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BIPOLAR DISORDERS (W CORYELL, SECTION EDITOR)

Current State of Biomarkers in Bipolar Disorder

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Abstract Bipolar disorder (BD) is a chronic psychiatric illness of which the etiology remains unknown. Extensive research has provided some hypotheses for the pathophysiology of this disorder; however, there are no molecular tests available to help support the diagnosis obtained by self-report and behavioral observations. A major requirement is to identify potential biomarkers that could be used for early diagnosis in patients susceptible to the disease and for its treatment. The most recently published findings regarding alterations in BD were found to be related to oxidative stress, inflammatory and trophic factor deregulation, and also polymorphisms of genes that are associated with the development of BD. Many of these targets are potential biomarkers which could help to identify the BD subgroups and to advance treatment strategies, which would beneficiate the quality of life of these patients. Therefore, the main objective of this review is to examine the recent findings and critically evaluate their potential as biomarkers for BD.

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Introduction

Bipolar disorder (BD) is defined by severe mood oscillations which alternate between mania and depression. The pathophysiology of BD is complex and presents many molecular and morphological alterations suggestive of impairment in cellular plasticity and resilience and also including a number of different factors such as oxidative stress, alterations to the expression of trophic factors, and inflammatory markers [1••]. A major target for the research community is to identify potential biomarkers that could be used for early diagnosis in patients susceptible to the disease and for its treatment [2••, 3]. Unfortunately, the current diagnosis of BD is based on information obtained by self-report and behavioral observations which lacks substantial biological validation and results in underdiagnoses and misdiagnosis therefore impacting treatment decisions [1••, 2••]. Due to the heterogeneity of BD, it is not expected to develop a general biomarker as patients in different stages (mania, euthymia, depression) present different profiles of the disease. Therefore, a set of different biomarkers that could identify the subgroups of patients could help to advance the treatment strategies and tailor a unique treatment for each stage of the disorder [4].

Biomarkers could improve diagnostic accuracy by indicating the specific features that are found in patients with BD and, more importantly, transform the treatment into a more personalized approach. Further, the use of biomarkers could help to identify the alterations found in patients with BD between manic and depressive stages and may also improve the treatment and quality of life for patients that have long been diagnosed with BD [1••, 2••, 3]. A recent report addressing the biomarkers network from the International Society for

Bipolar Disorder (ISBD-BIONET) [1••] has provided powerful insights for the identification of possible biomarkers for BD. With this introduction in mind, we aimed to incorporate and critically evaluate the recently published literature regarding specific alterations to BD and the potential peripheral biomarkers that could reflect brain alterations in BD.

Potential Peripheral Biomarkers for Bipolar Disorder

Mental health research for BD has increasingly provided evidence that peripheral biomarkers are a very important approach that could provide many answers using simple tests, which are widely available and are relatively low cost. More important, considering the inaccessibility of the brain, the use of peripheral tissues such as blood, urine, or cerebrospinal fluid could present accessible markers that may be associated with brain alterations in BD. Upon reviewing the latest literature, four important areas are of particular interest in presenting potential biomarkers: mitochondrial dysfunction and oxidative stress, trophic factors, inflammatory cytokines, and urinary metabolites. Within these topics, focus has been placed on factors that have been consistently linked to BD.

Mitochondrial Dysfunction and Oxidative Stress

The mitochondrial electron transport chain (ETC.) is the principal source for the generation of reactive oxygen species (ROS) in mammalian cells [5]. Oxygen is involved in vital biological processes including the production of energy through oxidative phosphorylation [6]. Therefore, dysfunction of the ETC., which is consistently reported in BD [7••], is associated with increased levels of ROS production. When ROS production overwhelms the ability of the endogenous/exogenous antioxidant system, a state known as oxidative stress takes place [8]. In this state, the macromolecules including proteins, lipids, and DNA are targets for oxidative damage, which can affect the membrane fluidity, protein functionality, and DNA structure [9, 10]. These alterations to proteins, lipids, and DNA induced by oxidative stress are widely reported using post-mortem brain samples [11, 12, 13•, 14] and peripheral blood cells as well [13•, 15–17] from patients with BD, suggesting that mitochondrial dysfunction and oxidative stress play an important role in the pathophysiology of BD.

Upon reviewing the literature regarding microarray studies in BD, Scola et al. (2013) reported important alterations to the subunit levels of the mitochondrial ETC. The expression levels of the subunits NDUFV1, NDUSF1, NDUFS7, and NDUFS8 of complex I were found to be reduced in BD. This reduction may suggest that patients with BD are prone to deregulation of the ETC., which could increase the production of ROS [7••] leading to oxidative stress. Interestingly, a different pathway was found to be altered in the ETC. in schizophrenia (SCZ), in which the subunits altered in complex I are responsible for the proton pump as opposed to the electron transfer as found in BD [7••]. For this reason, we do not find the same findings regarding the oxidative stress parameters in BD and SCZ. The findings regarding reduced expression levels for the NDUFS7 were previously supported in BD [3, 13•].

Oxidative damage to proteins includes the formation of 3-nitrotyrosine and increased protein carbonyl content. 3-Nitrotyrosine is an end product of nitrosative damage to a tyrosine residue induced by peroxynitrite/carbon dioxide-derived radicals. Equally, the formation of carbonyl content occurs when oxygen or peroxide radicals react with amine groups through a metal-cation-catalyzed reaction [2••]. Kapczinski and collaborators reported that increased serum carbonyl levels were also found in both manic and depressive stages of BD [18]. Andreazza et al. (2010 and 2013) showed that oxidative damage to proteins was also found in the post-mortem prefrontal cortex (PFC) of patients with BD, where elevated carbonyl levels were found in the synaptosomes, elevated 3-nitrotyrosine levels in the mitochondria, and globally elevated carbonyl group levels. More recently, Kim et al. found that increased oxidative and nitrosative modifications to dopamine-rich areas are present in the post-mortem PFC samples of patients with BD using immunohistochemistry and acceptor photobleaching Förster resonance energy transfer technique [19]. Another recent study reported that serum superoxide dismutase (SOD) levels, an endogenous antioxidant enzyme, were lower in patients with BD when compared to healthy controls [20]. Therefore, these findings suggest that oxidative damage to proteins could be important to the physiopathology of BD; however, less evidence has been found to support the use of protein alterations as a specific biomarker.

In a meta-analysis examining oxidative stress markers in BD, Brown et al. (2014) reported that lipid peroxidation showed a significant change in BD. Lipid peroxidation is a process initiated by the reaction of ROS; the initial phase of lipid peroxidation generates lipid hydroperoxides (LPH) that can be detoxified by the enzymatic antioxidant system. However, if the lipid peroxidation cascade is not stabilized, LPH reacts with other lipid molecules to form non-radical species including malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), 8-isoprostane (8-ISO), and acrolein [21, 22]. Considering that lipids represent around 70 % of the main component of white matter, this oxidative alteration may play an important role in the pathophysiology of BD [2••]. Oxidative damage to lipids was also found higher in patients with BD in the myelin through the measurement of 4-hydroxynonenal and 8-isoprostrane [14]. Banerjee et al. also found higher serum levels of lipid peroxidation in patients with BD using the TBARS method [23]. More recently, plasma MDA levels were found to be higher in patients with BD when compared to healthy controls [20]. Interestingly,

another study by our group through multivariate multiple regression analyses revealed that LPH correlates with brain white matter abnormalities [24•], supporting that lipid peroxidation may be an important biomarker for BD.

Additionally, nitric oxide (NO) levels and DNA/RNA damage also present an important correlation with BD [2••]. Several studies reported that plasma/serum NO levels were found to be higher in patients with BD compared to healthy controls [20, 25, 26] and reduced in pretreated patients with BD [27]. These findings could support the use of this molecule as a potential biomarker; however, more studies are required to substantiate this hypothesis.

Another important finding to be discussed is that oxidative stress could be responsible for epigenetic modifications in BD. Alterations in 5-methylcytosine levels have been reported at the BDNF promoter and the *COMT* gene in patients with BD [28, 29]. Global methylation levels were also found to be decreased in patients with BD and their relatives when compared to healthy controls [30]. Also, Scola and collaborators reported that mitochondrial dysfunction may lead to alteration on methylation and hydroxymethylation levels in cortical primary neurons [31]. Oxidative damage to guanosine, measured by 8-hydroxy-2-deoxyguanosine levels (8-OHdG), was found to be higher in patients with BD when compared to healthy controls, and, importantly, it was found to be positively correlated to the number of manic episodes [32]. The same study also found that patients with BD presented decreased global 5-methylcytosine (5mc) levels similarly to the findings reported by Huzayyin and collaborators (2014). In addition, Che et al. [6] found that oxidative damage to RNA was also increased in the post-mortem hippocampus of patients with BD [12]. Once again, the findings suggest that oxidative damage to DNA/RNA may be related to the pathophysiology of BD. Furthermore, alterations to DNA conformation and production of aberrations such as 8-OHdG and 5mc may be a potential biomarker for BD; however, more studies are required to verify the difference of expression of these alterations to DNA/RNA in the different stages of the illness.

Though many disorders present mitochondrial dysfunction, several different pathways can be involved, and subsequently, the findings in this section are more specific to BD. Together, the findings highlighted above suggest that oxidative damage specifically for lipid peroxidation and DNA is a potential peripheral marker and may be associated with brain alterations in BD.

Trophic Factors

Neurotrophins (NT) and other trophic factors are responsible for the regulation of cell dynamics and are expressed in the brain and in the peripheral tissues in a region-specific manner. Neurotrophins, such as brain-derived neurotrophic factor (BDNF), and other trophic factors including insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are capable of signaling neurons, glial cells, and other cellular systems to enable survival, differentiation, and growth [33–35]. The abovementioned NTs were selected specifically in order to explore the unique alterations found in BD. Attention has been focused on gaining a better understanding of the role these factors play in the different stages of BD and their potential as biomarkers. For a detailed review of trophic factors, refer to Scola and Andreazza (review submitted).

Most published reports on BDNF have suggested a strong correlation between low levels of this NT and BD [36–39]. Recently, a study describing two different cohorts (Sahlgrenska and Karolinska sets) reported the ratio of proBDNF to mature BDNF levels was higher in patients in comparison to healthy controls; however, serum proBDNF levels were found to be lower in patients when compared to controls, suggesting the alteration in the conversion of pro to mature BDNF may be associated with the pathophysiology of BD [40••]. These findings suggest that the decrease in the levels of global/mature BDNF found may impair long-term memory and may be less effective in supporting normal cell regulation, both of which are found to be altered in BD.

Similar to BDNF, IGF-1 and VEGF presented a strong association within the pathophysiology of BD. Drug treatment has an important regulatory effect on the expression levels of both trophic factors [41, 42]. Peripheral levels of IGF-1 were lower in patients with BD compared to patients with schizophrenia [43]. Studies have shown a potential effect of IGF-1 signaling cascade in regulating stress, depression, and hippocampal neurogenesis [43, 44]. Therefore, the findings provided regarding the effects of IGF-1 suggest the importance of this NT in the pathophysiology of BD and its potential to be used as a biomarker should be explored in greater detail.

VEGF has an important role in regulating neuron dynamics, and it is also implicated in neuronal protection and cellular differentiation [45, 46]. Studies have shown a correlation between higher levels of this factor and major depressive disorder [47, 48], while lower levels of VEGF may be linked with suicidal ideation [49]. Moreover, plasma VEGF levels were found to be increased in patients in manic [50] and depressive [51] stages; however, lithium treatment was able to decrease VEGF mRNA levels. The data shows that VEGF may be altered in a state-dependent manner in patients with BD, suggesting this factor may be associated with BD.

Alterations in trophic factor levels in the brain and periphery in BD may have an important pathophysiological implication, which could lead to the morphological alterations found in patients with BD. Abnormalities of the PFC white matter in patients with BD were already reported by our group [24•], and these alterations may be, in part, related to dysregulation of these trophic factors. Further studies will be required to elucidate and support that trophic factors may be an important tool for the diagnosis of BD.

Inflammation

Some studies have shown the importance of inflammation in the brain and periphery in the pathophysiology of BD [52–54]. A possible cause of the alterations in the inflammatory cytokines in this disorder could be related to the chronic activation of the immune system during the manic or depressive episodes [55]. However, just a few studies have described assays of chemokines in subjects with BD [54]. The deregulation between the different inflammatory markers may be related to the alterations found in this disorder [53]. Understanding the role of these inflammatory factors in the different stages of BD could lead to the development of inflammatory biomarkers.

Most recently published evidence by Rao et al. and Brietzke et al. showed that pro-inflammatory factors (interleukin (IL)) including IL-1, IL-2, IL-4, and IL-8 were increased in peripheral blood and port-mortem brain of subjects with BD [56, 57]. Other important inflammatory markers found to be consistently increased in patients with bipolar disorder include IL-6, IL-1β, and tumor necrosis factor alpha (TNF-α) [52, 58, 59]. Supporting these studies, Munkholm and collaborators compiled a meta-analysis examining studies regarding peripheral samples, where IL-4 and TNF-α were increased in patients when compared to healthy controls, identifying their possible role as biomarkers for BD [55]. However, inflammatory responses are dependent on mood states and the findings are still controversial [55, 58]. Therefore, more studies regarding the examination of these factors in the different stages and their relationship with the illness will be necessary [54]. Nevertheless, studies as of yet have shown that peripheral inflammation is increased in the manic state [57, 58].

Moreover, studies have shown that IL-13, apolipoprotein A1, and TNF-α are strongly correlated with BD [60]. Also, Goldstein et al. reported that high-sensitivity C-reactive protein (hsCRP) is correlated with manic symptoms in adolescents with BD. In addition, IL-6 levels were also found to be negatively correlated with BDNF levels [61•], suggesting that inflammation could be associated with the progression of illness [1••]. A number of abnormalities observed in BD could be explained by alterations in the expression of these cytokines, since they were found to play an important role in the mitochondria [62] leading to an increased production of oxidative stress in the brain [63]. Another important target of abnormal cytokine expression is the catecholamine system, where TNF-α and IL-1Ra were found to disrupt norepinephrine and dopamine signaling, which could lead to mood oscillations through alterations of the neurotransmitter levels [58]. Similarly, the mechanism of action of these cytokines remains to be fully understood, since all current evidence suggests that inflammation has an important role in BD. Importantly, Alsaif et al. (2012) reported that studies using plasma and serum presented important differences which could impact the identification of biomarkers using multiplex immunoassay analysis. The study also reported that in the BD group, six proteins were significantly changed in serum and ten in plasma, and it emphasized that each biofluid can provide independent information regarding the biological pathway targeted [64]. This area of research may open up more venues for the development of biomarkers and may also provide potential therapeutic targets for existing and novel drugs for BD treatment.

Urinary Metabolites

Metabolomic approaches, such as gas chromatography-mass spectrometry (GC-MS), to examine potential biomarkers have been increasingly used to capture disease-specific metabolic signatures [65]. Studies evaluating possible markers in the urine of patients with BD have shown that metabolites including choline, α-hydroxybutyrate, *N*-methylnicotinamide, and isobutyrate differed from healthy controls [66]. In addition, another study showed that a single compound, 2,4-dihydroxypyrimidine, may be a validated biomarker in BD [67].

Neuroimaging

Improvements in neuroimaging techniques and image analysis have allowed a better understanding of the neuronal changes in BD. Moreover, these techniques, which include diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and proton magnetic resonance spectroscopy (H-MRS), are effective tools in examining and identifying changes in the brain anatomy which subsequently help in diagnostic and prognostic processes as well as allowing for the determination of potential biomarkers [1••, 68].

Recent findings in the literature have shown that euthymic patients with bipolar disorder present abnormalities in the prefrontal white matter through DTI [24•]. Interestingly, the data obtained from this study revealed that the white matter abnormalities are correlated with the peripheral lipid peroxidation levels, highlighting the importance of this technique for the diagnostics of BD. Another recent review examining the data of late-onset disease concluded that the current findings in the literature do not support consistent differences between early and late onset in BD [68], suggesting that more studies are required to elucidate these differences. However, Huang and collaborators reported that elderly patients with early- and late-onset mania presented a substantial reduction in various cortical regions [69]. Another study using DTI reported abnormalities in gray matter, where it was found

to be reduced in different structures of the brain of patients with BD [70]. Moreover, Phillips and Swartz reported that BD presents abnormalities in the neural circuits regarding emotion processing, emotion regulation, and reward processing [71•]. For more information regarding neuroimaging studies, refer to Frey et al. (2013) and Phillips and Swartz (2014).

Nonetheless, there are still some gaps in the literature regarding neuroimaging studies; no longitudinal studies were found using different points in the course of the illness and the examination of treatment response [1••] and neural circuitry [71•]. Together, the findings suggest that neuroimaging techniques are powerful tools that could be used to search for functional modifications in the neuroanatomical structures among children, adolescents, and adults in the early and late onset of the different stages of BD. Further studies are encouraged to examine potential markers that may be associated with peripheral biomarkers.

Genetic Findings

Most published findings suggest an association with the *BDNF*, *COMT*, and 5-*HTT* genes, which is also found within other psychiatric disorders. Using the genome-wide association studies (GWAS) and whole-genome sequencing in BD, the strongest evidence related to the pathophysiology is the *CACNA1C* and *ANK3* polymorphisms [1••, 72–74]. Moreover, *CACNA1C* has been implicated with alterations of hippocampal, pregenual anterior cingulate cortex, and dorsolateral PFC functions, suggesting a dysfunctional regulatory circuit including limbic and prefrontal brain regions in patients with BD [75]. Through a meta-analysis, Nurnberger and collaborators (2014) reported that *CACNA1C*, *DTNA*, *FOXP1*, *GNG2*, *ITPR2*, *LSAMP*, *NPAS3*, *NCOA2*, and *NTRK3* genes differed in their expression levels in the dorsolateral PFC in patients with BD. The same study suggests that pathways underlying the predisposition to BD include alterations to the calcium channels, glutamate signaling, hormonal regulation, and second messenger systems [72]. Also, genetic polymorphisms in the progranulin gene (*GRN*), which is related to fronto-temporal lobar degeneration, were found to be involved in many pathophysiological processes in the brain and periphery and were also found to be decreased in the plasma of patients with BD [4]. Importantly, it was found that drug-free manic patients presented downregulation in the expression levels of miRNA [76], which has an important role in inflammation and gene expression. These findings tend to reinforce specific hypotheses regarding the pathophysiology of BD and may provide new venues for new approaches to treatment and moderation of the illness progression. For more information regarding genetic studies in BD, refer to Frey et al. (2013).

High-Risk Studies

Another important topic that deserves mention concerns the offspring of probands with BD, which present an increased risk of developing BD or any major affective disorder [77, 78]. A recent meta-analysis of family high-risk studies from Rasic and collaborators (2013) addressed that familial transmission of risk is partially diagnosis specific and, more importantly, of higher risk than previously thought [79]. Dr. Duffy also states that high-risk studies have contributed to understanding the heterogeneity of BD and suggests that more studies are necessary to refine the characterization of the early stages of BD [78]. In an overview, high-risk family studies are very important for identifying the subphenotypes and also to better understand the cohort-specific genetic risk markers. In accordance with these statements, it is necessary to highlight the necessity of studies that could address and identify early clinical stages in the development of BD as well as to determine the molecular targets involved in this process. This information could have a tremendous role in the understanding of the pathology and the development of stage-specific treatments with illness onset and progression.

Conclusions

In summary, this review aimed to provide an update of the potential biomarkers which may enhance diagnosis accuracy, to examine the progression of the illness, and to improve the treatment for BD. The main findings highlighted in this review were as follows: (*1*) oxidative damage, specifically lipid peroxidation and DNA, is a potential peripheral marker; (*2*) BDNF may be used for diagnosis as well as observation of illness progression; (*3*) IL-4 and TNF-α were identified as possible inflammatory targets; (*4*) 2,4-dihydroxypyrimidine metabolite may be a validated urinary biomarker; (*5*) *CACNA1C* and *ANK3* gene polymorphisms are the main findings of genetic studies of patients with BD; (*6*) BD presents abnormalities in the prefrontal white matter which is related with the peripheral lipid peroxidation levels and also presents abnormalities in the neural circuits regarding emotion processing, emotion regulation, and reward processing; and (*7*) high-risk family studies could identify the early clinical stages and also determine the molecular targets involved in BD. These findings emphasize the complexity of BD yet also present possible approaches that may help disease diagnosis and improve the development of novel therapies on those targets. Importantly, future studies are required to elucidate the usefulness of the potential biomarkers described in this review.

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Compliance with Ethics Guidelines

Conflict of Interest Gustavo Scola and Ana Cristina Andreazza have received an operating grant from the Canadian Institutes of Health Research.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Frey BN, Andreazza AC, Houenou J, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatr. 2013;47(4):321–32. *This positional report from the ISBD-BIONET explores the most significant data regarding the search and development of potential biomarkers*.
2.•• Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res. 2014;218(1–2):61–8. *This meta-analysis supports the involvment of oxidative stress in the pathophysiology of bipolar disorder, especially to lipids, DNA and RNA*.
3. Andreazza AC, Young LT. The neurobiology of bipolar disorder: identifying targets for specific agents and synergies for combination treatment. Int J Neuropsychopharmacol. 2014;17(7):1039–52.
4. Kittel-Schneider S, Weigl J, Volkert J, et al. Further evidence for plasma progranulin as a biomarker in bipolar disorder. J Affect Disord. 2014;157:87–91.
5. Halliwell B, Gutteridge JMC. Free radicals in biology and medicine. 4th ed. Oxford: Clarendon; 2007.
6. Adam-Vizi V, Starkov AA. Calcium and mitochondrial reactive oxygen species generation: how to read the facts. J Alzheimers Dis. 2010;20 Suppl 2:S413–26.
7.•• Scola G, Kim HK, Young LT, et al. A fresh look at complex I in microarray data: clues to understanding disease-specific mitochondrial alterations in bipolar disorder. Biol Psychiatry. 2013;73:e4–5. *This report discusses and emphasises that alterations to the mitochondrial electron transport chain may have an important role in the etiology of bipolar disorder*.
8. Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997;82:291–5.
9. Xing M. Oxidative stress: a new risk factor for thyroid cancer. Endocr Relat Cancer. 2012;19:C7–C11.
10. Hovatta I, Juhila J, Donner J. Oxidative stress in anxiety and comorbid disorders. Neurosci Res. 2010;68:261–75.
11. Wang JF, Shao L, Sun X, et al. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. Bipolar Disord. 2009;11:523–9.
12. Che Y, Wang JF, Shao L, et al. Oxidative damage to RNA but not DNA in the hippocampus of patients with major mental illness. J Psychiatry Neurosci. 2010;35:296–302.
13.• Andreazza AC, Shao L, Wang JF, et al. Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. Arch Gen Psychiatry. 2010;67:360–8. *In this post-translational study important findings were found to the mitochondrial complex I and identifies potential therapeutic targets for the treatment of bipolar disorder*.
14. Andreazza AC, Wang JF, Salmasi F, et al. Specific subcellular changes in oxidative stress in prefrontal cortex from patients with bipolar disorder. J Neurochem. 2013;127(4):552–61.
15. Machado-Vieira R, Andreazza AC, Viale CI, et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. Neurosci Lett. 2007;421:33–6.
16. Andreazza AC, Kauer-Sant'anna M, Frey BN, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008;111:135–44.
17. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, et al. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009;34:263–71.
18. Kapczinski F, Dal-Pizzol F, Teixeira AL, et al. Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res. 2011;45:156–61.
19. Kim HK, Andreazza AC, Yeung PY, et al. Oxidation and nitration in dopaminergic areas of the prefrontal cortex from patients with bipolar disorder and schizophrenia. J Psychiatry Neurosci. 2014;39:130155.
20. Aydemir O, Cubukçuo Lu Z, Erdin S, et al. Oxidative stress markers, cognitive functions, and psychosocial functioning in bipolar disorder: an empirical cross-sectional study. Rev Bras Psiquiatr. 2014.
21. Halliwell B. Reactive oxygen species and the central nervous system. J Neurochem. 1992;59:1609–23.
22. Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans. 2007;35:1147–50.
23. Banerjee U, Dasgupta A, Rout JK, et al. Effects of lithium therapy on Na+-K+-ATPase activity and lipid peroxidation in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2012;37:56–61.
24.• Versace A, Andreazza AC, Young LT, et al. Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. Mol Psychiatry. 2013;19(2):200–8. *This is one of the first reports regarding the correlation between lipid peroxidation and alterations to white matter*.
25. Gergerlioglu HS, Savas HA, Bulbul F, et al. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:697–702.
26. Selek S, Savas HA, Gergerlioglu HS, et al. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. J Affect Disord. 2008;107:89–94.
27. Ozcan ME, Gulec M, Ozerol E, et al. Antioxidant enzyme activities and oxidative stress in affective disorders. Int Clin Psychopharmacol. 2004;19:89–95.
28. Abdolmaleky HM, Cheng KH, Faraone SV, et al. Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Hum Mol Genet. 2006;15:3132–45.
29. D'Addario C, Dell'Osso B, Palazzo MC, et al. Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. Neuropsychopharmacology. 2012;37:1647–55.
30. Huzayyin AA, Andreazza AC, Turecki G, et al. Decreased global methylation in patients with bipolar disorder who respond to lithium. Int J Neuropsychopharmacol. 2014;17:561–9.
31. Scola G, Kim HK, Young LT, et al. Lithium reduces the effects of rotenone-induced complex I dysfunction on DNA methylation and hydroxymethylation in rat cortical primary neurons. Psychopharmacology (Berl). 2014.

32. Soeiro-de-Souza MG, Andreazza AC, Carvalho AF, et al. Number of manic episodes is associated with elevated DNA oxidation in bipolar I disorder. Int J Neuropsychopharmacol. 2013;16:1505–12.
33. Mufson EJ, Kroin JS, Sendera TJ, et al. Distribution and retrograde transport of trophic factors in the central nervous system: functional implications for the treatment of neurodegenerative diseases. Prog Neurobiol. 1999;57:451–84.
34. Kaplan DR, Miller FD. Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol. 2000;10:381–91.
35. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24:677–736.
36. Cunha AB, Frey BN, Andreazza AC, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett. 2006;398:215–9.
37. Lin PY. State-dependent decrease in levels of brain-derived neurotrophic factor in bipolar disorder: a meta-analytic study. Neurosci Lett. 2009;466:139–43.
38. Fernandes BS, Gama CS, Ceresér KM, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011;45:995–1004.
39. Rosa AR, Singh N, Whitaker E, et al. 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. 2014. 1–10.
40.•• Södersten K, Pålsson E, Ishima T, et al. Abnormality in serum levels of mature brain-derived neurotrophic factor [BDNF] and its precursor proBDNF in mood-stabilized patients with bipolar disorder: a study of two independent cohorts. J Affect Disord. 2014;160:1–9. *This study suggests that alterations in the conversion of pro to mature BDNF may be associated with the pathophysiology of bipolar disorder.*
41. Squassina A, Costa M, Congiu D, et al. Insulin-like growth factor 1 [IGF-1] expression is up-regulated in lymphoblastoid cell lines of lithium responsive bipolar disorder patients. Pharmacol Res. 2013;73:1–7.
42. Kikuchi K, Iga J, Tayoshi S, et al. Lithium decreases VEGF mRNA expression in leukocytes of healthy subjects and patients with bipolar disorder. Hum Psychopharmacol. 2011;26:358–63.
43. Palomino A, González-Pinto A, Martinez-Cengotitabengoa M, et al. Relationship between negative symptoms and plasma levels of insulin-like growth factor 1 in first-episode schizophrenia and bipolar disorder patients. Prog Neuropsychopharmacol Biol Psychiatry. 2013;44:29–33.
44. Pereira AC, McQuillin A, Puri V, et al. Genetic association and sequencing of the insulin-like growth factor 1 gene in bipolar affective disorder. Am J Med Genet B Neuropsychiatr Genet. 2011;156:177–87.
45. Fournier NM, Lee B, Banasr M, et al. Vascular endothelial growth factor regulates adult hippocampal cell proliferation through MEK/ERK- and PI3K/Akt-dependent signaling. Neuropharmacology. 2012;63:642–52.
46. Nowacka MM, Obuchowicz E. Vascular endothelial growth factor [VEGF] and its role in the central nervous system: a new element in the neurotrophic hypothesis of antidepressant drug action. Neuropeptides. 2012;46:1–10.
47. Takebayashi M, Hashimoto R, Hisaoka K, et al. Plasma levels of vascular endothelial growth factor and fibroblast growth factor 2 in patients with major depressive disorders. J Neural Transm. 2010;117:1119–22.
48. Iga J, Ueno S, Yamauchi K, et al. Gene expression and association analysis of vascular endothelial growth factor in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:658–63.
49. Isung J, Mobarrez F, Nordström P, et al. Low plasma vascular endothelial growth factor [VEGF] associated with completed suicide. World J Biol Psychiatry. 2012;13:468–73.
50. Lee BH, Kim YK. Increased plasma VEGF levels in major depressive or manic episodes in patients with mood disorders. J Affect Disord. 2012;136:181–4.
51. Shibata T, Yamagata H, Uchida S, et al. The alteration of hypoxia inducible factor-1 [HIF-1] and its target genes in mood disorder patients. Prog Neuropsychopharmacol Biol Psychiatry. 2013;43:222–9.
52. Goldstein BI, Fagiolini A, Houck P, et al. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord. 2009;11:657–62.
53. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord. 2012;141:1–10.
54. Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev. 2014;42C:93–115.
55. Munkholm K, Braüner JV, Kessing LV, et al. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res. 2013;47:1119–33.
56. Rao JS, Harry GJ, Rapoport SI, et al. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry. 2010;15:384–92.
57. Brietzke E, Stabellini R, Grassis-Oliveira R, et al. Cytokines in bipolar disorder: recent findings, deleterious effects but promise for future therapeutics. CNS Spectr. 2011;16:157–68.
58. Hope S, Dieset I, Agartz I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res. 2011;45(12):1608–16.
59. Drexhage RC, Knijff EM, Padmos RC, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother. 2010;10:59–76.
60. Herberth M, Koethe D, Levin Y, et al. Peripheral profiling analysis for bipolar disorder reveals markers associated with reduced cell survival. Proteomics. 2011;11:94–105.
61.• Goldstein BI, Collinger KA, Lotrich F, et al. Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. J Child Adolesc Psychopharmacol. 2011;21:479–84. *This report addresses novel evidence regarding biomarkers among adolescents with bipolar disorder.*
62. Zell R, Geck P, Werdan K, et al. TNF-alpha and IL-1 alpha inhibit both pyruvate dehydrogenase activity and mitochondrial function in cardiomyocytes: evidence for primary impairment of mitochondrial function. Mol Cell Biochem. 1997;177:61–7.
63. Behrens MM, Ali SS, Dugan LL. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. J Neurosci. 2008;28:13957–66.
64. Alsaif M, Guest PC, Schwarz E, et al. Analysis of serum and plasma identifies differences in molecular coverage, measurement variability, and candidate biomarker selection. Proteomics Clin Appl. 2012;6:297–303.
65. Zheng P, Chen JJ, Huang T, et al. A novel urinary metabolite signature for diagnosing major depressive disorder. J Proteome Res. 2013;12:5904–11.
66. Zheng P, Dong Wei. YD, Yao G, et al. Novel urinary biomarkers for diagnosing bipolar disorder. Metabolomics. Springer; 2013.
67. Xu XJ, Zheng P, Ren GP, et al. 2,4-Dihydroxypyrimidine is a potential urinary metabolite biomarker for diagnosing bipolar disorder. Mol Biosyst. 2014;10:813–9.
68. Hahn C, Lim HK, Lee CU. Neuroimaging findings in late-onset schizophrenia and bipolar disorder. J Geriatr Psychiatry Neurol. 2014;27:56–62.

69. Huang SH, Tsai SY, Hsu JL, et al. Volumetric reduction in various cortical regions of elderly patients with early-onset and late-onset mania. Int Psychogeriatr. 2011;23:149–54.
70. Haller S, Xekardaki A, Delaloye C, et al. Combined analysis of grey matter voxel-based morphometry and white matter tract-based spatial statistics in late-life bipolar disorder. J Psychiatry Neurosci. 2011;36:391–401.
71.• Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry. 2014;171(8):829–43. *This positional report discusses the limitations of neuroimaging studies and suggests new approaches to guide diagnosis and treatment for patients with bipolar disorder.*
72. Nurnberger JI, Koller DL, Jung J, et al. Identification of pathways for bipolar disorder: a meta-analysis. JAMA Psychiatry. 2014;71:657–64.
73. Group PGCBDW. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011;43(10):977–83.
74. Fiorentino A, O'Brien NL, Locke DP, et al. Analysis of ANK3 and CACNA1C variants identified in bipolar disorder whole genome sequence data. Bipolar Disord. 2014;16:583–91.
75. Erk S, Meyer-Lindenberg A, Linden DE, et al. Replication of brain function effects of a genome-wide supported psychiatric risk variant in the CACNA1C gene and new multi-locus effects. Neuroimage. 2014;94:147–54.
76. Rong H, Liu TB, Yang KJ, et al. MicroRNA-134 plasma levels before and after treatment for bipolar mania. J Psychiatr Res. 2011;45:92–5.
77. Nurnberger JI, McInnis M, Reich W, et al. A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. Arch Gen Psychiatry. 2011;68:1012–20.
78. Duffy A, Alda M, Hajek T, et al. Early stages in the development of bipolar disorder. J Affect Disord. 2010;121:127–35.
79. Rasic D, Hajek T, Alda M, et al. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. Schizophr Bull. 2014;40:28–38.