Targeting Mitochondrial Dysfunction for Bipolar Disorder

Maya Kuperberg, Sophie L. A. Greenebaum, and Andrew A. Nierenberg

Contents

Abstract People with bipolar disorder (BD) all too often have suboptimal long-term outcomes with existing treatment options. They experience relapsing episodes of depression and mania and also have interepisodic mood and anxiety symptoms. We need to have a better understanding of the pathophysiology of BD if we are to make progress in improving these outcomes. This chapter will focus on the critical role of mitochondria in human functioning, oxidative stress, and the biological

M. Kuperberg
Beer Yaakov-Ness Ziona Mental Health Center, Tel Aviv University, Tel-Aviv, Israel

S. L. A. Greenebaum (✉)
Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
e-mail: sgreenebaum@mgh.narvaid.edu

A. A. Nierenberg
Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Curr Topics Behav Neurosci (2021) 48: 61–100
https://doi.org/10.1007/7854_2020_152
Published Online: 13 February 2021

mechanisms of mitochondria in BD. Additionally, this chapter will present the evidence that, at least for some people, BD is a product of mitochondrial dysregulation. We review the modulators of mitochondria, the connection between current BD medication treatments and mitochondria, and additional medications that have theoretical potential to treat BD.

Keywords Bipolar disorder · Medication · Mitochondria · Treatment

Patients with bipolar disorder (BD) frequently experience recurrent episodes of depression and mania, along with interepisodic mood and anxiety symptoms. Despite effective treatments, even with the best guideline-concordant pharmacotherapy, relapse rates remain high, and interepisodic symptoms persist. Better treatments are needed. Advances in the neurobiological understanding of BD, coupled with the growing trend of repurposing medications for new indications, have led researchers to study interventions which target mitochondria to treat BD. This chapter aims to provide an introduction to the biological mechanisms underlying mitochondrial function and discuss the evidence for mitochondrial dysregulation in BD. We will then take a look at mitochondrial modulators and review their effects or theoretical potential in treating patients suffering from BD.

1 The Mitochondria

Mitochondria are intracellular organelles that have co-existed symbiotically with eukaryotic cells for nearly 2 billion years, serving many different functions within the cells. Most notably, mitochondria produce essential cellular energy in the form of adenosine triphosphate (ATP), regulate calcium homeostasis, and are involved in cellular death pathways (Cuperfain et al. 2018). We will now explore each of these functions and their relationship with bipolar disorder (BD).

1.1 Mitochondria as an Energy Source

The primary source of energy for the cell comes from glucose. Glucose can be metabolized in three distinct steps, the first occurring in the cell cytoplasm and the latter two in the mitochondria. The first step is *glycolysis*, a process that with a net energetic yield of only two molecules of ATP per molecule of glucose, but this process also provides other molecules essential for further pathways: pyruvate and nicotinamide adenine dinucleotide hydride (NADH). The second step of glucose metabolism is the *citric acid cycle* (*Krebs cycle*), which utilizes pyruvate (obtained either as a by-product of glycolysis from the first glycolysis step or other metabolic

sources) with a net yield of one ATP molecule, again providing essential molecules for the final step, NADH and flavin adenine dinucleotide (FADH2), which are passed on to the last phase of cellular respiration. The third and final step is oxidative phosphorylation (OXPHOS), in which the proteins of the electron transport chain (ETC) remove electrons from the substrates created in the previous two steps and shuttle them along with different complexes. This transport of electrons induces pumping of protons from the mitochondrial matrix to the mitochondrial intermembrane space (Bonora et al. 2012), creating the electrochemical gradient that drives the enzymatic conversion of ADP into ATP in the fifth and final complex of the ETC aptly named *ATP synthase* (Cuperfain et al. 2018). All in all, by going all the way through the OXPHOS pathway, one molecule of glucose will generate between 36 and 38 molecules of ATP, making it by and large the most efficient pathway for energy production (Li et al. 2015).

All cells require energy in order to function, but the human brain has an extremely high energetic demand, consuming about 20% of oxygen (at rest) despite weighing only 2% of body weight (Clarke 1999). Neurons require large amounts of ATP to maintain functions such as neurotransmission, neuronal plasticity, protein synthesis, osmolarity, and cell division (Jardim et al. 2018). In order to meet these demands, the mitochondria move to where they are needed, using microtubule networks, to provide energy in regions of intense energy demands, e.g., around synapses (where ATP is used for synaptic transmission) or in areas of neurite outgrowth (Srivastava et al. 2018; McCann and Ross 2018). As one of the major consumers of energy, the human brain may be especially sensitive to dysregulations in mitochondrial functioning, with the implication that even mild disruptions in energy supplies – so mild that they might not present systematically as a mitochondrial disease – could still have neuropsychiatric manifestations (Peters et al. 2004).

As in most other tissues, the brain's primary source of energy is the mitochondria, producing the vast majority of ATP by OXPHOS. While it has previously been thought that only 1% of brain ATP is provided by glycolysis – that first step in glucose metabolism detailed above (Erecinska and Silver 1989) – glycolysis is more central in neurons, providing between 8 and 15% of the brain's ATP (Blazey et al. 2018). Even though glycolysis is a much less efficient route for ATP production than OXPHOS, generating about 17 times less ATP per glucose molecule, it is 100 times faster (Liberti and Locasale 2016). This mean glycolysis can serve as a rapid source of energy under conditions of limited oxygen supply when impairments occur in the OXPHOS pathway for any reason or simply when energy demands exceed supply. The process of glycolysis leads to an accumulation of pyruvate and lactate, which can serve as detectable biomarkers for this pathway's activity (Dogan et al. 2018). Lactate itself is now known to be more than strictly a waste product of glycolysis, with functions as an intermediary in metabolic processes and even as quick accessible fuel (Gladden 2004). While there is no doubt that glucose is the preferred source of energy during both rest and activation, there is an ongoing debate regarding lactate's role in the brain's energy metabolism – some speculate lactate may be preferred when neurons fire at a high rate (Baltan 2015), while others see lactate as an "opportunistic" glucose-sparing substrate (Dienel 2012). Either way, changes in

concentrations of lactate might represent mitochondrial and metabolic dysfunction that shift the cell toward reliance on less efficient sources of energy (Lin et al. 2003).

Cells keep their ATP levels tightly controlled within a narrow range, but the ATP molecules themselves cannot be easily stored, due to their low stability in water and the high rate of ATP-dependent processes that would quickly utilize and deplete its levels (Bonora et al. 2012). When ATP levels rise beyond the energetic demand of the cell, excess energy needs to be stored away, and this can be done by attaching ATP's high-energy phosphate to creatine, generating one phosphocreatine (PCr) and one ADP (Guimaraes-Ferreira 2014). This reaction is catalyzed by the enzymes Creatine Kinase (CK), a bidirectional enzyme capable of both transferring a phosphate group from PCr to ADP (forming ATP and creatine) in times of energetic demand and transferring a phosphate from ADP to creatine (forming PCr and ADP) in times of energy surplus. Interestingly, since acute cellular activity depletes ATP, in order to maintain its tightly controlled levels, the cell needs to rapidly break down PCr and reproduce ATP – an action that leads to a measurable drop in PCr. With that mechanism in place, we can measure PCr levels as indicative of the cellular energy storage status (Allen 2012; Du et al. 2018; Sahlin and Harris 2011) – with high levels of PCr reflecting good or excess energy production and low levels of PCr reflecting insufficient energy production. It has even been suggested that chronically depleted PCr might be indicative of cellular hypometabolism due to mitochondrial dysfunction that caused chronic insufficient ATP supply (Modica-Napolitano and Renshaw 2004).

1.2 Other Functions of Mitochondria

As stated before, while the mitochondria are essential for cellular energy metabolism, they take an integral part in many more cellular functions. Our review of these functions is just the tip of the iceberg, as in-depth details of the molecular mechanisms are beyond the scope of this chapter. Interested readers are highly encouraged to delve into the finer details in other sources.

Calcium Homeostasis Calcium (Ca2+) are ions essential for the physiology of the organism, involved in many cellular processes and functions including metabolism, secretion, gene expression, cell survival, and cell death. The mitochondria and endoplasmic reticulum (ER) are two organelles serving as major reservoirs of intracellular calcium (Srivastava et al. 2018), by taking up calcium ions, releasing them back to the cytoplasm, and buffering intracellular calcium concentration to avoid high cytosolic levels that could be toxic to the cell (de Sousa et al. 2014). Calcium ions are not passive players in these interactions, and they can, in turn, affect mitochondrial functioning: not only can they affect mitochondrial membrane depolarization, but well-balanced calcium concentrations also are beneficial for mitochondrial functioning. They can contribute to faster activity of the respiratory chain enzymes and eventual higher ATP output. Calcium ions can also modulate the

clearance of reactive oxygen species (ROS) by increasing antioxidant defenses, helping to sustain the increased metabolic rate (Zhang et al. 2016). Despite all these beneficial effects, it turns out excessive calcium can cause problems: an overload of mitochondrial calcium can cascade and culminate in disturbed mitochondrial functioning, increased ROS production, and even cell death with apoptotic or necrotic mechanisms (Javadov et al. 2018). Calcium concentrations, like that of many other cellular components, need to be balanced in order to guarantee maximum gains at minimal costs.

In addition to the effects of calcium on the mitochondria, calcium also affects other biological systems relevant to BD and psychiatric illness. In the brain, calcium is essential for the proper effects of neurotransmission: the release of neurotransmitters can result in a rapid (but transient) rise in calcium levels in the post-synaptic neuron, leading to changes in neuron excitability and membrane structure for both the short- and long-term. Outside of the specific synaptic context, the influx of calcium to the post-synaptic neuron initiates a cascade of signaling events that affect cellular gene expression for processes such as dendritic growth, synapse development, and neuronal plasticity (Greer and Greenberg 2008). Lastly, calcium levels have been shown to have effects on the activity of the circadian clock and circadian rhythms. A construct was shown to be involved in the pathophysiology of BD (McCarthy et al. 2016).

Apoptosis Mitochondria have a major role in apoptosis, or programmed cellular death, via both its intrinsic and extrinsic pathways (de Sousa et al. 2014), for example, due to triggers such as excessively high cytosolic levels of calcium, excessive activity of free radicals, and other perturbations in the balance of pro- and anti-apoptotic factors. Apoptosis is not necessarily a deleterious process, but a physiological part of normal cell turnover and brain development, even in adults. For example, apoptosis can lead to the selective destruction of synapses (Lee et al. 2018; Flippo and Strack 2017) – which at appropriate levels could be related to beneficiary neuroplasticity and pruning, but when utilized inappropriately could result in an extensive synaptic loss (Baranov et al. 2019; de Sousa et al. 2014).

In the context of mitochondria's role, and like any other balanced biological processes, cells have developed defense mechanisms to prevent excessive cellular death by inappropriate apoptotic mechanisms brought about by aberrant mitochondria. By the process of mitochondrial autophagy (mitophagy), cells segregate their damaged components and divide them by mitochondrial fission, degrading the dysfunctional mitochondrion and retaining healthy ones. Modest mitophagy can be compensated for by the cells' mitochondrial reserve and mitochondrial biogenesis to maintain energy production. Excessive mitophagy, however, or lack of compensatory mitochondrial biogenesis, will result in cell death (Kubli and Gustafsson 2012). A dysregulation in the process of mitophagy could lead to accumulation of damaged mitochondria, resulting in decreased energy production, increased oxidative stress (explained in a subsequent section), and decreased mitochondrial calcium buffering capacity – conditions that are especially harmful to postmitotic cells, such as neurons in the brain (Scaini et al. 2019).

2 Reactive Oxygen Species and Oxidative Stress

Mitochondria are a major source of reactive oxygen species (ROS, and to a lesser degree of reactive nitrogen species, RNS). ROS are highly reactive oxygen-containing free radical molecules that continuously form in all aerobic organisms. Free radicals are highly reactive due to their chemical structure, containing a single unpaired electron in their outermost shell of electrons, which makes them able to interact with and damage cellular components such as proteins, lipids, and nucleic acids (Zhang et al. 2016), leading to cell injury and death. For example, in the case of the mitochondria, ROS activity could damage mitochondrial DNA, proteins of the respiratory chain, or lipids of the mitochondrial membrane lipids. This resulting dysfunction could increase membrane permeability and disrupt the calcium homeostasis (Guo et al. 2013), affecting the antioxidant activity and ROS production (Zhang et al. 2016). In this manner, excessive or unopposed ROS activity in the mitochondria could set off a chain of events resulting in cellular damage.

During normal aerobic cellular respiration, a small percentage of the electrons passing through the electron transfer chain (ETC) in the mitochondria can escape, and this leakage can lead to the formation of ROS (Srivastava et al. 2018). This is generally a normal and balanced process, but under pathological conditions – such as diminished or heightened activity of the ETC complexes – mitochondrial ROS formation can increase further, beyond the limits of normal and balanced concentrations (Raha and Robinson 2000). In addition to the electron leakage that happens during oxidative phosphorylation (OXPHOS), many cellular processes (both physiological and pathological) as well as environmental exposures can also lead to generation of reactive species. These include – but are not limited to – immune system activation, tissue ischemia, mental stress, aging, synthesis of prostaglandins, phagocytosis, cytochrome P450 activity, exposure to pollutants, or ionizing radiations and more (Pizzino et al. 2017).

While ROS have potentially harmful effects, they also have important functions in cellular functioning. These reactive species can be used as signaling and modulating molecules, involved in major biological pathways such as adaptation to hypoxia, cell differentiation, and phagocytosis (Sena and Chandel 2012; Pizzino et al. 2017; Droge 2002). To counterbalance the toxic potential, tight regulation is required so that ROS could participate in physiological cell signaling without causing structural damage or cellular death. Cells have developed antioxidant defenses and ROS scavenging capacities, allowing moderate levels of ROS for their beneficial roles while preventing their accumulation to dangerous levels. Antioxidant defenses include endogenous molecules such as glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), coenzyme Q10, melatonin or uric acid, and exogenous antioxidants such as vitamin C, vitamin E, zinc, and drugs, for example, acetylcysteine, a precursor of GSH (Liguori et al. 2018). GSH is the most important antioxidant molecule, and the mitochondria contain about 10–15% of the total GSH in the cell (Matschke et al. 2019). It should be noted, of course, that medicine and biology are rarely unidirectional – the oxidative balance is a complex

process, with many antioxidants also having pro-oxidant abilities under certain conditions or concentrations (Matschke et al. 2019).

If the ROS-homeostasis is perturbed, due to either increased production or reduced antioxidant defenses, cells might reach a state termed *oxidative stress*, meaning the balance between pro-oxidant and antioxidant mechanisms has shifted in favor of the pro-oxidants (Pizzino et al. 2017). When oxidative stress occurs, cells are exposed to oxidative damage of essential macromolecules including DNA, lipids, proteins, and carbohydrates. The consequences of damage caused by free radicals can be extremely deleterious and lead to many ailments, both acute and chronic, including cancer, cardiovascular and neurodegenerative disorders, as well as aging processes (Pizzino et al. 2017; Pham-Huy et al. 2008). In particular, the mitochondrial DNA (mtDNA) that has no protective histones and lacks repair mechanisms present for nuclear DNA is particularly vulnerable to damage caused by such oxidative modifications (McCann and Ross 2018). Researchers have sought whether increasing the body's antioxidant defenses could slow or even stop the progression of many of these diseases, with generally conflicting results (Liguori et al. 2018).

The brain is especially vulnerable to shifts in the ROS balance and oxidative stress for several reasons: first, because of its high metabolic rate and high lipid content, it is easier to achieve high concentrations of reactive species in the brain, naturally shifting the balance in favor of the pro-oxidants (Massaad and Klann 2011). Second, neurons have lower levels of antioxidant defenses than other cells in the nervous system, naturally making the shift toward the pro-oxidant factors easier (Steckert et al. 2010; Matschke et al. 2019). Third, since neuronal cells are mostly postmitotic, they accumulate damage throughout life (Matschke et al. 2019). Studies of the nervous system have shown that psychiatric patients endure excessive levels of oxidative stress (Srivastava et al. 2018), and this is a possible mechanism by which neuropsychiatric illnesses result in pathophysiologic changes – and a possible mechanism that can be targeted by medications.

3 Mitochondria in Bipolar Disorder

Bipolar disorder (BD) is a neuropsychiatric disorder with a cyclical nature, alternating between periods of euthymia, mania, and depression. The precise pathophysiological pathways responsible for BD remain elusive even after many years of research, likely due to multifactorial etiology involving many different molecular disturbances, arising from mutations in many small genetic risk areas and accumulation of environmental stressors (Szczepankiewicz 2013).

Originally, BD was thought to reflect an adrenergic-cholinergic imbalance, with higher adrenaline activity in mania and higher acetylcholine activity in depression. This hypothesis has since been updated, describing mania as a state of higher *catecholaminergic* status (i.e., both dopaminergic and adrenergic) relative to cholinergic status and vice versa in depression. Medication studies generally supported

this hypothesis: drugs that increase acetylcholine in the central nervous system (CNS) increase depressive symptoms, and drugs that increase adrenaline and dopamine can induce or exacerbate manic symptoms (van Enkhuizen et al. 2015). The efficacy of selective serotonin reuptake inhibitors (SSRI) in the treatment of depression and their propensity to induce a switch to a manic state in patients with BD have led to a more general "monoamine dysregulation" theory of BD that includes not only catecholamines but also serotonin. This hypothesis is backed by the effects of serotonergic agents but also by molecular imaging studies, and associated genetic studies pointed at genes that influence monoamine systems, including transporters and catalyzers (Sigitova et al. 2017). However, decades of studies and many similar drug developments later, there is disagreement regarding the precise mechanisms causing the monoamine imbalances. Nowadays, it is apparent that additional neurotransmission systems participate in the pathophysiology of BD other than the monoamines, including glutamatergic, GABAergic, and even opioid dysregulation (Blacker et al. 2017; Lutz and Kieffer 2013).

Despite the many drugs that have gained FDA approval for BD, current treatment options remain unsatisfactory, and many patients continue to experience intra-episodic symptoms or even full-blown episodes that are resistant to treatment, particularly of the depressive polarity (Geddes and Miklowitz 2013). In the search for greater pathophysiological understanding and effective treatment modalities, research has been inspecting the role of mitochondrial dysfunction and oxidative damage in BD. This idea has been proposed by Kato and Kato in 2000 and is based on relevant study findings, the increased likelihood of maternal inheritance in generational transmission of BD, abnormal findings in the mitochondrial DNA (mtDNA) of patients with BD, and comorbidity of affective disorder with mitochondrial disorders (Kato and Kato 2000; Kato et al. 2018). For example, the manic phase in BD seems to be particularly prone to increases in energy production and oxidative stress, with manic patients showing increased mitochondrial respiration and ATP utilization (Weber et al. 2013). One proposed mechanism for these observations is that an initial increase in oxidative stress at the beginning of a manic episode leads to increased mitochondrial functioning, with consequent increases both in ROS production and in the activity of mitigating factors that are attempting to control the potentially toxic state of oxidative stress. By increasing antioxidant defenses, mitochondrial activity (and ROS production) can be elevated without yet triggering apoptotic mechanisms. Eventually, however, the defensive pathways become overwhelmed, mitochondrial functioning begins to deteriorate, and cellular damage occurs. Nearing the end of the manic episode, oxidative stress levels decrease, potentially provoking a transition from mania to euthymia or depression (Morris et al. 2017). This is just one proposed mechanism, and not all evidence is consistent with it.

While behaviorally, BD can easily be described as a disorder of energy levels – an abundance in mania versus a deficit in depression – attempts at direct translations from the phenomenological level to the molecular level are scantily successful, and evidence is accumulating that aberrations in bioenergetic mechanisms exist in *all* phases of the illness. In addition to the specific processes and pathways, patients with

BD demonstrated abnormalities in the structure and distribution of mitochondria within the cell, both in the brain and peripheral cells (Cataldo et al. 2010). Results from different studies are often inconsistent, limited by a small number of patients, different stages of disease, and different pharmacotherapies. It seems that while the mitochondrial function is overall somewhat disrupted, the specific pattern of disruption is inconclusive. Below we will explore potential molecular mechanisms by which mitochondrial dysfunction could be associated with BD.

3.1 Possible Mechanisms of Mitochondrial Dysfunction in Bipolar Disorder

3.1.1 A Shift from OXPHOS to Glycolysis

Studies demonstrate a shift from OXPHOS to glycolysis in at least several brain areas, if not globally, as evident by decreased phosphocreatine (PCr) and increased lactate in magnetic resonance spectroscopy (MRS) studies (Dudley et al. 2015, 2016; Dogan et al. 2018; Nierenberg et al. 2013). As a quick reminder, glycolysis is the fastest but least efficient pathway from glucose to ATP, while OXPHOS takes (relatively) much more time but yields many more ATP molecules per glucose. PCr serves as the cell's energy storage with lower PCr levels implying energy stores are low, either due to decreased production or increased utilization of ATP. Cellular conditions of high energetic demand, or a dysfunction in the OXPHOS pathways, could lead to increased reliance on glycolysis for ATP supply with the associated lactate accumulation and reduced energy production (Callaly et al. 2015). A 2018 meta-analysis reported that overall, and despite some contradictory findings, lactate levels were indeed elevated in the brains of patients with BD compared to healthy controls. That treatment with a mood stabilizer was somewhat able to restore brain lactate to levels comparable to healthy control (Kuang et al. 2018). These findings suggest that patients with BD indeed shift away from OXPHOS toward the largely inefficient process of glycolysis as an energy source, leading to reduced total energy output of the mitochondria.

Electron Transport Chain (ETC) Interestingly, it has been shown that under normal conditions, the expression of ETC genes was the same in patients with BD as in healthy controls, but during stress conditions of glucose deprivation where upregulation of ETC genes is expected and was indeed observed in healthy controls, patients with BD displayed *reduced* expression for the entire ETC. This pattern is consistent with the notion of mitochondrial inability to adapt to energetic stress in BD (Naydenov et al. 2007). Many studies detected disturbances in the activity and regulation of complexes of the ETC, but the direction of change is inconsistent. Most likely, these changes are dependent on the polarity of the current mood episode and on the specific brain and region assessed and possibly could also be affected by the

type of psychotropic medication the patients received before assessment (Holper et al. 2019).

- *ETC Complex I*: Complex I is the primary site of ROS production, and its inhibition is linked to decreased energy production (Callaly et al. 2015) and increased oxidative stress (Onukwufor et al. 2019). Compared to healthy controls, a 2010 postmortem study found decreased activity and levels of complex I in the prefrontal cortex (PFC) of patients with BD. No differences were detected between patients who were treated with antipsychotic medications, known to inhibit complex I activity and those who were not (Andreazza et al. 2010). More recently, 2018 meta-analysis found complex I subunits expression to be generally *reduced*, but certain units' expression increased (Holper et al. 2019), while a 2019 study found *increased* complex I activity in medicated patients with bipolar depression. It has been speculated that this increased activity is a compensatory response to decreases in activity of other complexes (Zverova et al. 2019).
- *ETC Complex II*: During a bipolar depressive episode, activity of complex II decreased when compared to euthymic patients, and the activity was also negatively correlated with scores on a depression scale (Valvassori et al. 2018; Zverova et al. 2019) – that is, the lower the activity of complex II, the more severe their depression.
- *ETC Complex IV*: During a bipolar depressive episode, levels of complex IV were decreased (Zverova et al. 2019).

3.1.2 Creatine Kinase

CK is the enzyme responsible for the reversible transfer of a high-energy phosphate group between ATP and creatine, creating PCr stores when supply exceeds demand or rapidly generating ATP in times of energetic need (Yuksel et al. 2015; MacDonald et al. 2006). During periods of tissue activation, the predicted response observed in healthy individuals is a reduction in PCr levels with no change in ATP levels, reflecting the cell's ability to regenerate ATP from PCr – and the importance of constant ATP levels. In patients with BD who were undergoing a visual stimulation test, ATP levels decreased, while PCr levels did not change, implying no generation of ATP despite the need. Suspecting a specific defect in the CK reaction, a recent study found a significant reduction in the reaction rate constant of the CK enzymes in patients with BD, compared to healthy controls. This implies that patients with BD have abnormalities in their ability to generate ATP during times of stress, despite normal levels at rest – and this might be related to the patients' sensitivity to conditions of increased stress (Du et al. 2018).

3.1.3 Calcium

Impaired regulation of calcium signaling is a highly reproducible abnormality in BD. Peripheral blood cells of patients with BD show elevated calcium, associated with dysfunction in both endoplasmic reticulum (ER) and mitochondrial activity (Machado-Vieira et al. 2011). Dysregulated calcium homeostasis has also been associated with excessive ROS production (Fonseca et al. 2015). Interestingly, studies of patients with the mitochondrial disease chronic progressive external ophthalmoplegia (CPEO) showed that 16–21% of them were diagnosed as having BD, a rate much higher than the population reported prevalence of 1%. Mice with mutants in the gene responsible for CPEO, polymerase gamma (POLG, which is a mitochondrial DNA polymerase), exhibited depressive and manic-like symptoms, were affected by treatment with lithium, and also showed altered calcium signaling (Kato 2019).

Calcium signaling is affected by the *inositol signaling pathway* – inositol being an essential substrate for signaling molecules, involved in multiple cellular events. Of particular relevance, this pathway can lead to increased calcium release in the brain, and when inositol levels are deficient, the calcium response mediated by this pathway will be attenuated (Harwood 2005). Studies have shown that optimal mitochondrial functioning is required for common pathways of inositol-triggered calcium release, tying together inositol and mitochondrial functioning (Wilson et al. 2019). The "inositol depletion hypothesis" of BD claims that the periodic switching between manic and depressive episodes results from neuronal activity driven by an altered inositol signaling and calcium signaling (Berridge 2014). Higher inositol signals were detected during the manic phase and lower levels during the depressive phase (Yu and Greenberg 2016). Lithium, a commonly used and useful drug in the treatment of BD, reduces the supply of inositol by inhibiting inositol-monophosphatase (IMPase) – a key enzyme in the production of inositol – implying lithium can prevent abnormal increases in calcium as part of its therapeutic actions (Kato 2019).

3.1.4 Increased Oxidative Stress

Many studies have shown increased levels of lipid and protein peroxidation, reflecting oxidative damage, in patients with BD compared to healthy controls (Akarsu et al. 2018; Brown et al. 2014). Whether these findings reflect a state marker of acute episodes or a trait marker of BD, and precisely how they result from an overproduction of free radicals or decreased antioxidant defenses, are points of disagreement – with different studies reporting contradictory results (Valvassori et al. 2018; Siwek et al. 2016; Kim et al. 2017). For example, some studies find levels of the important antioxidant GSH to be reduced (Rosa et al. 2014; Tsai and Huang 2015), others find GSH levels increased (Ngamchuea et al. 2018), and others are not able to detect any significant differences from healthy controls at all (Lagopoulos et al. 2013; Soeiro-de-Souza et al. 2016). These are but a few examples and many other factors are at play in the ROS balance.

3.1.5 Neurotransmitters

One interesting focus of study combines oxidative stress, mitochondrial functioning, and neurotransmitter hypothesis of BD pathophysiology. This merge of fields could mean that the findings are links of the same chain, each affecting the others, and not separate pathophysiologic pathways.

Dopamine is a catecholamine neurotransmitter with many functions in the brain, including essential roles in the modulation of behavior and cognition and also serving as a precursor for (nor)epinephrine production. Dopamine is central in various neural pathways related to motivation, reward, sleep, mood, attention, and learning (Juarez Olguin et al. 2016). Studies have found that in patients with BD, the density of dopamine receptors is increased during psychotic mania, and manic patients also demonstrate hyperactivity in dopaminergic circuits of the reward system. Studies are less consistent regarding dopamine and its receptors during times of euthymia and depression (Ashok et al. 2017). Regarding mitochondrial and brain functioning, dopamine has complex actions. On the one hand, elevated levels can lead to mitochondrial dysfunction by inhibiting mitochondrial motility (Chen et al. 2008), inhibiting subunits of the ETC (Czerniczyniec et al. 2007) and increasing oxidative stress with possible eventual cell death (Monzani et al. 2019). On the other hand, dopamine also has neuroprotective properties, working in synergism with uric acid to repair DNA damage and protecting neurons against glutamatergic excitotoxicity (Vaarmann et al. 2013) – which is thought to be a possible process in BD.

Glutamate is the main excitatory neurotransmitter in the brain, primarily binding to *N*-methyl-D-aspartate (NMDA) receptors and affecting calcium channels. As described before, calcium is involved in many cellular pathways, and the mitochondria and the ER tightly regulate its levels. Activation of glutamate receptors induces calcium influx into the cytosol of neurons, where the mitochondria buffer the ions. Increased levels of glutamate may lead to calcium overload – also known as *glutamate excitotoxicity* – a process that can result in overproduction of ROS and eventual cell death. Abnormal increases in glutamate have been reported in patients with BD (Bustillo et al. 2019), and several mood stabilizers are capable of regulating its levels (Soeiro-de-Souza et al. 2018a). A possible mechanism is that a genetic mutation in mtDNA of patients with BD leads to abnormalities in the mitochondria's ability to buffer calcium, resulting in a decreased capacity to handle glutamate excitotoxicity without resorting to apoptosis (Callaly et al. 2015).

3.1.6 Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a type of neurotrophic factor, which are molecules essential for neuronal proliferation and differentiation during brain development, and that also play critical roles in plasticity, survival, and connectivity in the adult brain. BDNF also has various neuroprotective effects – mitigating glutamate excitotoxicity, anti-apoptotic,

and antioxidant activities, at times as a response to mitochondrial dysfunction (Chen et al. 2017; Markham et al. 2014). Impairment in BDNF signaling have been found in a wide range of neurologic and psychiatric disorders, including BD: patients during acute episodes, whether manic or depressive, had significantly lower levels of BDNF compared to healthy controls, while during euthymia no differences were detected (de Oliveira et al. 2009). The decreased levels of BDNF may make patients with BD less resilient to small impairments in mitochondrial functioning.

3.1.7 NAA

N-Acetylaspartate (NAA) is a metabolite highly concentrated in neurons, with roles in myelination and energy metabolism in mitochondria (likely through the generation and use of acetyl-CoA). Levels of NAA reflect the health of neurons and their mitochondria and act as reliable markers for neuronal energy impairment or dysfunction (Moffett et al. 2013). NAA can be measured using proton magnetic resonance spectroscopy (^{1}H-MRS) studies, but results are difficult to interpret as NAA levels are sensitive to pharmacological and behavioral treatments, the current mood state, and illness duration. In light of this, and as seems to be the theme when attempting to study a topic as diverse as "mitochondrial functioning" – different studies often end up with conflicting results (Soeiro-de-Souza et al. 2018b). Overall, studies do indicate abnormalities in energy balance, evidenced by differences in NAA levels between patients with BD and healthy controls.

3.1.8 Bcl-2

The anti-apoptotic protein B cell lymphoma protein-2 (Bcl-2) prevents cellular apoptosis by preventing the release of cytochrome-c in the mitochondria. Increased Bcl-2 activity is known to correspond to an increase in OXPHOS and ATP production (Manfredi et al. 2003), and elevated levels of Bcl-2 can increase the mitochondria's capacity for calcium uptake and resistance to calcium influx, preventing impairments due to incapacitating calcium overload (Murphy et al. 1996). In patients with BD, levels of Bcl-2 were found to be lower in the prefrontal cortex (Kim et al. 2010), while serum levels during a manic episode were negatively correlated with the severity of manic symptoms (Chen et al. 2015) – that is, lower levels of Bcl-2 were correlated with more severe mania. It should also be noted that BDNF exerts part of his anti-apoptotic effects via the Bcl-2 protein (Chen et al. 2017), and as noted before, its levels were found to be decreased in patients with BD.

3.2 Mitochondrial Genes

The vast majority of genes involved in mitochondrial function are located in the cell nucleus (about 1,200), but 37 genes are encoded directly by mitochondrial DNA

(mtDNA) located within the organelle itself (Chinnery and Hudson 2013). mtDNA does not undergo recombination during meiosis like nuclear (autosomal) DNA, is strictly maternally inherited through the ovum, and lacks the protective repair mechanisms nuclear DNA has – leading to about 10 times the frequency of polymorphisms (Howell et al. 2003). The close physical proximity of mtDNA to ROS generated by the mitochondrion itself might be another factor in its high mutation rate (Pei and Wallace 2018). Mitochondria can increase the numbers of mtDNA copies when needed by using the polymerase POLG, and alterations in whole blood mtDNA copy number are considered indicative of mitochondrial dysfunction (Yamaki et al. 2018). Since POLG is a protein prone to suffering from oxidative damage, it has been postulated that oxidative stress could be causing POLG downregulation in acute phases of BD, resulting in the observed decreases in mtDNA copy numbers during those episodes (Wang et al. 2018). A recent study has shown that in patients with BD, the levels of mtDNA copy numbers are significantly lower during acute episodes (of either mania or depression) and at least in mania are inversely correlated to the number of previous mood episodes – that is, the more previous episodes a patient has had, the lower their mtDNA copy numbers. Studies on the topic are less consistent when assessing periods of euthymia, with some finding a reduction in mtDNA copy numbers even then, some limiting their findings to BD type I or advanced disease only, and others still finding no significant differences when comparing patients with BD to healthy controls (Kim et al. 2019; Yamaki et al. 2018). It should be noted that certain antipsychotic agents by themselves are associated with decreasing the mtDNA copy number (Kumar et al. 2018), and this might be at the root of some of these contradictory findings on the matter. In addition to these examples, many studies on patients with BD have found loci of interest in areas related to mitochondrial functioning. Since this chapter's aim is to focus on potential treatments for BD, we will not explore this topic further.

4 How Conventional Drugs for Bipolar Disorder Relate to Mitochondrial Functioning

Current available treatments for bipolar disorder (BD) address different pathways and, generally, have multiple molecular targets. Many of these drugs have effects on the mitochondria or related pathways, with more significant effects observed in patients who have shown a clinical response to the drug in question. While these pathways are not necessarily the drugs' sole mechanism of action in BD – they are more pieces of the puzzle.

Electron Transport Chain (ETC) Lithium seems to overall increase complex I expression and activity, albeit inconsistently (de Sousa et al. 2014, 2015). Lithium-responsive patients showed differential expression of mitochondrial-related genes involved in the ETC and OXPHOS, compared to lithium-unresponsive patients

(Stacey et al. 2018). Another mood stabilizer, valproate, also has effects on the ETC and is able to reverse methamphetamine-induced inhibition of ETC complexes in the brains of rodents (Valvassori et al. 2010).

Antioxidant Properties Both lithium and valproate increase the levels of the most important antioxidant in the brain, GSH (Nascimento et al. 2015; Chiu et al. 2013), and the mood stabilizer lamotrigine appears to have antioxidant properties as well (Ozkul et al. 2014; Kim et al. 2007). Patients with BD who were treated with lithium had lower levels of lipid peroxidation markers during mood episodes, with the effect more pronounced in patients who also demonstrated a clinical response to lithium (Data-Franco et al. 2017). Patients with BD suffer from more oxidative stress, especially during acute episodes, and so it is possible that reducing oxidative stress is one of the mechanisms by which these drugs exert their clinical effects.

Anti-apoptotic Properties Lithium, valproate, and electro-convulsive treatment (ECT) all increase the expression of the anti-apoptotic protein Bcl-2, which has the ability to inhibit mitochondrially mediated apoptosis, consequentially increasing the mitochondria's resistance to toxic effects in the environment (Orrenius 2004). It should be noted though that these results are not always reproduced, and studies on the matter are plagued by methodological difficulties (Odeya et al. 2018).

Hyperexcitability Pluripotent stem-cell (iPSC) technology allows researchers to take fibroblasts and differentiate them into neurons. When using fibroblasts obtained from patients with BD type I, these neurons then showed hyperexcitability, smaller mitochondria size, and enhanced mitochondrial function, with the authors suggesting these mitochondrial properties lead to the excessive neuronal activity. Of relevance, in neurons derived from patients who showed a clinical response to lithium, applying lithium to the cells had profound effects on hyperexcitability and mitochondria size. In contrast, in cells derived from lithium-nonresponders, the drug did not induce any obvious changes. Further analysis showed that when applying lithium to cells derived from the lithium-responsive patients, a change was observed in the expression of 560 genes, compared to merely 40 genes in the lithium-nonresponsive group (Mertens et al. 2015; Stern et al. 2018).

Calcium Mood stabilizers can modulate calcium channels and increase levels of brain-derived neurotrophic factor (BDNF), a neurotrophic factor with the ability to mitigate glutamate excitotoxicity (Callaly et al. 2015; Data-Franco et al. 2017; Kato 2019). In addition, and as discussed previously, lithium is an inhibitor of IMPase decreasing levels of inositol and attenuating the intra-cellular calcium response (Harwood 2005). It is possible that reducing calcium overload is one of the pathways targeted by these drugs.

Lactate Lithium and valproic acid have shown to normalize elevated lactate levels in patients with BD (Kuang et al. 2018), while quetiapine – an antipsychotic drug – is able to decrease lactate levels in manic patients, again with a more prominent decrease in patients who have shown a clinical response to treatment (Kim et al. 2007). These findings are likely not causal, as increased lactate levels could be

indicative of a larger problem these drugs are targeting, but it is yet again tying together treatments for BD with mitochondrial dysfunction.

5 Mitochondrial Potential Treatments

After conceptualizing bipolar disorder (BD) as a disorder of mitochondrial and energetic dysregulation, we can now explore mitochondrial treatment modalities. Research has mainly focused on attempting to *balance* mitochondrial functioning – for example, enhancing it in depression and diminishing during mania or increasing antioxidant defenses to prevent damage from ROS due to insufficient antioxidant activity or increased cellular respiration (Nierenberg et al. 2013). One thing to keep in mind is that mitochondrial modulators may take a long time to bring about clinical effects, certainly longer than antipsychotics or mood stabilizers, and are hence often explored as adjuvant therapeutic options and not necessarily monotherapy (Berk et al. 2008).

5.1 Likely Beneficial

5.1.1 PPAR Agonists

The PPARs (peroxisome proliferator-activated receptor) are a family of three receptors in the cell's nuclear, with the isomers α, δ, and γ. These receptors function as transcription regulators, regulating the expression of genes related to energy homeostasis, oxidative stress, metabolism, cell differentiation, inflammation, and importantly – mitochondrial biogenesis. In the brain, they also regulate genes related to excitatory neurotransmission and myelination (Grings et al. 2017; Nierenberg et al. 2013). Traditionally, drugs targeting the PPARs were used in general medicine to treat hypertriglyceridemia and type II diabetes, but their wide array of effects makes them potential therapeutic targets to ameliorate many other disorders, including mitochondrial dysfunction. Of specific relevance to BD, the gene for a coactivator of PPAR, PGC-1α, has been weakly linked to clinical response to lithium (Geoffroy et al. 2016).

A PPAR agonist may target one of the receptor isomers selectively or several at the same time. The selective PPAR-γ agonists and antidiabetic drugs troglitazone, rosiglitazone, and pioglitazone have shown mostly positive effects in the treatment of depression, either alone or as add-on therapy. Alas, troglitazone has been withdrawn from the market due to hepatotoxicity, and rosiglitazone use is strictly limited by the FDA (and suspended by the European Medicine Agency) due to increased cardiovascular risk. This leaves mainly pioglitazone, but its use is also severely limited by side effects such as weight gain, congestive heart failure, edema, and bone fractures (Colle et al. 2017).

Another promising member of the PPAR-agonists family is bezafibrate, a pan-agonist that targets all isomers of PPAR – α, δ, and γ. Bezafibrate is used in general medicine as a common treatment for hypertriglyceridemia, can increase mitochondrial biogenesis, and also has antioxidant and anti-inflammatory effects (Grings et al. 2017). It is known to have favorable safety and side effect profile, and a clinical study attempting to repurpose this drug for bipolar depression is currently underway (Bezafibrate Treatment for Bipolar Depression: A Proof of Concept Study 2015).

5.1.2 Minocycline

Minocycline is a safe and well-tolerated tetracycline antibiotic. It was also found to have multiple interlocking mechanisms that converge on neuroprotective properties relevant to the putative mitochondrial pathophysiology of BD – with effects as an antioxidant, anti-apoptotic, and glutamate neurotransmission modulator. Minocycline is thought to exert its neuroprotective effects by reducing oxidative damage, scavenging ROS and normalizing levels of GSH and markers of oxidative stress, and mitigating glutamate excitotoxicity. It can also modulate apoptotic signaling pathways and increase the expression of the anti-apoptotic gene Bcl-2, affecting the mitochondrial pathway of apoptosis (Zheng et al. 2019; Shultz and Zhong 2017).

Minocycline has been shown to induce psychotropic effects in schizophrenia, improving symptoms and gray matter volume (Robertson et al. 2019). Its effects on mood disorders have not been as consistent, with some studies showing beneficial effects and others failing to detect differences from placebo (Zheng et al. 2019). Two studies are currently underway, assessing the efficacy of minocycline as add-on treatment for bipolar depression (A Pilot Study Investigating the Efficacy of Minocycline and N-Acetyl Cysteine for Bipolar Depression 2016; Minocycline for Bipolar Depression 2012).

5.1.3 N-Acetyl-Cysteine (NAC)

NAC has several mechanisms of action that make it relevant to psychiatric disorders. It has well-known anti-inflammatory, antioxidant, and glutamatergic modulating effects, including protection from glutamate excitotoxicity (Samuni et al. 2013; Naziroglu et al. 2013), and rodent models for neurodegenerative diseases have shown it is able to restore mitochondrial respiration and complex activity (Pereira et al. 2018). Among its many effects, NAC provides the rate-limiting cysteine for GSH production, and supplementation of NAC can increase GSH synthesis (Berk et al. 2008). By increasing GSH, NAC is both protecting the cell from oxidative damage and augmenting its mitochondrial respiratory capacity – as it is now able to withstand more of its own noxious by-products. Its effects on the glutamatergic system are of particular interest, as this system has been correlated with increased

impulsivity (Ende et al. 2016; Pattij and Vanderschuren 2008), a trait often associated with BD. It is this effect that might be behind NAC's beneficial effects in the treatment of pathological gambling, a disorder characterized by deficiencies in impulse-control (Grant et al. 2014).

To date (Pereira et al. 2018), three trials have assessed NAC as an adjunctive treatment for bipolar depression, one study in 2008 and two in 2019. Two of the three have shown a similar pattern of results – improvement in depressive symptoms, but one that is only evident only after a long duration of treatment (between 16 and 20 weeks) (Berk et al. 2008; Bauer et al. 2018). The third study did not find any significant differences between the placebo and NAC at any time point. However, it did note that the group who received a combination of NAC and other mitochondrial agents (but not NAC alone) has shown improvement 20 weeks after discontinuation of the study drugs – suggesting either the delayed onset of effects or improvement upon withdrawal of the medications (Berk et al. 2019). This study also mentioned an increase in manic symptoms at week 4 for some participants. While this finding did not survive correction for multiple testing, it still brings to light the possibility of inducing a manic switch by driving mitochondrial biogenesis – even without improvement in depressive symptoms. All in all, it seems that NAC might indeed possess antidepressant effects that only become manifest after continued long-term treatment.

5.1.4 Co-enzyme Q10

Co-Q10, also known as ubiquinone, plays many roles in the cell: It is a vital cofactor in the mitochondrial ETC, assisting in the shuttling of electrons between subunits and helping to establish the proton gradient needed for ATP production (Neergheen et al. 2017). Co-Q10 also has antioxidant and anti-inflammatory properties, is involved in DNA replication and repair, supports membrane stabilization, mitigates glutamate-induced excitotoxicity, serves as an essential cofactor of uncoupling proteins, and can regulate gene expression and programmed cell death (Mantle and Hargreaves 2019; Alcazar-Fabra et al. 2018; Kumari et al. 2016). Most of the body's CoQ10 requirements are derived from endogenous synthesis that declines with age naturally (Morris et al. 2013). Low Co-Q10 levels are associated with various pathological conditions, such as hypertension, diabetes, cardiovascular diseases, and importantly neurological and psychiatric disorders (Morris et al. 2013; Maes et al. 2009). In general medicine, administration of supplemental Co-Q10 has shown, if inconsistently, to reduce inflammatory mediators (Fan et al. 2017); to have beneficial effects in medical conditions such as heart failure, atherosclerosis, hypertension, hyperlipidemia, and diabetes (Garrido-Maraver et al. 2014); and even to reduce symptoms in neurodegenerative disorders such as Parkinson's and multiple sclerosis (Sanoobar et al. 2015; Shults et al. 2002).

Regarding BD, two recent studies examining adjuvant Co-Q10 have shown it can reduce symptoms of depression (Forester et al. 2015; Mehrpooya et al. 2018), with

one of the studies noting the effect might be delayed and not prominent until at least 8 weeks of use.

5.1.5 Melatonin

Melatonin is a hormone synthesized by many tissues, known mostly for its regulatory effects on rhythmic processes such as circadian rhythm, growth hormone stimulation, and insulin secretion. Evidence has shown melatonin, and its metabolites have antioxidant properties, acting as direct scavengers of ROS, stimulators of GSH production, and increasers of mRNA expression of antioxidant genes. In the mitochondria, melatonin can increase the activity and expression of ETC proteins, increase mitochondrial biogenesis, increase mitochondrial membrane fluidity, and prevent changes to the mitochondrial permeability transition pore (MPTP), protecting the organelle from calcium overload. It has additional effects on mitochondrial gene expression, by preventing degradation of mitochondrial DNA (mtDNA) and modulating the expression of genes encoded by mtDNA (Reiter et al. 2017; Acuna-Castroviejo et al. 2007; Hardeland 2017; Jou 2011). The net result of all these processes is an increase in OXPHOS and decreases in ATP depletion and cell death.

Patients with BD were found to have decreased serum levels of melatonin, with possible variations dependent on mood state (Novakova et al. 2015). In addition, about half of patients with BD show circadian rhythm disturbances that are associated with a higher risk of BD relapse (Kishi et al. 2019). Studies researching the effects of treatment with melatonin receptor agonists have shown mixed results. A 2019 meta-analysis found ramelteon to be well-tolerated and clinically superior to placebo in the prevention of a depressive relapse, with no effects on scales of mania, sleep, quality of life, or other causes for relapse such as a manic or mixed episode. While this result is promising – especially in light of melatonin's ability to improve cardiometabolic outcomes for patients receiving antipsychotic treatment – it is limited by the small number of studies and tendency for conflicting results in the scientific literature (Kishi et al. 2019).

5.2 Theoretically Beneficial, but No Studies Have Been Published

5.2.1 Ebselen

Ebselen is a seleno-organic compound – that is, a compound containing carbon-to-selenium chemical bonds. It has an antioxidant and ROS scavenging activity similar to that of glutathione (GSH) and has been shown to protect neurons from damage caused by ischemic and glutamate excitotoxicity (Jia et al. 2018; Slusarczyk et al. 2019). Ebselen also works as an inhibitor of inositol monophosphatase (IMP),

making it an IMPase that can effectively lower inositol levels in the brain and prevent abnormal, potentially toxic increases in calcium levels. As discussed, inhibition of IMP is also one of the key effects of lithium when used at clinically effective doses (Forlenza et al. 2014). This shared mechanism of action, combined with studies showing ebselen can alter emotional processing and impulsivity in humans and reduce symptoms in animal models of mania and depression, makes it a candidate for the treatment for BD, perhaps as a "lithium-mimetic" with good safety and tolerability (Masaki et al. 2016). A clinical trial is currently underway to assess whether Ebselen can reduce symptoms of (hypo)mania in patients with BD (Ebselen as an add-on Treatment in Hypo/Mania 2017).

5.2.2 Mangosteen

Garcinia mangostana Linn, commonly known as mangosteen, is a tropical fruit with antioxidant, anti-inflammatory, and anti-apoptotic effects. Studies suggest mangosteen might have specific effects on the GSH system, with the ability to increase the levels of this protective antioxidant.

Rodent models have shown mangosteen pericarp to have antidepressant – and antipsychotic-like effects, specifically affecting the serotonergic system, which is implicated in the pathophysiology of both conditions. Human studies have shown some efficacy of mangosteen as an anti-inflammatory and antioxidant agent. However, most trials included mangosteen pericarp in combination with other bioactive compounds – and by doing so have limited our ability to conclude specifically on mangosteen's effects. Only one study directly assessed mangosteen's utility in mental health in a randomized controlled study (RCT), finding it was able to improve scores of psychotic and depressive symptoms in patients with schizophrenia or schizoaffective disorder (Ashton et al. 2019). As mangosteen pericarp has a good safety profile and is generally well-tolerated, these preliminary studies justify further assessment of its effect on mental health patients – all the while keeping in mind potential pharmacological interactions, especially due to serotonergic activity.

5.2.3 Ketogenic Diet

A ketogenic diet is a high-fat, very low-carbohydrate diet that forces the body to rely on ketone bodies as a source of energy instead of dietary glucose. Briefly, by depriving the body of carbohydrates that can be converted into glucose, the liver turns instead to convert fat into fatty acids and ketone bodies, who then pass into the brain and replace glucose as an energy source (Brietzke et al. 2018). In regard to mitochondrial functioning, the ketogenic diet has been shown to induce an increase in mitochondrial biogenesis proteins, OXPHOS and subsequent ATP production, increase levels of the antioxidant GSH, reduce ROS production, and induce epigenetic changes in genes related to the mitochondria (Campbell and Campbell 2019). Animal models have shown the ketogenic diet to have antidepressant-like effects

similar to those of antidepressant drugs, and several human case reports have been published detailing patients with treatment-resistant mood disorders who have responded to a ketogenic diet (Kovacs et al. 2019). The ketogenic diet is a particularly interesting option because of patients' own reports of improvements in their symptoms when adhering to it (Campbell and Campbell 2019), and even though this treatment is not without its side effects – notably gastrointestinal disturbances, dyslipidemia, and renal calculi – for patients who are able to comply with the diet, it might yet prove to be a beneficial solution.

5.2.4 Resveratrol

Resveratrol is a polyphenol naturally found in grapes and berries and has been considered for many years to be part of the mechanism for the "French paradox" – a term coined in 1992 to describe the low incidence of coronary heart diseases in France, despite a diet high in saturated fats. Originally, it was proposed that moderate red wine consumption – and hence resveratrol consumption – explained this unexpected finding, although it is now known that its levels in red wine are likely not high enough to account for the paradox fully. Regardless, resveratrol has many health and longevity promoting effects, with antioxidant, anti-inflammatory, anti-apoptotic, and even anti-carcinogenic effects (Jardim et al. 2018). Resveratrol has the ability to modulate the central nervous system, increase levels of monoamines, and act as a neuroprotective agent and has been studies in animal models as a potential aid for improving sleep quality, anxiety, and depression (Moore et al. 2018). Regarding mitochondrial functioning, resveratrol can improve mitochondrial function, mitochondrial biogenesis, and oxidative stress (Jardim et al. 2018). Several research groups have shown resveratrol's antidepressant-like effects in animal models, and a study in humans is currently underway to assess its efficacy in the treatment of depression (Efficacy of Resveratrol in Depression 2017). No studies have been done or registered involving patients with BD, but the postulated mechanism of action implies potential beneficial effects.

Pterostilbene A naturally occurring, dimethylated analog of resveratrol, with higher bioavailability. It likewise has antioxidant and neuroprotective effects and in rodent studies was shown to reverse the deleterious effects of aging on cognitive performance (Lange and Li 2018) and improve depression-like behaviors (Yang et al. 2019), but no human studies have been done or registered for mood disorders yet.

5.2.5 Taurine

A free amino acid with antioxidant and neuromodulator functions, able to protect the neuron against glutamate-induced neurotoxicity, reduce oxidative stress, and maintain mitochondrial function (Jakaria et al. 2019). In animals, it has shown an

antidepressant-like effect (Wu et al. 2017), but no studies have been published specifically on mood disorders as of now. One study of its effects as an antimanic agent has been completed, but its results have not been published so far (Bezafibrate Treatment for Bipolar Depression: A Proof of Concept Study 2015).

5.3 Unlikely to Be Beneficial

5.3.1 Alpha-Lipoic Acid (ALA)

ALA, also known as thioctic acid, is a naturally occurring and dietarily obtained substance. It can be synthesized in the mitochondria, where it functions as a coenzyme for the formation of pyruvate dehydrogenase and α-ketoglutarate, components of the Krebs cycle. Its ability to increase the activity of the Krebs cycle leads to a reduction in glycolysis and lactate levels (Gomes and Negrato 2014). ALA also has antioxidant and anti-inflammatory effects, with studies demonstrating beneficial effects on metabolic syndrome and related diagnosis, coronary vascular diseases, and even cancer (Haghighatdoost and Hariri 2019; de Sousa et al. 2019). The specific mechanisms by which it exerts these effects are not fully understood. In the central nervous system, ALA affects the levels of the neurotransmitters norepinephrine, dopamine, and acetylcholine and blocks the dopamine D2 receptor. Studies have shown it can improve symptom severity and side effects for patients who have schizophrenia, prevent the progression of Alzheimer's disease, and improve outcomes for stroke survivors (de Sousa et al. 2019).

Regarding mood disorders, rodent models have shown beneficial effects of ALA as an antidepressant and antimanic drug, but only one study assessed ALA in patients with bipolar depression and did not reach a statistically significant result (Brennan et al. 2013). However, due to the positive effects of ALA in other psychiatric and neurological disorders, additional well-designed clinical trials are warranted before reaching a verdict on its efficiency for BD.

5.3.2 Pyrimidines

Uridine and its prodrug triacetyluridine (TAU) are pyrimidine nucleosides of RNA, with roles in glutamatergic transmission, metabolism of a cerebral phospholipid, mitochondrial functioning, and catecholamine synthesis – processes that have been linked to the pathophysiology of BD (Pereira et al. 2018). Cytidine is also a pyrimidine nucleoside of RNA that can be metabolized into uridine when administered orally, as cytidine-diphosphocholine (CDP-choline) (Wurtman et al. 2000).

Uridine While some preliminary studies have shown promising results in bipolar depression, including an open-label study on adolescent patients (Kondo et al. 2011), a recent study on adult patients with bipolar depression was unable to

statistically distinguish the effects of uridine from those of placebo (Herlihy 2011). No other studies have been published since.

Triacetyluridine (TAU) A uridine prodrug, that is, our body can metabolize it into free uridine. One study assessing the efficacy of TAU in bipolar depression found it is effective as adjuvant treatment, and it seems its effects were greatest for people with worse depression severity at baseline. In addition to improvements in clinical measures of depression, patients who responded to treatment with TAU demonstrated greater increases in pH levels compared to nonresponders (Jensen et al. 2008).

Cytidine Cytidine has shown antidepressant-like effects in rodents and was reported to improve symptoms of depression in humans. A 2009 study of adjuvant cytidine in the treatment of bipolar depression has shown cytidine results in earlier improvement in depressive symptoms and in a greater reduction in glutamate/glutamine levels in the brain – pointing at a potential mechanism for its clinical effect (Yoon et al. 2009). A more recent study, on the combination of cytidine with omega-3 fatty acids as add-on treatment for BD, was not able to prove clinical benefits greater than placebo (Murphy et al. 2012).

5.4 Potential Risk of a Manic Switch

5.4.1 ALC (Acetyl-L-Carnitine)

ALC is an acetylated version of L-carnitine, rendering it better absorbed and more able to cross the BBB. L-Carnitine is a compound that can be endogenously generated or obtained through diet – as is the case for about 75% of carnitine in humans. Carnitines transport fatty acids into mitochondria, where they can be used as a source of energy. While the brain prefers glucose as its primary energy source, under metabolically compromised conditions, fatty acids become pivotal energy substrates. Carnitines can also directly affect OXPHOS by upregulating gene expression and protein activity of mitochondrial respiratory structures, enhancing mtDNA transcription, and stabilizing mitochondrial mRNA and membrane integrity against lipid peroxidation. As we age and our muscle mass is reduced, the plasma concentrations of carnitine decline as well.

ALC has been shown to upregulate genes related to proteins with antioxidant, anti-apoptotic, and neuroprotective properties. In the central nervous system, ALC assists in acetylcholine synthesis, enhances dopamine release, prevents loss of D1 dopamine receptor activity with age, counters glutamate-induced excitotoxicity, and increases GABA levels (Traina 2016; Pereira et al. 2018). It should be noted, however, that high levels of ACL are not without their cost – they can lead to lowered antioxidant status in the liver (possibly as a result of increased OXPHOS), meaning that any treatment with supplemental ALC should be combined with antioxidants, for example, ALA or NAC mentioned before (Hagen et al. 2002).

Studies in rats have shown it to improve cognitive functioning and lifespan, reversing the age-associated decline of mitochondrial functions. Rodent models were also able to show antidepressant-like effects. However, the only RCT performed so far in humans reported no effects for the combined administration of ALC and ALA, nor did it detect changes in PCr levels reflecting energy stores – a finding that was previously reported in case reports of depressed geriatric patients treated with ALC (Brennan et al. 2013). In addition, there have been two case reports of patients with BD who developed psychotic and manic episodes during treatment with ALC, suggesting caution when considering its clinical use in this population.

5.4.2 Creatine Monohydrate (CM)

Creatine is a nonessential dietary component that can be found in protein-rich foods such as meat, milk, and nuts and can also be synthesized endogenously in the body. In addition to its antioxidant properties, creatine is the precursor of PCr that holds an integral role in energy metabolism as a reservoir of inorganic phosphate, buffering energy concentrations in tissues with significant and fluctuating energy demands – such as the brain (Pereira et al. 2018; Allen 2012). Oral consumption of creatine monohydrate (as a dietary supplement) increases both brain creatine and PCr concentrations (Lyoo et al. 2003) and was therefore studied as an adjunctive treatment for depression. In the treatment of patients with MDD, this approach has generally shown promising results, but several patients with BD experienced a (hypo)manic switch during CM treatment (Toniolo et al. 2018; Roitman et al. 2007). Mood switching is particularly intriguing in this context, as we have previously noted patients with BD might have a specific deficit in turning the energy-storing PCr into available energy in the form of ATP (Du et al. 2018).

5.4.3 SAMe (S-Adenosyl-Methionine)

SAMe is a naturally occurring biological component of all living cells, formed from the combination of methionine and ATP. In addition to its critical role as a methyl donor, SAMe is also a precursor molecule for GSH, one of the body's most potent antioxidants. In the CNS, SAMe is critical in the synthesis and regulation of monoamines, making it possibly relevant in the pathophysiology – and treatment – of mood disorders (Pereira et al. 2018). As far back as 1989, trials demonstrated its efficacy in the treatment of depressive symptoms, but the risk of a manic switch in BD population was not negligible (Carney et al. 1989; Abeysundera and Gill 2018). SAMe augmentation of modern-day antidepressants and even as monotherapy has been shown to be beneficial in patients with MDD (Papakostas et al. 2010; Sarris et al. 2014), but two recent trials have not been able to replicate these results (Sarris et al. 2018, 2019). In addition to strong placebo effects, gender differences in reaction to SAMe may be responsible for some of the negative studies, with

SAMe having a greater effect in males than females (Sarris et al. 2015). Due to the high risk of manic switching, SAMe is contraindicated for patients with BD.

5.5 Vitamins

5.5.1 Vitamin A

Vitamin A is an essential molecule for many physiological processes in the body, including vision, immunity, and gene transcription and as a co-factor for redox activation (Hammerling 2016). Intoxication with vitamin A can lead to increased oxidative stress and dangerous side effects, such as cognitive decline, depression, and suicidality (de Oliveira 2015). It has been shown that the brains of persons suffering from mood disorders or schizophrenia have abnormalities in pathways related to vitamin A signaling (Haybaeck et al. 2015), reflecting the increased tone of retinoic acid (a derivative of vitamin A) and marking this as a possible pathway in the pathophysiology and eventual treatment of BD. No studies have been conducted so far on vitamin A-related drugs in the treatment of mood disorders.

5.5.2 Vitamin C

Known as ascorbic acid, vitamin C is an antioxidant acting both directly and as a co-substrate for many important cellular oxidation and reduction processes (Pehlivan 2017). Vitamin C has been linked to improvements in anxiety and mood (Pullar et al. 2018; Kocot et al. 2017), but studies could not prove statistically significant effects on mood (Sahraian et al. 2015). Few studies on BD population from the 1960s and 1980s have shown positive results, but have not been replicated since.

5.5.3 Vitamin D

Vitamin D is involved in calcium and phosphate metabolism but has many more roles in physiological pathways – including immune modulation, antioxidant and anti-inflammatory effects, and monoamine metabolism (Jamilian et al. 2019; Sabir et al. 2018). Vitamin D receptors (VDR) can even translocate into the mitochondria and affect their function (Ricca et al. 2018). Vitamin D-related disturbances have been linked to depressive and manic symptoms (Altunsoy et al. 2018), but when taking several meta-analyses into account, there are no conclusive results whether vitamin D supplementation is useful in the treatment of depressive symptoms (Gowda et al. 2015; Vellekkatt and Menon 2019). Despite the fact that many patients with mood disorders are vitamin D deficient (Cuomo et al. 2019; Petrov et al. 2018), supplementation has not been found beneficial for the treatment of bipolar

depression (Marsh et al. 2017), and only one small study reported beneficiary effects on mania ratings (Sikoglu et al. 2015).

5.5.4 Vitamin E

Also called tocopherol, vitamin E is a fat-soluble antioxidant exclusively obtained from the diet, whose ability for ROS scavenging and lipid peroxidation reduction can lead to stabilization cellular and mitochondrial membranes (Rizvi et al. 2014). Vitamin E seems to be more potent when combined with vitamin C or Co-Q10 (Kontush and Schekatolina 2004; Dhitavat et al. 2005), and animal models show some improved neurological and mitochondrial function in aging mice. One study on older human adults was completed in 2018, seeking to assess the effectiveness of ascorbic acid (vitamin C) and tocopherol (vitamin E) in the treatment of depression (Effectiveness of Ascorbic Acid and Tocopherol for Depression in Elderly 2016), but its results have not yet been published.

5.5.5 Vitamins B

B1: Thiamine Thiamine is an an essential cofactor for the Krebs cycle. A 2016 study on patients with major depressive disorder (MDD) showed that while vitamin B1 supplementation did not improve depressive symptoms any more than placebo, it was able to bring about the positive change earlier (Ghaleiha et al. 2016). No studies have been done on BD population.

B3: Niacin Nicotinic acid, nicotinamide (also called *niacinamide*), and nicotinamide riboside, collectively termed vitamin B3, are precursor molecules for NAD+ and NADP+ in all body tissues – meaning they are indirectly involved in hundreds of enzymatic reactions related to OXPHOS, glycolysis, and lipid oxidation (Depeint et al. 2006; Conze et al. 2019). Each precursor has unique effects: nicotinic acid can lower "bad" lipids such as LDL or triglycerides and elevate "good" lipids like HDL and is taken as a treatment for dyslipidemia with a notable side effect of flushing (Boden et al. 2014). In contrast, niacinamide does not affect blood lipids, nor does it cause flushing, but it affects other systems – for example, it can elevate homocysteine levels and thereby increase the risk of vascular disease. Nicotinamide riboside also does not induce flushing and only elevates homocysteine to a lesser degree. It has been shown in rodent models to prevent adverse outcomes in various systems such as diet-induced weight gain, neuropathy, hearing loss, heart failure, irradiation damage, and central brain injury (Conze et al. 2019). Mouse models have shown supplementation of mothers with nicotinamide riboside could lead to stronger, less anxious, and more cognitively able offsprings (Ear et al. 2019).

Regarding mood, nicotinic acid is used as an active placebo in psychedelic studies due to its ability to induce flushing without altering the psychological state (Ross et al. 2016; Grob et al. 2011), although a case report of a manic episode during treatment with it for dyslipidemia was reported in a 54-year-old man with no history

of mental illness (Loebl and Raskin 2013). Regarding niacinamide, animal models for depression have shown it to have similar effects on fluoxetine (Rex et al. 2004), but no human studies have been published showing similar efficacy. Niacinamide riboside seems to be the most promising of the three, and a study assessing its effects on mood has been recently completed, with the results of yet unpublished (A Study by ChromaDex to Assess the Effects of TRU NIAGEN on Cognitive Function, Mood and Sleep in Older Adults 2018).

Vitamin B6 Vitamin B6 again refers to a group of chemically similar compounds, with the active form serving as a coenzyme in many biological processes including preventing ROS generation and lipid peroxidation (Kannan and Jain 2004). Most studies on vitamin B6, especially on its own and not in addition to other supplementals, failed to detect effects on mood. In addition, vitamin B6 supplementation is not without risks, and patients were reported to suffer from adverse drug reactions that resemble Wernicke's encephalopathy, thankfully a reaction that was able to be reversed by vitamin B1 (thiamine) supplementation (Pereira et al. 2018).

B9: Folate Folic acid plays an essential role in mitochondrial energy production (Depeint et al. 2006), and deficiencies have been associated with depression, BD, and cognitive dysfunction (Baek et al. 2013). According to a recent review, several studies from the 1980s found associations between folate and affective morbidity, and more recently a couple of studies have shown supplementation with folate (or its metabolites) to have an effect on both manic and depressive symptoms. However, other studies found no discernible effect on patients who were not specifically folate-deficient (Pereira et al. 2018), and folic acid has the potential to negate the therapeutic effects of lamotrigine, a popular treatment for bipolar depression (Simon et al. 2018). It also appears that folic acid supplementation does not reduce the incidence of a mood disorder, albeit it may be able to delay the onset of the first mood episode or mitigate its severity (Sharpley et al. 2014; Okereke et al. 2015).

B12: Cobalamin Vitamin B12 is a cofactor for methionine, DNA, and myelin synthesis and is necessary for the maintenance of neuronal integrity and regulating neurotransmitters. Despite the fact that vitamin B12 deficiency is a known cause for mood deficits (Issac et al. 2015), cobalamin supplementation has not been proven to improve depressive symptoms (Pereira et al. 2018; Almeida et al. 2015).

Vitamins B2 (riboflavin), *B5* (pantothenic acid), and *B7* (biotin) are all important for biological mitochondrial pathways, and their deficiencies might be related to neurological deficits, but they have not been studied as specific treatments for depression or BD.

6 Summary

In this chapter, we have described how the central nervous system is particularly vulnerable to dysregulations of mitochondrial function due to its high energetic demands. Convergent data implicated subtle mitochondrial dysfunction as an

important component of the pathophysiology of bipolar disorder (BD) and led to the exploration of alternative therapeutic targets. While some negative results have been published, targeting mitochondrial pathways seems to have a measurable effect on mood, evidenced not only by alleviation of depressive symptoms but also by induction of manic switches for certain compounds. When discussing mitochondrial treatments, combinations of several mitochondrial agents could be of interest as their actions can be synergistic or complementary to the prevention of side effects. For example, increasing energy production comes at the cost of increased free radical production and might justify a "mitochondrial cocktail" that includes an energy-enhancing agent with an antioxidant agent. Many studies have been conducted, and more are underway attempting to elucidate the role of mitochondrial agents in the treatment of BD. While effect sizes at the moment do not support any single drug as possible monotherapy or "the new lithium," it is important to keep in mind that BD is not one disease caused by one pathway, but has heterogenic presentations and heterogenic underlying pathways. The mitochondrial hypothesis and mitochondrial modulators provide viable alternatives to current treatments and a path toward drug discovery to achieve better outcomes for people with BD.

	ATP production	Mitochondrial biogenesis	Oxidative stress	Clinical evidence in mood disorder
Bezafibrate (Ioannou et al. 2010; Huang et al. 2017)	Increase	Increase	Decrease	Evidence in depression. Studies on BD underway
Minocycline	–	–	Decrease	Inconsistent. Studies underway
N-Acetyl-cysteine (NAC) (Tardiolo et al. 2018)	–	–	Decrease	Inconsistent, but positive evidence in bipolar depression. Effects take a long time to become apparent
Co-enzyme Q10	Increase	?	Decrease	Evidence in bipolar depression. Effects take a long time to become apparent
Melatonin	Increase	Increase	Decrease	Evidence in unipolar and bipolar depression
Ebselen	–	–	Decrease	Studies currently underway
Mangosteen	Increase	–	Decrease	Improvement in psychotic and affective symptoms of schizophrenia
Ketogenic diet	Increase	Increase	Decrease	Animal models and human case reports
Resveratrol and pterostilbene	Increase	Increase	Decrease	Animal models show effectiveness. Human studies underway for resveratrol
Taurine	Increase	?	Decrease	Animal models only

References

A Pilot Study Investigating the Efficacy of Minocycline and N-Acetyl Cysteine for Bipolar Depression (2016). https://clinicaltrials.gov/ct2/show/NCT02719392

A Study by ChromaDex to Assess the Effects of TRU NIAGEN on Cognitive Function, Mood and Sleep in Older Adults (2018). https://clinicaltrials.gov/ct2/show/NCT03562468

Abeysundera H, Gill R (2018) Possible SAMe-induced mania. BMJ Case Rep 2018

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

Akarsu S, Bolu A, Aydemir E et al (2018) The relationship between the number of manic episodes and oxidative stress indicators in bipolar disorder. Psychiatry Investig 15:514–519

Alcazar-Fabra M, Trevisson E, Brea-Calvo G (2018) Clinical syndromes associated with coenzyme Q10 deficiency. Essays Biochem 62:377–398

Allen PJ (2012) Creatine metabolism and psychiatric disorders: does creatine supplementation have therapeutic value? Neurosci Biobehav Rev 36:1442–1462

Almeida OP, Ford AH, Flicker L (2015) Systematic review and meta-analysis of randomized placebo-controlled trials of folate and vitamin B12 for depression. Int Psychogeriatr 27:727–737

Altunsoy N, Yuksel RN, Cingi Yirun M et al (2018) Exploring the relationship between vitamin D and mania: correlations between serum vitamin D levels and disease activity. Nord J Psychiatry 72:221–225

Andreazza AC, Shao L, Wang JF et al (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

Ashok AH, Marques TR, Jauhar S et al (2017) The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry 22:666–679

Ashton MM, Dean OM, Walker AJ et al (2019) The therapeutic potential of mangosteen pericarp as an adjunctive therapy for bipolar disorder and schizophrenia. Front Psych 10:115

Baek JH, Bernstein EE, Nierenberg AA (2013) One-carbon metabolism and bipolar disorder. Aust N Z J Psychiatry 47:1013–1018

Baltan S (2015) Can lactate serve as an energy substrate for axons in good times and in bad, in sickness and in health? Metab Brain Dis 30:25–30

Baranov SV, Baranova OV, Yablonska S et al (2019) Mitochondria modulate programmed neuritic retraction. Proc Natl Acad Sci U S A 116:650–659

Bauer IE, Green C, Colpo GD et al (2018) A double-blind, randomized, placebo-controlled study of aspirin and N-acetylcysteine as adjunctive treatments for bipolar depression. J Clin Psychiatry 80

Berk M, Copolov DL, Dean O et al (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468–475

Berk M, Turner A, Malhi GS et al (2019) A randomised controlled trial of a mitochondrial therapeutic target for bipolar depression: mitochondrial agents, N-acetylcysteine, and placebo. BMC Med 17:18

Berridge MJ (2014) Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia. Cell Tissue Res 357:477–492

Bezafibrate Treatment for Bipolar Depression: A Proof of Concept Study (2015). https://clinicaltrials.gov/ct2/show/NCT02481245

Blacker CJ, Lewis CP, Frye MA et al (2017) Metabotropic glutamate receptors as emerging research targets in bipolar disorder. Psychiatry Res 257:327–337

Blazey T, Snyder AZ, Goyal MS et al (2018) A systematic meta-analysis of oxygen-to-glucose and oxygen-to-carbohydrate ratios in the resting human brain. PLoS One 13:e0204242

Boden WE, Sidhu MS, Toth PP (2014) The therapeutic role of niacin in dyslipidemia management. J Cardiovasc Pharmacol Ther 19:141–158

Bonora M, Patergnani S, Rimessi A et al (2012) ATP synthesis and storage. Purinergic Signal 8:343–357

Brennan BP, Jensen JE, Hudson JI et al (2013) A placebo-controlled trial of acetyl-L-carnitine and alpha-lipoic acid in the treatment of bipolar depression. J Clin Psychopharmacol 33:627–635
Brietzke E, Mansur RB, Subramaniapillai M et al (2018) Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. Neurosci Biobehav Rev 94:11–16
Brown NC, Andreazza AC, Young LT (2014) An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res 218:61–68
Bustillo JR, Jones T, Qualls C et al (2019) Proton magnetic resonance spectroscopic imaging of gray and white matter in bipolar-I and schizophrenia. J Affect Disord 246:745–753
Callaly E, Walder K, Morris G et al (2015) Mitochondrial dysfunction in the pathophysiology of bipolar disorder: effects of pharmacotherapy. Mini Rev Med Chem 15:355–365
Campbell IH, Campbell H (2019) Ketosis and bipolar disorder: controlled analytic study of online reports. BJPsych Open 5:e58
Carney MW, Chary TK, Bottiglieri T et al (1989) The switch mechanism and the bipolar/unipolar dichotomy. Br J Psychiatry 154:48–51
Cataldo AM, McPhie DL, Lange NT et al (2010) Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. Am J Pathol 177:575–585
Chen S, Owens GC, Edelman DB (2008) Dopamine inhibits mitochondrial motility in hippocampal neurons. PLoS One 3:e2804
Chen WT, Huang TL, Tsai MC (2015) Bcl-2 associated with severity of manic symptoms in bipolar patients in a manic phase. Psychiatry Res 225:305–308
Chen SD, Wu CL, Hwang WC et al (2017) More insight into BDNF against neurodegeneration: anti-apoptosis, anti-oxidation, and suppression of autophagy. Int J Mol Sci 18:545
Chinnery PF, Hudson G (2013) Mitochondrial genetics. Br Med Bull 106:135–159
Chiu CT, Wang Z, Hunsberger JG et al (2013) Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. Pharmacol Rev 65:105–142
Clarke DDS (1999) Regulation of cerebral metabolic rate. In: Basic neurochemistry: molecular cellular and medical aspects, 6th edn. Lippincott-Raven, Philadelphia
Colle R, de Larminat D, Rotenberg S et al (2017) PPAR-gamma agonists for the treatment of major depression: a review. Pharmacopsychiatry 50:49–55
Conze D, Brenner C, Kruger CL (2019) Safety and metabolism of long-term administration of NIAGEN (nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. Sci Rep 9:9772
Cuomo A, Maina G, Bolognesi S et al (2019) Prevalence and correlates of vitamin D deficiency in a sample of 290 inpatients with mental illness. Front Psych 10:167
Cuperfain AB, Zhang ZL, Kennedy JL et al (2018) The complex interaction of mitochondrial genetics and mitochondrial pathways in psychiatric disease. Mol Neuropsychiatry 4:52–69
Czerniczyniec A, Bustamante J, Lores-Arnaiz S (2007) Dopamine enhances mtNOS activity: implications in mitochondrial function. Biochim Biophys Acta 1767:1118–1125
Data-Franco J, Singh A, Popovic D et al (2017) Beyond the therapeutic shackles of the monoamines: new mechanisms in bipolar disorder biology. Prog Neuro-Psychopharmacol Biol Psychiatry 72:73–86
de Oliveira MR (2015) Vitamin A and retinoids as mitochondrial toxicants. Oxidative Med Cell Longev 2015:140267
de Oliveira GS, Cereser KM, Fernandes BS et al (2009) Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J Psychiatr Res 43:1171–1174
de Sousa RT, Machado-Vieira R, Zarate CA Jr et al (2014) Targeting mitochondrially mediated plasticity to develop improved therapeutics for bipolar disorder. Expert Opin Ther Targets 18:1131–1147
de Sousa RT, Streck EL, Zanetti MV et al (2015) Lithium increases leukocyte mitochondrial complex I activity in bipolar disorder during depressive episodes. Psychopharmacology 232:245–250

de Sousa CNS, da Silva Leite CMG, da Silva Medeiros I et al (2019) Alpha-lipoic acid in the treatment of psychiatric and neurological disorders: a systematic review. Metab Brain Dis 34:39–52

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

Dhitavat S, Ortiz D, Rogers E et al (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

Dienel GA (2012) Brain lactate metabolism: the discoveries and the controversies. J Cereb Blood Flow Metab 32:1107–1138

Dogan AE, Yuksel C, Du F et al (2018) Brain lactate and pH in schizophrenia and bipolar disorder: a systematic review of findings from magnetic resonance studies. Neuropsychopharmacology 43:1681–1690

Droge W (2002) Free radicals in the physiological control of cell function. Physiol Rev 82:47–95

Du F, Yuksel C, Chouinard VA et al (2018) Abnormalities in high-energy phosphate metabolism in first-episode bipolar disorder measured using (31)P-magnetic resonance spectroscopy. Biol Psychiatry 84:797–802

Dudley JA, Lee JH, Durling M et al (2015) Age-dependent decreases of high energy phosphates in cerebral gray matter of patients with bipolar I disorder: a preliminary phosphorus-31 magnetic resonance spectroscopic imaging study. J Affect Disord 175:251–255

Dudley J, DelBello MP, Weber WA et al (2016) Tissue-dependent cerebral energy metabolism in adolescents with bipolar disorder. J Affect Disord 191:248–255

Ear PH, Chadda A, Gumusoglu SB et al (2019) Maternal nicotinamide riboside enhances postpartum weight loss, juvenile offspring development, and neurogenesis of adult offspring. Cell Rep 26:969–983.e964

Ebselen as an add-on Treatment in Hypo/Mania (2017). https://clinicaltrials.gov/ct2/show/NCT03013400

Effectiveness of Ascorbic Acid and Tocopherol for Depression in Elderly (2016). https://clinicaltrials.gov/ct2/show/NCT02793648

Efficacy of Resveratrol in Depression (2017). https://clinicaltrials.gov/ct2/show/NCT03384329

Ende G, Cackowski S, van Eijk J et al (2016) Impulsivity and aggression in female BPD and ADHD patients: association with ACC glutamate and GABA concentrations. Neuropsychopharmacology 41:410–418

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

Fan L, Feng Y, Chen GC et al (2017) Effects of coenzyme Q10 supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 119:128–136

Flippo KH, Strack S (2017) Mitochondrial dynamics in neuronal injury, development and plasticity. J Cell Sci 130:671–681

Fonseca AC, Moreira PI, Oliveira CR et al (2015) Amyloid-beta disrupts calcium and redox homeostasis in brain endothelial cells. Mol Neurobiol 51:610–622

Forester BP, Harper DG, Georgakas J et al (2015) Antidepressant effects of open label treatment with coenzyme Q10 in geriatric bipolar depression. J Clin Psychopharmacol 35:338–340

Forlenza OV, De-Paula VJ, Diniz BS (2014) Neuroprotective effects of lithium: implications for the treatment of Alzheimer's disease and related neurodegenerative disorders. ACS Chem Neurosci 5:443–450

Garrido-Maraver J, Cordero MD, Oropesa-Avila M et al (2014) Clinical applications of coenzyme Q10. Front Biosci (Landmark Ed) 19:619–633

Geddes JR, Miklowitz DJ (2013) Treatment of bipolar disorder. Lancet 381:1672–1682

Geoffroy PA, Etain B, Lajnef M et al (2016) Circadian genes and lithium response in bipolar disorders: associations with PPARGC1A (PGC-1alpha) and RORA. Genes Brain Behav 15:660–668

Ghaleiha A, Davari H, Jahangard L et al (2016) Adjuvant thiamine improved standard treatment in patients with major depressive disorder: results from a randomized, double-blind, and placebo-controlled clinical trial. Eur Arch Psychiatry Clin Neurosci 266:695–702
Gladden LB (2004) Lactate metabolism: a new paradigm for the third millennium. J Physiol 558:5–30
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
Gowda U, Mutowo MP, Smith BJ et al (2015) Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition 31:421–429
Grant JE, Odlaug BL, Chamberlain SR et al (2014) A randomized, placebo-controlled trial of N-acetylcysteine plus imaginal desensitization for nicotine-dependent pathological gamblers. J Clin Psychiatry 75:39–45
Greer PL, Greenberg ME (2008) From synapse to nucleus: calcium-dependent gene transcription in the control of synapse development and function. Neuron 59:846–860
Grings M, Moura AP, Parmeggiani B et al (2017) Bezafibrate prevents mitochondrial dysfunction, antioxidant system disturbance, glial reactivity and neuronal damage induced by sulfite administration in striatum of rats: implications for a possible therapeutic strategy for sulfite oxidase deficiency. Biochim Biophys Acta Mol basis Dis 1863:2135–2148
Grob CS, Danforth AL, Chopra GS et al (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68:71–78
Guimaraes-Ferreira L (2014) Role of the phosphocreatine system on energetic homeostasis in skeletal and cardiac muscles. Einstein (Sao Paulo) 12:126–131
Guo C, Sun L, Chen X et al (2013) Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen Res 8:2003–2014
Hagen TM, Liu J, Lykkesfeldt J et al (2002) 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
Haghighatdoost F, Hariri M (2019) The effect of alpha-lipoic acid on inflammatory mediators: a systematic review and meta-analysis on randomized clinical trials. Eur J Pharmacol 849:115–123
Hammerling U (2016) Retinol as electron carrier in redox signaling, a new frontier in vitamin a research. Hepatobiliary Surg Nutr 5:15–28
Hardeland R (2017) Melatonin and the electron transport chain. Cell Mol Life Sci 74:3883–3896
Harwood AJ (2005) Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. Mol Psychiatry 10:117–126
Haybaeck J, Postruznik M, Miller CL et al (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
Herlihy WC (2011) Repligen reports phase 2b results for RG2417 for bipolar depression. https://www.businesswire.com/news/home/20110307005868/en/Repligen-Reports-Phase-2b-Results-RG2417-Bipolar
Holper L, Ben-Shachar D, Mann JJ (2019) Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease. Neuropsychopharmacology 44:837–849
Howell N, Smejkal CB, Mackey DA et al (2003) The pedigree rate of sequence divergence in the human mitochondrial genome: there is a difference between phylogenetic and pedigree rates. Am J Hum Genet 72:659–670
Huang Y, Powers C, Moore V et al (2017) The PPAR pan-agonist bezafibrate ameliorates cardiomyopathy in a mouse model of Barth syndrome. Orphanet J Rare Dis 12:49
Ioannou N, Hargreaves IP, Allen G et al (2010) Bezafibrate induced increase in mitochondrial electron transport chain complex IV activity in human astrocytoma cells: implications for mitochondrial cytopathies and neurodegenerative diseases. Biofactors 36:468–473

Issac TG, Soundarya S, Christopher R et al (2015) Vitamin B12 deficiency: an important reversible co-morbidity in neuropsychiatric manifestations. Indian J Psychol Med 37:26–29
Jakaria M, Azam S, Haque ME et al (2019) Taurine and its analogs in neurological disorders: focus on therapeutic potential and molecular mechanisms. Redox Biol 24:101223
Jamilian H, Amirani E, Milajerdi A et al (2019) The effects of vitamin D supplementation on mental health, and biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: a systematic review and meta-analysis of randomized controlled trials. Prog Neuro-Psychopharmacol Biol Psychiatry 94:109651
Jardim FR, de Rossi FT, Nascimento MX et al (2018) Resveratrol and brain mitochondria: a review. Mol Neurobiol 55:2085–2101
Javadov S, Chapa-Dubocq X, Makarov V (2018) Different approaches to modeling analysis of mitochondrial swelling. Mitochondrion 38:58–70
Jensen JE, Daniels M, Haws C et al (2008) Triacetyluridine (TAU) decreases depressive symptoms and increases brain pH in bipolar patients. Exp Clin Psychopharmacol 16:199–206
Jia ZQ, Li SQ, Qiao WQ et al (2018) Ebselen protects mitochondrial function and oxidative stress while inhibiting the mitochondrial apoptosis pathway after acute spinal cord injury. Neurosci Lett 678:110–117
Jou MJ (2011) Melatonin preserves the transient mitochondrial permeability transition for protection during mitochondrial Ca(2+) stress in astrocyte. J Pineal Res 50:427–435
Juarez Olguin H, Calderon Guzman D, Hernandez Garcia E et al (2016) The role of dopamine and its dysfunction as a consequence of oxidative stress. Oxidative Med Cell Longev 2016:9730467
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
Kato T (2019) Current understanding of bipolar disorder: toward integration of biological basis and treatment strategies. Psychiatry Clin Neurosci 73:526–540
Kato T, Kato N (2000) Mitochondrial dysfunction in bipolar disorder. Bipolar Disord 2:180–190
Kato TM, Kubota-Sakashita M, Fujimori-Tonou N et al (2018) Ant1 mutant mice bridge the mitochondrial and serotonergic dysfunctions in bipolar disorder. Mol Psychiatry 23:2039–2049
Kim DJ, Lyoo IK, Yoon SJ et al (2007) Clinical response of quetiapine in rapid cycling manic bipolar patients and lactate level changes in proton magnetic resonance spectroscopy. Prog Neuro-Psychopharmacol Biol Psychiatry 31:1182–1188
Kim HW, Rapoport SI, Rao JS (2010) Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. Neurobiol Dis 37:596–603
Kim Y, Santos R, Gage FH et al (2017) Molecular mechanisms of bipolar disorder: progress made and future challenges. Front Cell Neurosci 11:30
Kim Y, Vadodaria KC, Lenkei Z et al (2019) Mitochondria, metabolism, and redox mechanisms in psychiatric disorders. Antioxid Redox Signal 31:275–317
Kishi T, Nomura I, Sakuma K et al (2019) Melatonin receptor agonists-ramelteon and melatonin-for bipolar disorder: a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials. Neuropsychiatr Dis Treat 15:1479–1486
Kocot J, Luchowska-Kocot D, Kielczykowska M et al (2017) Does vitamin C influence neurodegenerative diseases and psychiatric disorders? Nutrients 9:659
Kondo DG, Sung YH, Hellem TL et al (2011) Open-label uridine for treatment of depressed adolescents with bipolar disorder. J Child Adolesc Psychopharmacol 21:171–175
Kontush K, Schekatolina S (2004) Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann N Y Acad Sci 1031:249–262
Kovacs Z, D'Agostino DP, Diamond D et al (2019) Therapeutic potential of exogenous ketone supplement induced ketosis in the treatment of psychiatric disorders: review of current literature. Front Psych 10:363
Kuang H, Duong A, Jeong H et al (2018) Lactate in bipolar disorder: a systematic review and meta-analysis. Psychiatry Clin Neurosci 72:546–555

Kubli DA, Gustafsson AB (2012) Mitochondria and mitophagy: the yin and yang of cell death control. Circ Res 111:1208–1221

Kumar P, Efstathopoulos P, Millischer V et al (2018) Mitochondrial DNA copy number is associated with psychosis severity and anti-psychotic treatment. Sci Rep 8:12743

Kumari S, Mehta SL, Milledge GZ et al (2016) Ubisol-Q10 prevents glutamate-induced cell death by blocking mitochondrial fragmentation and permeability transition pore opening. Int J Biol Sci 12:688–700

Lagopoulos J, Hermens DF, Tobias-Webb J et al (2013) In vivo glutathione levels in young persons with bipolar disorder: a magnetic resonance spectroscopy study. J Psychiatr Res 47:412–417

Lange KW, Li S (2018) Resveratrol, pterostilbene, and dementia. Biofactors 44:83–90

Lee A, Hirabayashi Y, Kwon SK et al (2018) Emerging roles of mitochondria in synaptic transmission and neurodegeneration. Curr Opin Physiol 3:82–93

Li XB, Gu JD, Zhou QH (2015) Review of aerobic glycolysis and its key enzymes – new targets for lung cancer therapy. Thorac Cancer 6:17–24

Liberti MV, Locasale JW (2016) The Warburg effect: how does it benefit cancer cells? Trends Biochem Sci 41:211–218

Liguori I, Russo G, Curcio F et al (2018) Oxidative stress, aging, and diseases. Clin Interv Aging 13:757–772

Lin DD, Crawford TO, Barker PB (2003) Proton MR spectroscopy in the diagnostic evaluation of suspected mitochondrial disease. AJNR Am J Neuroradiol 24:33–41

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

Lutz PE, Kieffer BL (2013) Opioid receptors: distinct roles in mood disorders. Trends Neurosci 36:195–206

Lyoo IK, Kong SW, Sung SM et al (2003) Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate. Psychiatry Res 123:87–100

MacDonald ML, Naydenov A, Chu M et al (2006) Decrease in creatine kinase messenger RNA expression in the hippocampus and dorsolateral prefrontal cortex in bipolar disorder. Bipolar Disord 8:255–264

Machado-Vieira R, Pivovarova NB, Stanika RI et al (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

Maes M, Mihaylova I, Kubera M et al (2009) Lower plasma coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness. Neuro Endocrinol Lett 30:462–469

Manfredi G, Kwong JQ, Oca-Cossio JA et al (2003) BCL-2 improves oxidative phosphorylation and modulates adenine nucleotide translocation in mitochondria of cells harboring mutant mtDNA. J Biol Chem 278:5639–5645

Mantle D, Hargreaves I (2019) Coenzyme Q10 and degenerative disorders affecting longevity: an overview. Antioxidants (Basel) 8:44

Markham A, Bains R, Franklin P et al (2014) Changes in mitochondrial function are pivotal in neurodegenerative and psychiatric disorders: how important is BDNF? Br J Pharmacol 171:2206–2229

Marsh WK, Penny JL, Rothschild AJ (2017) Vitamin D supplementation in bipolar depression: a double blind placebo controlled trial. J Psychiatr Res 95:48–53

Masaki C, Sharpley AL, Cooper CM et al (2016) Effects of the potential lithium-mimetic, ebselen, on impulsivity and emotional processing. Psychopharmacology 233:2655–2661

Massaad CA, Klann E (2011) Reactive oxygen species in the regulation of synaptic plasticity and memory. Antioxid Redox Signal 14:2013–2054

Matschke V, Theiss C, Matschke J (2019) Oxidative stress: the lowest common denominator of multiple diseases. Neural Regen Res 14:238–241

McCann RF, Ross DA (2018) So happy together: the storied marriage between mitochondria and the mind. Biol Psychiatry 83:e47–e49
McCarthy MJ, Le Roux MJ, Wei H et al (2016) Calcium channel genes associated with bipolar disorder modulate lithium's amplification of circadian rhythms. Neuropharmacology 101:439–448
Mehrpooya M, Yasrebifar F, Haghighi M et al (2018) Evaluating the effect of coenzyme Q10 augmentation on treatment of bipolar depression: a double-blind controlled clinical trial. J Clin Psychopharmacol 38:460–466
Mertens J, Wang QW, Kim Y et al (2015) Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature 527:95–99
Minocycline for Bipolar Depression (2012). https://clinicaltrials.gov/ct2/show/NCT01514422
Modica-Napolitano JS, Renshaw PF (2004) Ethanolamine and phosphoethanolamine inhibit mitochondrial function in vitro: implications for mitochondrial dysfunction hypothesis in depression and bipolar disorder. Biol Psychiatry 55:273–277
Moffett JR, Arun P, Ariyannur PS et al (2013) N-Acetylaspartate reductions in brain injury: impact on post-injury neuroenergetics, lipid synthesis, and protein acetylation. Front Neuroenerg 5:11
Monzani E, Nicolis S, Dell'Acqua S et al (2019) Dopamine, oxidative stress and protein-quinone modifications in Parkinson's and other neurodegenerative diseases. Angew Chem Int Ed Engl 58:6512–6527
Moore A, Beidler J, Hong MY (2018) Resveratrol and depression in animal models: a systematic review of the biological mechanisms. Molecules 23:2197
Morris G, Anderson G, Berk M et al (2013) Coenzyme Q10 depletion in medical and neuropsychiatric disorders: potential repercussions and therapeutic implications. Mol Neurobiol 48:883–903
Morris G, Walder K, McGee SL et al (2017) A model of the mitochondrial basis of bipolar disorder. Neurosci Biobehav Rev 74:1–20
Murphy AN, Bredesen DE, Cortopassi G et al (1996) Bcl-2 potentiates the maximal calcium uptake capacity of neural cell mitochondria. Proc Natl Acad Sci U S A 93:9893–9898
Murphy BL, Stoll AL, Harris PQ et al (2012) Omega-3 fatty acid treatment, with or without cytidine, fails to show therapeutic properties in bipolar disorder: a double-blind, randomized add-on clinical trial. J Clin Psychopharmacol 32:699–703
Nascimento C, Kim HK, Young LT et al (2015) Glutathione-mediated effects of lithium in decreasing protein oxidation induced by mitochondrial complex I dysfunction. J Neural Transm (Vienna) 122:741–746
Naydenov AV, MacDonald ML, Ongur D et al (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
Naziroglu M, Cig B, Ozgul C (2013) Neuroprotection induced by N-acetylcysteine against cytosolic glutathione depletion-induced Ca2+ influx in dorsal root ganglion neurons of mice: role of TRPV1 channels. Neuroscience 242:151–160
Neergheen V, Chalasani A, Wainwright L, Yubero D, Montero R, Artuch R, Hargreaves I (2017) Coenzyme Q10 in the treatment of mitochondrial disease. J Inborn Errors Metabol Screen 5
Ngamchuea K, Batchelor-McAuley C, Williams C et al (2018) Salivary glutathione in bipolar disorder: a pilot study. J Affect Disord 238:277–280
Nierenberg AA, Kansky C, Brennan BP et al (2013) Mitochondrial modulators for bipolar disorder: a pathophysiologically informed paradigm for new drug development. Aust N Z J Psychiatry 47:26–42
Novakova M, Prasko J, Latalova K et al (2015) The circadian system of patients with bipolar disorder differs in episodes of mania and depression. Bipolar Disord 17:303–314
Odeya D, Galila A, Lilah T (2018) The observed alteration in BCL2 expression following lithium treatment is influenced by the choice of normalization method. Sci Rep 8:6399
Okereke OI, Cook NR, Albert CM et al (2015) Effect of long-term supplementation with folic acid and B vitamins on risk of depression in older women. Br J Psychiatry 206:324–331

Onukwufor JO, Berry BJ, Wojtovich AP (2019) Physiologic implications of reactive oxygen species production by mitochondrial complex I reverse electron transport. Antioxidants (Basel) 8:285
Orrenius S (2004) Mitochondrial regulation of apoptotic cell death. Toxicol Lett 149:19–23
Ozkul A, Sair A, Akyol A et al (2014) Effects of lithium and lamotrigine on oxidative-nitrosative stress and spatial learning deficit after global cerebral ischemia. Neurochem Res 39:853–861
Papakostas GI, Mischoulon D, Shyu I et al (2010) S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry 167:942–948
Pattij T, Vanderschuren LJ (2008) The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci 29:192–199
Pehlivan FE (2017) Vitamin C: an antioxidant agent. Vitamin C. https://doi.org/10.5772/intechopen.69660
Pei L, Wallace DC (2018) Mitochondrial etiology of neuropsychiatric disorders. Biol Psychiatry 83:722–730
Pereira C, Chavarria V, Vian J et al (2018) Mitochondrial agents for bipolar disorder. Int J Neuropsychopharmacol 21:550–569
Peters A, Schweiger U, Pellerin L et al (2004) The selfish brain: competition for energy resources. Neurosci Biobehav Rev 28:143–180
Petrov B, Aldoori A, James C et al (2018) Bipolar disorder in youth is associated with increased levels of vitamin D-binding protein. Transl Psychiatry 8:61
Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. Int J Biomed Sci 4:89–96
Pizzino G, Irrera N, Cucinotta M et al (2017) Oxidative stress: harms and benefits for human health. Oxidative Med Cell Longev 2017:8416763
Pullar JM, Carr AC, Bozonet SM et al (2018) High vitamin C status is associated with elevated mood in male tertiary students. Antioxidants (Basel) 7:91
Raha S, Robinson BH (2000) Mitochondria, oxygen free radicals, disease and ageing. Trends Biochem Sci 25:502–508
Reiter RJ, Rosales-Corral S, Tan DX et al (2017) Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. Cell Mol Life Sci 74:3863–3881
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
Ricca C, Aillon A, Bergandi L et al (2018) Vitamin D receptor is necessary for mitochondrial function and cell health. Int J Mol Sci 19:1672
Rizvi S, Raza ST, Ahmed F et al (2014) The role of vitamin e in human health and some diseases. Sultan Qaboos Univ Med J 14:e157–e165
Robertson OD, Coronado NG, Sethi R et al (2019) Putative neuroprotective pharmacotherapies to target the staged progression of mental illness. Early Interv Psychiatry 13:1032–1049
Roitman S, Green T, Osher Y et al (2007) Creatine monohydrate in resistant depression: a preliminary study. Bipolar Disord 9:754–758
Rosa AR, Singh N, Whitaker E et al (2014) Altered plasma glutathione levels in bipolar disorder indicates higher oxidative stress; a possible risk factor for illness onset despite normal brain-derived neurotrophic factor (BDNF) levels. Psychol Med 44:2409–2418
Ross S, Bossis A, Guss J et al (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 30:1165–1180
Sabir MS, Haussler MR, Mallick S et al (2018) Optimal vitamin D spurs serotonin: 1,25-dihydroxyvitamin D represses serotonin reuptake transport (SERT) and degradation (MAO-A) gene expression in cultured rat serotonergic neuronal cell lines. Genes Nutr 13:19
Sahlin K, Harris RC (2011) The creatine kinase reaction: a simple reaction with functional complexity. Amino Acids 40:1363–1367

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 et al (2013) The chemistry and biological activities of N-acetylcysteine. Biochim Biophys Acta 1830:4117–4129

Sanoobar M, Eghtesadi S, Azimi A et al (2015) Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutr Neurosci 18:169–176

Sarris J, Papakostas GI, Vitolo O et al (2014) S-adenosyl methionine (SAMe) versus escitalopram and placebo in major depression RCT: efficacy and effects of histamine and carnitine as moderators of response. J Affect Disord 164:76–81

Sarris J, Price LH, Carpenter LL et al (2015) Is S-adenosyl methionine (SAMe) for depression only effective in males? A re-analysis of data from a randomized clinical trial. Pharmacopsychiatry 48:141–144

Sarris J, Byrne GJ, Bousman C et al (2018) Adjunctive S-adenosylmethionine (SAMe) in treating non-remittent major depressive disorder: an 8-week double-blind, randomized, controlled trial. Eur Neuropsychopharmacol 28:1126–1136

Sarris J, Byrne GJ, Stough C et al (2019) Nutraceuticals for major depressive disorder- more is not merrier: an 8-week double-blind, randomised, controlled trial. J Affect Disord 245:1007–1015

Scaini G, Barichello T, Fries GR et al (2019) TSPO upregulation in bipolar disorder and concomitant downregulation of mitophagic proteins and NLRP3 inflammasome activation. Neuropsychopharmacology 44:1291–1299

Sena LA, Chandel NS (2012) Physiological roles of mitochondrial reactive oxygen species. Mol Cell 48:158–167

Sharpley AL, Hockney R, McPeake L et al (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

Shults CW, Oakes D, Kieburtz K et al (2002) Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 59:1541–1550

Shultz RB, Zhong Y (2017) Minocycline targets multiple secondary injury mechanisms in traumatic spinal cord injury. Neural Regen Res 12:702–713

Sigitova E, Fisar Z, Hroudova J et al (2017) Biological hypotheses and biomarkers of bipolar disorder. Psychiatry Clin Neurosci 71:77–103

Sikoglu EM, Navarro AA, Starr D et al (2015) Vitamin D3 supplemental treatment for mania in youth with bipolar spectrum disorders. J Child Adolesc Psychopharmacol 25:415–424

Simon J, Geddes JR, Gardiner A et al (2018) Comparative economic evaluation of quetiapine plus lamotrigine combination vs quetiapine monotherapy (and folic acid vs placebo) in patients with bipolar depression (CEQUEL). Bipolar Disord 20:733–745

Siwek M, Sowa-Kucma M, Styczen K et al (2016) Thiobarbituric acid-reactive substances: markers of an acute episode and a late stage of bipolar disorder. Neuropsychobiology 73:116–122

Slusarczyk W, Olakowska E, Larysz-Brysz M et al (2019) Use of ebselen as a neuroprotective agent in rat spinal cord subjected to traumatic injury. Neural Regen Res 14:1255–1261

Soeiro-de-Souza MG, Pastorello BF, Leite Cda C et al (2016) Dorsal anterior cingulate lactate and glutathione levels in euthymic bipolar I disorder: 1H-MRS study. Int J Neuropsychopharmacol 19:pyw032

Soeiro-de-Souza MG, Otaduy MCG, Machado-Vieira R et al (2018a) Anterior cingulate cortex glutamatergic metabolites and mood stabilizers in euthymic bipolar I disorder patients: a proton magnetic resonance spectroscopy study. Biol Psychiatry Cogn Neurosci Neuroimaging 3:985–991

Soeiro-de-Souza MG, Otaduy MCG, Machado-Vieira R et al (2018b) Lithium-associated anterior cingulate neurometabolic profile in euthymic bipolar I disorder: a (1)H-MRS study. J Affect Disord 241:192–199

Srivastava R, Faust T, Ramos A et al (2018) Dynamic changes of the mitochondria in psychiatric illnesses: new mechanistic insights from human neuronal models. Biol Psychiatry 83:751–760
Stacey D, Schubert KO, Clark SR et al (2018) A gene co-expression module implicating the mitochondrial electron transport chain is associated with long-term response to lithium treatment in bipolar affective disorder. Transl Psychiatry 8:183
Steckert AV, Valvassori SS, Moretti M et al (2010) Role of oxidative stress in the pathophysiology of bipolar disorder. Neurochem Res 35:1295–1301
Stern S, Santos R, Marchetto MC et al (2018) Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium. Mol Psychiatry 23:1453–1465
Szczepankiewicz A (2013) Evidence for single nucleotide polymorphisms and their association with bipolar disorder. Neuropsychiatr Dis Treat 9:1573–1582
Tardiolo G, Bramanti P, Mazzon E (2018) Overview on the effects of N-acetylcysteine in neurodegenerative diseases. Molecules 23:3305
Taurine as an Anti-Manic Agent: A Double-Blind, Placebo-Controlled Study (2005). https://clinicaltrials.gov/ct2/show/NCT00217165
Toniolo RA, Silva M, Fernandes FBF et al (2018) A randomized, double-blind, placebo-controlled, proof-of-concept trial of creatine monohydrate as adjunctive treatment for bipolar depression. J Neural Transm (Vienna) 125:247–257
Traina G (2016) The neurobiology of acetyl-L-carnitine. Front Biosci (Landmark Ed) 21:1314–1329
Tsai MC, Huang TL (2015) Thiobarbituric acid reactive substances (TBARS) is a state biomarker of oxidative stress in bipolar patients in a manic phase. J Affect Disord 173:22–26
Vaarmann A, Kovac S, Holmstrom KM et al (2013) Dopamine protects neurons against glutamate-induced excitotoxicity. Cell Death Dis 4:e455
Valvassori SS, Rezin GT, Ferreira CL et al (2010) Effects of mood stabilizers on mitochondrial respiratory chain activity in brain of rats treated with d-amphetamine. J Psychiatr Res 44:903–909
Valvassori SS, Bavaresco DV, Feier G et al (2018) Increased oxidative stress in the mitochondria isolated from lymphocytes of bipolar disorder patients during depressive episodes. Psychiatry Res 264:192–201
van Enkhuizen J, Janowsky DS, Olivier B et al (2015) The catecholaminergic-cholinergic balance hypothesis of bipolar disorder revisited. Eur J Pharmacol 753:114–126
Vellekkatt F, Menon V (2019) Efficacy of vitamin D supplementation in major depression: a meta-analysis of randomized controlled trials. J Postgrad Med 65:74–80
Wang D, Li Z, Liu W et al (2018) Differential mitochondrial DNA copy number in three mood states of bipolar disorder. BMC Psychiatry 18:149
Weber WA, Dudley J, Lee JH et al (2013) A pilot study of alterations in high energy phosphoryl compounds and intracellular pH in unmedicated adolescents with bipolar disorder. J Affect Disord 150:1109–1113
Wilson C, Lee MD, Heathcote HR et al (2019) Mitochondrial ATP production provides long-range control of endothelial inositol trisphosphate-evoked calcium signaling. J Biol Chem 294:737–758
Wu GF, Ren S, Tang RY et al (2017) Antidepressant effect of taurine in chronic unpredictable mild stress-induced depressive rats. Sci Rep 7:4989
Wurtman RJ, Regan M, Ulus I et al (2000) Effect of oral CDP-choline on plasma choline and uridine levels in humans. Biochem Pharmacol 60:989–992
Yamaki N, Otsuka I, Numata S et al (2018) Mitochondrial DNA copy number of peripheral blood in bipolar disorder: the present study and a meta-analysis. Psychiatry Res 269:115–117
Yang L, Ran Y, Quan Z et al (2019) Pterostilbene, an active component of the dragon's blood extract, acts as an antidepressant in adult rats. Psychopharmacology 236:1323–1333

Yoon SJ, Lyoo IK, Haws C et al (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

Yu W, Greenberg ML (2016) Inositol depletion, GSK3 inhibition and bipolar disorder. Future Neurol 11:135–148

Yuksel C, Du F, Ravichandran C et al (2015) Abnormal high-energy phosphate molecule metabolism during regional brain activation in patients with bipolar disorder. Mol Psychiatry 20:1079–1084

Zhang J, Wang X, Vikash V et al (2016) ROS and ROS-mediated cellular signaling. Oxidative Med Cell Longev 2016:4350965

Zheng W, Zhu XM, Zhang QE et al (2019) Adjunctive minocycline for major mental disorders: a systematic review. J Psychopharmacol 33:1215–1226

Zverova M, Hroudova J, Fisar Z et al (2019) Disturbances of mitochondrial parameters to distinguish patients with depressive episode of bipolar disorder and major depressive disorder. Neuropsychiatr Dis Treat 15:233–240