys Res Commun 169:851–857.

Kannan K, Jain SK (2004) Effect of vitamin B6 on oxygen radicals, mitochondrial membrane potential, and lipid peroxidation in H2o2-treated U937 monocytes. Free Radic Biol Med 36:423–428.

Karalija A, Novikova LN, Kingham PJ, Wiberg M, Novikov LN (2014) The effects of N-acetyl-cysteine and acetyl-L-carnitine on neural survival, neuroinflammation and regeneration following spinal cord injury. Neuroscience 269:143–151.

Kato T (2007) Mitochondrial dysfunction as the molecular basis of bipolar disorder: therapeutic implications. CNS Drugs 21:1–11.

Kato T (2008) Role of mitochondrial DNA in calcium signaling abnormality in bipolar disorder. Cell Calcium 44:92–102.

Kato T (2010) Mitochondrial dysfunction and bipolar disorder. In: Current topics in behavioral neurosciences, pp 187–200.

Kato T (2011) Mitochondrial dysfunction and bipolar disorder. Curr Top Behav Neurosci 5:187–200.

Kato T, Kato N (2000) Mitochondrial dysfunction in bipolar disorder. Bipolar Disord 2:180–190.

Kay DS, Naylor GJ, Smith AH, Greenwood C (1984) The therapeutic effect of ascorbic acid and EDTA in manic-depressive psychosis: double-blind comparisons with standard treatments. Psychol Med 14:533–539.

Khairova R, Pawar R, Salvadore G, Juruena MF, de Sousa RT, Soeiro-de-Souza MG, Salvador M, Zarate CA, Gattaz WF, Machado-Vieira R (2011) Effects of lithium on oxidative stress parameters in healthy subjects. Mol Med Rep 5:680–682.

Khan NA, Auranen M, Paetau I, Pirinen E, Euro L, Forsström S, Pasila L, Velagapudi V, Carroll CJ, Auwerx J, Suomalainen A (2014) Effective treatment of mitochondrial myopathy by nicotinamide riboside, a vitamin B3. EMBO Mol Med 6:721–731.

Kleinkauf-Rocha J, Bobermin LD, Machado Pde M, Gonçalves CA, Gottfried C, Quincozes-Santos A (2013) Lipoic acid increases glutamate uptake, glutamine synthetase activity and glutathione content in C6 astrocyte cell line. Int J Dev Neurosci 31:165–170.

Kondo DG, Sung YH, Hellem TL, Delmastro KK, Jeong EK, Kim N, Shi X, Renshaw PF (2011) Open-label uridine for treatment of depressed adolescents with bipolar disorder. J Child Adolesc Psychopharmacol 21:171–175.

Konradi C, Eaton M, MacDonald ML, Walsh J, Benes FM, Heckers S (2004) Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch Gen Psychiatry 61:300–308.

Kontush A, Schrkatolina S (2004) Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann N Y Acad Sci 1031:249–262.

Korkmaz A, Reiter RJ, Topal T, Manchester LC, Oter S, Tan DX (2009) Melatonin: an established antioxidant worthy of use in clinical trials. Mol Med 15:43–50.

Lawler JM, Barnes WS, Wu G, Song W, Demaree S (2002) Direct antioxidant properties of creatine. Biochem Biophys Res Commun 290:47–52.

Leibenluft E, Feldman-Naim S, Turner EH, Wehr TA, Rosenthal NE (1997) Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. J Clin Psychiatry 58:383–388.

Lenaz G, Bovina C, D'Aurelio M, Fato R, Formiggini G, Genova ML, Giuliano G, Merlo Pich M, Paolucci U, Parenti Castelli G, Ventura B (2002) Role of mitochondria in oxidative stress and aging. Ann N Y Acad Sci 959:199–213.

León J, Acuña-Castroviejo D, Escames G, Tan DX, Reiter RJ (2005) Melatonin mitigates mitochondrial malfunction. J Pineal Res 38:1–9.

Li G, Mbuagbaw L, Samaan Z, Falavigna M, Zhang S, Adachi JD, Cheng J, Papaioannou A, Thabane L (2014) Efficacy of vitamin D supplementation in depression in adults: a systematic review. J Clin Endocrinol Metab 99:757–767.

Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH (1988) Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 318:1720–1728.

Lipinski JF, Cohen BM, Frankenburg F, Tohen M, Waternaux C, Altesman R, Jones B, Harris P (1984) Open trial of S-adenosylmethionine for treatment of depression. Am J Psychiatry 141:448–450.

Liu J (2008) The effects and mechanisms of mitochondrial nutrient alpha-lipoic acid on improving age-associated mitochondrial and cognitive dysfunction: an overview. Neurochem Res 33:194–203.

Liu J, Head E, Gharib AM, Yuan W, Ingersoll RT, Hagen TM, Cotman CW, Ames BN (2002) Memory loss in old rats is associated with brain mitochondrial decay and RNA/DNA oxidation: partial reversal by feeding acetyl-L-carnitine and/or R-alpha -lipoic acid. Proc Natl Acad Sci U S A 99:2356–2361.

Loebl T, Raskin S (2013) A novel case report: acute manic psychotic episode after treatment with niacin. J Neuropsychiatry Clin Neurosci 25:E14.

López-Burillo S, Tan DX, Mayo JC, Sainz RM, Manchester LC, Reiter RJ (2003) Melatonin, xanthurenic acid, resveratrol, EGCG, vitamin C and alpha-lipoic acid differentially reduce oxidative DNA damage induced by fenton reagents: a study of their individual and synergistic actions. J Pineal Res 34:269–277.

Ludot M, Mouchabac S, Ferreri F (2015) Inter-relationships between isotretinoin treatment and psychiatric disorders: depression, bipolar disorder, anxiety, psychosis and suicide risks. World J Psychiatry 5:222–227.

Lykkesfeldt J, Hagen TM, Vinarsky V, Ames BN (1998) Age-associated decline in ascorbic acid concentration, recycling, and biosynthesis in rat hepatocytes–reversal with ®-alpha-lipoic acid supplementation. Faseb J 12:1183–1189.

Lyoo IK, Kong SW, Sung SM, Hirashima F, Parow A, Hennen J, Cohen BM, Renshaw PF (2003a) Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine monohydrate. Psychiatry Res 123:87–100.

Lyoo IK, Demopulos CM, Hirashima F, Ahn KH, Renshaw PF (2003b) 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.

Macêdo DS, Medeiros CD, Cordeiro RC, Sousa FC, Santos JV, Morais TA, Hyphantis TN, McIntyre RS, Quevedo J, Carvalho AF (2012) Effects of alpha-lipoic acid in an animal model of mania induced by D-amphetamine. Bipolar Disord 14:707–718.

Machado-Vieira R, Manji HK, Zarate CA Jr (2009) The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disord 11:92–109.

Machado-Vieira R, Pivovarova NB, Stanika RI, Yuan P, Wang Y, Zhou R, Zarate CA Jr, Drevets WC, Brantner CA, Baum A, Laje G, McMahon FJ, Chen G, Du J, Manji HK, Andrews SB (2011) The bcl-2 gene polymorphism rs956572aa increases inositol 1,4,5-trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. Biol Psychiatry 69:344–352.

Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2011a) N-acetylcysteine for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr 33:374–378.

Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2011b) N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord 129:317–320.

Magalhães PV, Dean OM, Bush AI, Copolov DL, Weisinger D, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2012) Systemic illness moderates the impact of N-acetyl cysteine in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 37:132–135.

Magalhães PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2013) A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. Aust N Z J Psychiatry 47:564–568.

Mahableshwarkar AR, Calabrese JR, Macek TA, Budur K, Adefuye A, Dong X, Hanson E, Sachs GS (2017) Efficacy and safety of sublingual ramelteon as an adjunctive therapy in the maintenance treatment of bipolar I disorder in adults: a phase 3, randomized controlled trial. J Affect Disord 221:275–282.

Martín M, Macías M, León J, Escames G, Khaldy H, Acuña-Castroviejo D (2002) Melatonin increases the activity of the oxidative phosphorylation enzymes and the production of ATP in rat brain and liver mitochondria. Int J Biochem Cell Biol 34:348–357.

Matthews RT, Yang L, Browne S, Baik M, Beal MF (1998) Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc Natl Acad Sci U S A 95:8892–8897.

Mattson MP, Shea TB (2003) Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci 26:137–146.

McElroy SL, Winstanley EL, Martens B, Patel NC, Mori N, Moeller D, McCoy J, Keck PE Jr (2011) A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance. Int Clin Psychopharmacol 26:48–53.

Mescka C, Moraes T, Rosa A, Mazzola P, Piccoli B, Jacques C, Dalazen G, Coelho J, Cortes M, Terra M, Regla Vargas C, Dutra-Filho CS (2011) In vivo neuroprotective effect of L-carnitine against oxidative stress in maple syrup urine disease. Metab Brain Dis 26:21–28.

Michels AJ, Joisher N, Hagen TM (2003) Age-related decline of sodium-dependent ascorbic acid transport in isolated rat hepatocytes. Arch Biochem Biophys 410:112–120.

Miller AL (2008) The methylation, neurotransmitter, and antioxidant connections between folate and depression. Altern Med Rev 13:216–226.

Moini H, Packer L, Saris NE (2002) Antioxidant and prooxidant activities of alpha-lipoic acid and dihydrolipoic acid. Toxicol Appl Pharmacol 182:84–90.

Morris G, Anderson G, Berk M, Maes M (2013) Coenzyme Q10 depletion in medical and neuropsychiatric disorders: potential repercussions and therapeutic implications. Mol Neurobiol 48:883–903.

Munakata K, Tanaka M, Mori K, Washizuka S, Yoneda M, Tajima O, Akiyama T, Nanko S, Kunugi H, Tadokoro K, Ozaki N, Inada T, Sakamoto K, Fukunaga T, Iijima Y, Iwata N, Tatsumi M, Yamada K, Yoshikawa T, Kato T (2004) Mitochondrial DNA 3644T–>C mutation associated with bipolar disorder. Genomics 84:1041–1050.

Murakami K, Miyake Y, Sasaki S, Tanaka K, Arakawa M (2010) Dietary folate, riboflavin, vitamin B-6, and vitamin B-12 and depressive symptoms in early adolescence: the ryukyus child health study. Psychosom Med 72:763–768.

Murphy BL, Babb SM, Ravichandran C, Cohen BM (2014) Oral same in persistent treatment-refractory bipolar depression: a double-blind, randomized clinical trial. J Clin Psychopharmacol 34:413–416.

Myint AM, Kim YK (2014) Network beyond IDO in psychiatric disorders: revisiting neurodegeneration hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 48:304–313.

Naaldijk YM, Bittencourt MC, Sack U, Ulrich H (2016) Kinins and microglial responses in bipolar disorder: a neuroinflammation hypothesis. Biol Chem 397:283–296.

Nacz K, Miecz D, Berezowski V, Cecchelli R (2004) Carnitine: transport and physiological functions in the brain. Mol Aspects Med 25:551–567.

Nałecz KA, Nałecz MJ (1996) Carnitine–a known compound, a novel function in neural cells. Acta Neurobiol Exp (Wars) 56:597–609.

Nałecz KA, Miecz D, Berezowski V, Cecchelli R (2004) Carnitine: transport and physiological functions in the brain. Mol Aspects Med 25:551–567.

Navarro A, Gómez C, Sánchez-Pino MJ, González H, Bández MJ, Boveris AD, Boveris A (2005) Vitamin E at high doses improves survival, neurological performance, and brain mitochondrial function in aging male mice. Am J Physiol Regul Integr Comp Physiol 289:R1392–R1399.

Naydenov AV, MacDonald ML, Ongur D, Konradi C (2007) Differences in lymphocyte electron transport gene expression levels between subjects with bipolar disorder and normal controls in response to glucose deprivation stress. Arch Gen Psychiatry 64:555–564.

Naylor GJ, Smith AH (1981) Vanadium: a possible aetiological factor in manic depressive illness. Psychol Med 11:249–256.

Negida A, Menshawy A, El Ashal G, Elfouly Y, Hani Y, Hegazy Y, El Ghonimy S, Fouda S, Rashad Y (2016) Coenzyme Q10 for patients with parkinson's disease: a systematic review and meta-analysis. CNS Neurol Disord Drug Targets 15:45–53.

Nierenberg AA, Kansky C, Brennan BP, Shelton RC, Perlis R, Iosifescu DV (2013) Mitochondrial modulators for bipolar disorder: a pathophysiologically informed paradigm for new drug development. Aust N Z J Psychiatry 47:26–42.

Nierenberg AA, Montana R, Kinrys G, Deckersbach T, Dufour S, Baek JH (2017) L-methylfolate for bipolar I depressive episodes: an open trial proof-of-concept registry. J Affect Disord 207:429–433.

Norris ER, Karen Burke, Correll JR, Zemanek KJ, Lerman J, Primelo RA, Kaufmann MW (2013) A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. J Affect Disord 144:141–147.

O'Donnell CP, Allott KA, Murphy BP, Yuen HP, Proffitt TM, Papas A, Moral J, Pham T, O'Regan MK, Phassouliotis C, Simpson R, McGorry PD (2016) Adjunctive taurine in first-episode psychosis. J Clin Psychiatry 77:e1610–e1617.

Oikawa H, Sng JC (2016) Valproic acid as a microrna modulator to promote neurite outgrowth. Neural Regen Res 11:1564–1565.

Oliveira MR (2015) The neurotoxic effects of vitamin A and retinoids. An Acad Bras Cienc 87:1361–1373.

Oren DA, Teicher MH, Schwartz PJ, Glod C, Turner EH, Ito YN, Sedway J, Rosenthal NE, Wehr TA (1994) A controlled trial of cyanocobalamin (vitamin B12) in the treatment of winter seasonal affective disorder. J Affect Disord 32:197–200.

Ou P, Tritschler HJ, Wolff SP (1995) Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant? Biochem Pharmacol 50:123–126.

Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M (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.

Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M (2012) l-Methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry 169:1267–1274.

Paredes SD, Forman KA, García C, Vara E, Escames G, Tresguerres JA (2014) Protective actions of melatonin and growth hormone on the aged cardiovascular system. Horm Mol Biol Clin Investig 18:79–88.

Patel SP, Sullivan PG, Pandya JD, Goldstein GA, VanRooyen JL, Yonutas HM, Eldahan KC, Morehouse J, Magnuson DS, Rabchevsky AG (2014) N-acetylcysteine amide preserves mitochondrial bioenergetics and improves functional recovery following spinal trauma. Exp Neurol 257:95–105.

Perlis RH, Welge JA, Vornik LA, Hirschfeld RM, Keck PE Jr (2006) Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. J Clin Psychiatry 67:509–516.

Pettegrew JW, Levine J, Gershon S, Stanley JA, Servan-Schreiber D, Panchalingam K, McClure RJ (2002) 31P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results. Bipolar Disord 4:61–66.

Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. Int J Biomed Sci 4:89–96.

Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CM, Mintz J (2006) Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 189:124–131.

Prüfer K, Veenstra TD, Jirikowski GF, Kumar R (1999) Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. J Chem Neuroanat 16:135–145.

Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK (1996) Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Brain Res Mol Brain Res 36:193–196.

Qi XR, Zhao J, Liu J, Fang H, Swaab DF, Zhou JN (2015) Abnormal retinoid and trkb signaling in the prefrontal cortex in mood disorders. Cereb Cortex 25:75–83.

Rao KV, Mawal YR, Qureshi IA (1997) Progressive decrease of cerebral cytochrome C oxidase activity in sparse-fur mice: role of acetyl-L-carnitine in restoring the ammonia-induced cerebral energy depletion. Neurosci Lett 224:83–86.

Regenold WT, Phatak P, Marano CM, Sassan A, Conley RR, Kling MA (2009) Elevated cerebrospinal fluid lactate concentrations in patients with bipolar disorder and schizophrenia: implications for the mitochondrial dysfunction hypothesis. Biol Psychiatry 65:489–494.

Rex A, Schickert R, Fink H (2004) Antidepressant-like effect of nicotinamide adenine dinucleotide in the forced swim test in rats. Pharmacol Biochem Behav 77:303–307.

Reynolds E (2002) Effects of folic acid. Lancet 359:2039.

Ricciardi CJ, Bae J, Esposito D, Komarnytsky S, Hu P, Chen J, Zhao L (2015) 1,25-dihydroxyvitamin D3/vitamin D receptor suppresses brown adipocyte differentiation and mitochondrial respiration. Eur J Nutr 54:1001–1012.

Riccio P, Rossano R, Larocca M, Trotta V, Mennella I, Vitaglione P, Ettorre M, Graverini A, De Santis A, Di Monte E, Coniglio MG (2016) Anti-inflammatory nutritional intervention in patients with relapsing-remitting and primary-progressive multiple sclerosis: a pilot study. Exp Biol Med (Maywood) 241:620–635.

Robinson M, Whitehouse AJ, Newnham JP, Gorman S, Jacoby P, Holt BJ, Serralha M, Tearne JE, Holt PG, Hart PH, Kusel MM (2014) Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. Arch Womens Ment Health 17:213–219.

Rodriguez C, Mayo JC, Sainz RM, Antolín I, Herrera F, Martín V, Reiter RJ (2004) Regulation of antioxidant enzymes: a significant role for melatonin. J Pineal Res 36:1–9.

Rodriguez MC, MacDonald JR, Mahoney DJ, Parise G, Beal MF, Tarnopolsky MA (2007) Beneficial effects of creatine, coq10, and lipoic acid in mitochondrial disorders. Muscle Nerve 35:235–242.

Roitman S, Green T, Osher Y, Karni N, Levine J (2007) Creatine monohydrate in resistant depression: a preliminary study. Bipolar Disord 9:754–758.

Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM (2014) Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord 16:410–421.

Rosenthal RE, Williams R, Bogaert YE, Getson PR, Fiskum G (1992) Prevention of postischemic canine neurological injury through potentiation of brain energy metabolism by acetyl-L-carnitine. Stroke 23:1312–1317; discussion 1317.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 356:1711–1722.

Saengsirisuwan V, Perez FR, Sloniger JA, Maier T, Henriksen EJ (2004) Interactions of exercise training and alpha-lipoic acid on insulin signaling in skeletal muscle of obese zucker rats. Am J Physiol Endocrinol Metab 287:E529–E536.

Sahraian A, Ghanizadeh A, Kazemeini F (2015) Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo-controlled clinical trial. Trials 16:94.

Samuni Y, Goldstein S, Dean OM, Berk M (2013) The chemistry and biological activities of N-acetylcysteine. Biochim Biophys Acta 1830:4117–4129.

Sandhir R, Sood A, Mehrotra A, Kamboj SS (2012) N-acetylcysteine reverses mitochondrial dysfunctions and behavioral abnormalities in 3-nitropropionic acid-induced Huntington's disease. Neurodegener Dis 9:145–157.

Schou M, Mortensen E, Vestergaard P (1986) Erythrocyte folate before and during treatment with lithium. Hum Psychopharmacol Clin Exp 1:29–33.

Scumpia PO, Kelly-Scumpia K, Stevens BR (2014) Alpha-lipoic acid effects on brain glial functions accompanying double-stranded RNA antiviral and inflammatory signaling. Neurochem Int 64:55–63.

Selhub J, Bagley LC, Miller J, Rosenberg IH (2000) B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 71:614S–620S.

Selhub J, Morris MS, Jacques PF, Rosenberg IH (2009) Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr 89:702S–706S.

Sepehrmanesh Z, Kolahdooz F, Abedi F, Mazroii N, Assarian A, Asemi Z, Esmaillzadeh A (2016) Vitamin D supplementation affects the beck depression inventory, insulin resistance, and biomarkers of oxidative stress in patients with major depressive disorder: a randomized, controlled clinical trial. J Nutr 146:243–248.

Sharma A, Gerbarg P, Bottiglieri T, Massoumi L, Carpenter LL, Lavretsky H, Muskin PR, Brown RP, Mischoulon D, Work Group of the American Psychiatric Association Council on Research (2017) S-adenosylmethionine (same) for neuropsychiatric disorders. J Clin Psychiatry 78:e656–e667.

Sharpley AL, Hockney R, McPeake L, Geddes JR, Cowen PJ (2014) Folic acid supplementation for prevention of mood disorders in young people at familial risk: a randomised, double blind, placebo controlled trial. J Affect Disord 167:306–311.

Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, Waichunas D, Bumgarner L, Bourdette D, Silbert L, Kaye J (2014) A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in alzheimer's disease. J Alzheimers Dis 38:111–120.

Sigitova E, Fišar Z, Hroudová J, Cikánková T, Raboch J (2017) Biological hypotheses and biomarkers of bipolar disorder. Psychiatry Clin Neurosci 71:77–103.

Sikoglu EM, Navarro AA, Starr D, Dvir Y, Nwosu BU, Czerniak SM, Rogan RC, Castro MC, Edden RA, Frazier JA, Moore CM (2015) Vitamin D3 supplemental treatment for mania in youth with bipolar spectrum disorders. J Child Adolesc Psychopharmacol 25:415–424.

Silvagno F, Pescarmona G (2017) Spotlight on vitamin D receptor, lipid metabolism and mitochondria: some preliminary emerging issues. Mol Cell Endocrinol 450:24–31.

Simões D, Riva P, Peliciari-Garcia RA, Cruzat VF, Graciano MF, Munhoz AC, Taneda M, Cipolla-Neto J, Carpinelli AR (2016) Melatonin modifies basal and stimulated insulin secretion via NADPH oxidase. J Endocrinol 231:235–244.

Singh SP, Singh V, Kar N (2012) Efficacy of agomelatine in major depressive disorder: meta-analysis and appraisal. Int J Neuropsychopharmacol 15:417–428.

Smidt LJ, Cremin FM, Grivetti LE, Clifford AJ (1991) Influence of thiamin supplementation on the health and general well-being of an elderly irish population with marginal thiamin deficiency. J Gerontol 46:M16–M22.

Spedding S (2014) Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients 6:1501–1518.

St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, Spiegelman BM (2006) Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell 127:397–408.

Stoll AL, Sachs GS, Cohen BM, Lafer B, Christensen JD, Renshaw PF (1996) Choline in the treatment of rapid-cycling bipolar disorder: clinical and neurochemical findings in lithium-treated patients. Biol Psychiatry 40:382–388.

Stoney PN, McCaffery P (2016) A vitamin on the mind: new discoveries on control of the brain by vitamin A. World Rev Nutr Diet 115:98–108.

Stork C, Renshaw PF (2005) Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research. Mol Psychiatry 10:900–919.

Suh JH, Moreau R, Heath SH, Hagen TM (2005) Dietary supplementation with ®-alpha-lipoic acid reverses the age-related accumulation of iron and depletion of antioxidants in the rat cerebral cortex. Redox Rep 10:52–60.

Sullivan PG, Geiger JD, Mattson MP, Scheff SW (2000) Dietary supplement creatine protects against traumatic brain injury. Ann Neurol 48:723–729.

Sun X, Wang JF, Tseng M, Young LT (2006a) Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. J Psychiatry Neurosci 31:189–196.

Sun X, Wang JF, Tseng M, Young LT (2006b) Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder. J Psychiatry Neurosci 31:189–196.

Suzuki YJ, Tsuchiya M, Packer L (1991) Thioctic acid and dihydrolipoic acid are novel antioxidants which interact with reactive oxygen species. Free Radic Res Commun 15:255–263.

Tarnopolsky MA (2008) The mitochondrial cocktail: rationale for combined nutraceutical therapy in mitochondrial cytopathies. Adv Drug Deliv Rev 60:1561–1567.

Tarnopolsky MA, Beal MF (2001) Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. Ann Neurol 49:561–574.

Taylor D, Sparshatt A, Varma S, Olofinjana O (2014) Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies. Bmj 348:g1888.

Timbrell JA, Seabra V, Waterfield CJ (1995) The in vivo and in vitro protective properties of taurine. Gen Pharmacol 26:453–462.

Toyoda A, Iio W (2013) Antidepressant-like effect of chronic taurine administration and its hippocampal signal transduction in rats. Adv Exp Med Biol 775:29–43.

Trinko JR, Land BB, Solecki WB, Wickham RJ, Tellez LA, Maldonado-Aviles J, de Araujo IE, Addy NA, DiLeone RJ (2016) Vitamin D3: a role in dopamine circuit regulation, diet-induced obesity, and drug consumption. eNeuro 3:doi: 10.1523/ENEURO.0122-15.2016.

van Dyck CH, Lyness JM, Rohrbaugh RM, Siegal AP (2009) Cognitive and psychiatric effects of vitamin B12 replacement in dementia with low serum B12 levels: a nursing home study. Int Psychogeriatr 21:138–147.

Venkatasubramanian R, Kumar CN, Pandey RS (2013) A randomized double-blind comparison of fluoxetine augmentation by high and low dosage folic acid in patients with depressive episodes. J Affect Disord 150:644–648.

Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PK, Landén M (2014) The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 171:1067–1073.

Walker JG, Batterham PJ, Mackinnon AJ, Jorm AF, Hickie I, Fenech M, Kljakovic M, Crisp D, Christensen H (2012) Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms–the beyond ageing project: a randomized controlled trial. Am J Clin Nutr 95:194–203.

Wang W, Lu Y, Xue Z, Li C, Wang C, Zhao X, Zhang J, Wei X, Chen X, Cui W, Wang Q, Zhou W (2015) Rapid-acting antidepressant-like effects of acetyl-l-carnitine mediated by PI3K/AKT/BDNF/VGF signaling pathway in mice. Neuroscience 285:281–291.

Wong KE, Kong J, Zhang W, Szeto FL, Ye H, Deb DK, Brady MJ, Li YC (2011) Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. J Biol Chem 286:33804–33810.

Wright DJ, Renoir T, Smith ZM, Frazier AE, Francis PS, Thorburn DR, McGee SL, Hannan AJ, Gray LJ (2015) N-acetylcysteine improves mitochondrial function and ameliorates behavioral deficits in the R6/1 mouse model of huntington's disease. Transl Psychiatry 5:e492.

Xu S, He M, Zhong M, Li L, Lu Y, Zhang Y, Zhang L, Yu Z, Zhou Z (2015) The neuroprotective effects of taurine against nickel by reducing oxidative stress and maintaining mitochondrial function in cortical neurons. Neurosci Lett 590:52–57.

Yamada T, Hashida K, Takarada-Iemata M, Matsugo S, Hori O (2011) A-lipoic acid (LA) enantiomers protect SH-SY5Y cells against glutathione depletion. Neurochem Int 59:1003–1009.

Yatham LN, Vieta E, Goodwin GM, Bourin M, de Bodinat C, Laredo J, Calabrese J, Agomelatine Study Group (2016) Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. Br J Psychiatry 208:78–86.

Ye HB, Shi HB, Yin SK (2013) Mechanisms underlying taurine protection against glutamate-induced neurotoxicity. Can J Neurol Sci 40:628–634.

Yoon SJ, Lyoo IK, Haws C, Kim TS, Cohen BM, Renshaw PF (2009) Decreased glutamate/glutamine levels may mediate cytidine's efficacy in treating bipolar depression: a longitudinal proton magnetic resonance spectroscopy study. Neuropsychopharmacology 34:1810–1818.

Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC, Cache County Study Group (2004) Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements. Arch Neurol 61:82–88.

Zanelli SA, Solenski NJ, Rosenthal RE, Fiskum G (2005) Mechanisms of ischemic neuroprotection by acetyl-L-carnitine. Ann N Y Acad Sci 1053:153–161.

Zhang L, Cao J, Wang Z, Dong Y, Chen Y (2016) Melatonin modulates monochromatic light-induced GHRH expression in the hypothalamus and GH secretion in chicks. Acta Histochem 118:286–292.

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