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Putative biological predictors of treatment response in bipolar disorders

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ABSTRACT

Bipolar disorder (BD) is a debilitating illness that affects millions of Americans each year and is the 6th leading cause of disability in the world. Although standard treatments are available for management of BD, approximately half of all BD patients are either non-adherent or poorly adherent with prescribed medication regimens, resulting in decreased quality of life and increases in relapse rates, costs of care, and suicide attempts. Noncompliance in BD is often related to medication side effects and perceived lack of efficacy, which underscores the importance of trying to improve the "trial and error" process of finding optimal individualized treatments. There is a great need for more specific and sensitive biomarkers for the monitoring of BD treatment response, as well as predictive biomarkers to identify who is most likely to respond to these treatments and to avoid adverse effects. Here, we provide a comprehensive review on the utility of peripheral biomarkers for treatment response in bipolar disorder. We focus on the five most promising key areas for biological predictors of treatment response: 1) cell growth, cell survival, and synaptic plasticity (neurotrophins and growth factors), 2) energy metabolism (oxidative stress and mitochondrial function), 3) inflammation (pro- and anti-inflammatory cytokines), 4) stress response (neuroendocrine response), and 5) peripheral gene expression.

Abbreviations: BD, bipolar disorder; CSF, cerebrospinal fluid; BDNF, brain-derived neurotrophic factor; NT3, neurotrophin-3; NT4, neurotrophin-4; NGF, nerve growth factor; Trk, tyrosine kinase receptor; p75, TNF receptor superfamily member 1B; CNS, central nervous system; MDD, major depressive disorder; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; GDNF, glial-derived growth factor; TGFβ, transforming growth factor beta; VEGFA, vascular endothelial growth factor A; FGF-2, fibroblast growth factor 2; IGF-1, insulin-like growth factor 1; BMPs, bone morphogenic proteins; MRS, magnetic resonance spectroscopy; ETC, electron transport chain; iPSCs, induced pluripotent stem cells; PFC, prefrontal cortex; TBARS, thiobarbituric acid reactive substances; NO, nitric oxide; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; IL, interleukin; TNF, tumor necrosis factor; IFN-γ, interferon-gamma; sIL-2R, soluble IL-2 receptor; sIL-6R, soluble IL-6 receptor; CRP, C-reactive protein; TFN, transferrin; HPA, hypothalamicpituitaryadrenal; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; GR, glucocorticoid receptors; DST, dexamethasone suppression test; Dex, dexamethasone; FKBP5, FK506 binding protein 5; BAG1, BCL2 associated athanogene 1; PTGES3, prostaglandin E synthase 3; HSP70, heat shock protein 70; TSH, thyroid-stimulating hormone; T4, thyroxine; TRH, thyrotropin-releasing hormone; PFDN4, prefoldin subunit 4; DPY19L2P2, DPY19L2 pseudogene 2; PCMT1, protein-L-isoaspartate (D-aspartate) *O*-methyltransferase; ICE1, interactor of little elongation complex ELL subunit 1; RNMT, RNA guanine-7 methyltransferase; SS18, SS18, nBAF chromatin remodeling complex subunit; NF1, neurofibromin 1; SLC35D1, solute carrier family 35 member D1; E2F4, E2F transcription factor 4; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; MTF1, metal regulatory transcription factor 1; FAM21A/B/C/D, family with sequence similarity 21 member A/B/C/D; VAMP3, vesicle associated membrane protein 3; C9orf16, chromosome 9 open reading frame 16; IKBKG, inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma; STX11, syntaxin 11; PSMD1, proteasome 26S subunit, non-ATPase 1; Plec, plectin; SPR, sepiapterin reductase; MAPK6, mitogen-activated protein kinase 6; CCL2, CC motif chemokine ligand 2; PTX3, pentraxin 3; EMP1, epithelial membrane protein 1; BCL2A1, BCL2 related protein A1; PDE4B, phosphodiesterase 4B; IL1B, interleukin 1 beta; IL6, interleukin 6; TNFAIP3, TNF alpha induced protein 3; PTGS2, prostaglandin-endoperoxide synthase 2; CCL7, CC motif chemokine ligand 7; CCL20, CC motif chemokine ligand 20; CXCL2, C-X-C motif chemokine ligand 2; CCR2, CC motif chemokine receptor 2; CDC42, cell division cycle 42; DUSP2, dual specificity phosphatase 2; NAB2, NGFI-A binding protein 2; ATF3, activating transcription factor 3.

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Introduction

Neuropsychiatric disorders are the leading cause of disability in the U.S. There were an estimated 9.6 million adults aged 18 years or older in the U.S. with serious mental illness in 2012, representing 4.1% of all U.S. adults [1]. Conservative estimates of the total costs associated with serious mental illness exceed $300 billion per year [2]. Bipolar disorder (BD) is amongst the most of the severe mental disorders, with lifetime prevalence rates of 3.9% in the US adult population [3]. The phenotypic expression of BD varies extensively among individuals, and familial coaggregation and comorbidity of other neuropsychiatric disorders are prevalent in extended family pedigrees. Evidence from various studies suggests that the mode of transmission of BD is complex, including multiple, possibly interacting genes exerting effects, along with genetic and clinical heterogeneity and incomplete penetrance [4]. These findings suggest that individuals carry different sets of susceptibility genes, which in combination with environmental factors determine the diathesis for and overall clinical phenotype.

Standard treatments commonly recommended for management of BD include mood-stabilizing medications such as lithium, certain anticonvulsants, antidepressants, and/or atypical antipsychotic drugs. However, approximately half of all BD patients are either non-adherent or poorly adherent to prescribed medication regimens, resulting in profound negative consequences. [5]. These include decreased quality of life and increases in relapse rates, costs of care, and suicide attempts. Suicidality is of the utmost concern, as BD patients have alarming rates of attempted and completed suicide [6,7]. Side effects are among the most frequent reasons for medication non-adherence. Side effects of mood stabilizers, antipsychotics, antidepressants and anticonvulsants include gastrointestinal problems, weight-gain and metabolic effects, hypothyroidism, rashes, cognitive impairment, sexual dysfunction, extrapyramidal symptoms, nephrotoxic, hepatotoxic, and teratogenic side-effects [8–13]. Before starting a patient on a medication with potentially devastating side effects, it would be valuable to have some indicator or reassurance regarding eventual response. Therapeutic biomarkers can not only serve to predict efficacy for a given treatment in a given patient but may be invaluable tools for diminishing adverse side effects, because they may be used to detect the early effectiveness of treatments at the lowest possible dosage without impacting efficacy.

The major objective at the time of the initial diagnosis is to arrest disease progression and diminish symptom severity [14]. The unpredictable efficacy of FDA-approved treatments reflects the heterogeneity of BD. There is a great need for more specific and sensitive biomarkers for the monitoring of BD treatment response, as well as predictive biomarkers to identify who is most likely to respond to these treatments and to avoid unnecessary or harmful side effects and adverse events. This paper reviews the literature on bipolar disorder biomarkers for assessing therapeutic efficacy. We focus on peripheral (serum/blood) markers, which could be obtained in the general psychiatric clinician's office without special equipment. Cerebrospinal fluid (CSF) [15], non-invasive electrophysiology [16], and brain imaging [17,18] are also viable biomarkers, but would be difficult to obtain outside specialized academic centers. The peripheral biomarker literature has examined five key areas: cell growth, cell survival, and synaptic plasticity (neurotrophins and growth factors); energy metabolism (oxidative stress and mitochondrial function); inflammation (pro- and anti-inflammatory cytokines); stress response (neuroendocrine response), and peripheral gene expression. This literature review was initiated using the following terms on PubMed: [growth factor, OR BDNF, OR GDNF, OR VEGF,OR energy metabolism, OR mitochondria, OR oxidative stress, OR cytokine, OR HLA, OR neuroendocrine, OR HPA, OR gene expression, OR gene association] AND bipolar disorder AND [biomarker OR treatment response]; restricted to English language. The National Human Genome Research Institute (NHGRI) Catalog of Published Genome-Wide Association Studies (accessed 11 Nov 2016) was reviewed for genetic associations for treatment response to lithium, antidepressant, antipsychotic treatment, pharmacokinetics of antiepileptic drugs in severe mental disorders, and genetic predictors of long-term (more than 6 months) treatment efficacy in BD [19].

Cell growth, cell survival, and synaptic plasticity

Brain-derived neurotrophic factor (BDNF)

BDNF is the most well-studied member of the neurotrophin family of growth factors. Other members of this family include pro-BDNF, neurotrophin-3 (NT3), neurotrophin-4 (NT4), and nerve growth factor (NGF). These factors bind to the Trk family of receptors, as well as the p75 receptor. When they bind their cognate Trk receptors, neurotrophins support neuronal growth and survival, whereas neurotrophin binding to p75 generally functions as a pro-apoptotic signal [20]. BDNF is important for neurogenesis, neuronal survival, and normal maturation of neural developmental pathways. In adults, BDNF is not only important for synaptic plasticity and dendritic growth, but is also essential for the formation of long-term memories [21,22]. Genetic variants in BDNF are associated with vulnerability to various psychiatric [23–30] and neurodegenerative disorders [31–36]. BDNF is present in both human blood and brain tissue [37,38], although the source of serum BDNF may be platelets or another peripheral source [39]. Although the degree to which serum BDNF levels precisely reflect brain BDNF levels is unclear, rat models suggest that BDNF levels in brain and peripheral blood undergo similar changes during maturation and aging [40].

Studies utilizing a variety of methodologies support a key role for BDNF in the pathogenesis of mood disorders [41–44], in the progression of BD [45], and in the mechanism of action of therapeutic agents [46–49]. BDNF protects against stress-induced neuronal damage in mouse models, and may regulate neurogenesis in the hippocampus [50], which has been posited to be involved in the pathogenesis of mood disorders [51]. Decreased peripheral BDNF levels have been consistently reported in both serum [52–55] and plasma samples [56,57] from BD patients compared to control samples. Decreased protein and mRNA levels of BDNF have also been reported in the frontal cortex in postmortem BD brain specimens [58], suggesting that perhaps lower peripheral BDNF levels may mirror CNS processes. BDNF levels may also be important in normal brain function; higher serum levels of BDNF were associated with improved performance on a test of verbal fluency in both BD patients and controls [47]. However, higher levels of BDNF are not necessarily beneficial in all cases; prolonged BDNF overexpression in principal neurons of the forebrain causes deficits in learning and memory formation in mouse models [59]. Lithium treatment in cultured rat hippocampal neurons was correlated with activation of BDNF transcription, which may be one mechanism by which lithium protects neurons in bipolar disorder [60].

Treatment outcome

Increased blood concentrations of BDNF have been reported following treatment with antidepressants or mood stabilizers in BD and other mood disorders [52,61–64]. A 16-week open trial of quetiapine XR for BD suggested that the serum BDNF response differed depending on the polarity of illness; peripheral BDNF levels increased patients with in bipolar depression but decreased in

manic and mixed patients; this change appeared to be independent of clinical response to treatment [65]. Barbosa et al. reported that plasma BDNF levels did not differ in BD patients categorized according to the use of mood stabilizing drugs (i.e. antipsychotics, lithium, anticonvulsants, or antidepressants) [57]; Fernandes and colleagues also observed no differences in serum BDNF levels between medicated and unmedicated BD patients [55]. However, a study by Dias et al. suggested that peripheral BDNF levels were dependent on medication type: serum BDNF levels were lower in patients medicated with antipsychotics and/or lithium, whereas patients on valproate and/or antidepressants exhibited higher serum BDNF levels [47]. Suwalska et al. reported lithium-treated patients as a group had lower BDNF levels compared to healthy controls, and more specifically, lithium non-responders had significantly lower BDNF levels compared with the healthy control subjects, suggesting that serum BDNF is associated with lithium efficacy [48]. This effect may be mediated by polymorphisms in the BDNF gene, as one study has suggested [66]. Overall, the data suggest that lithium nonresponders do not upregulate BDNF when treated with lithium, and lithium responders do, but these studies are all quite small and were not designed to address the specific question of whether BDNF levels mediate lithium responsiveness.

Several studies have attempted to correlate peripheral BDNF levels to treatment response in acute mania. Two independent longitudinal studies conducted with manic patients found that peripheral BDNF levels increase after successful pharmacological treatment [46,62]. A significant increase in plasma BDNF levels was observed by de Sousa et al. after 28 days of lithium monotherapy for acute mania compared to pre-treatment, with 87% of responders showing an increase in BDNF levels after treatment [46]. Lithium may exert its therapeutic action by up-regulating BDNF expression to achieve euthymia, because serum BDNF levels were positively correlated with lithium levels [49]. It has been suggested that BDNF levels normalize with mood stabilization. Tramontina et al. suggested that changes in serum BDNF levels may be associated with treatment response in acute mania. BDNF levels were decreased in BD patients during mania when compared to controls; however, this difference was no longer significant after treatment as a sharp increase in BDNF levels was noted post-treatment [62]. Huang et al. reported neither significant differences in serum BDNF concentrations between patients with bipolar mania and healthy controls nor changes in serum BDNF levels after a 4-week treatment with mood stabilizers [67]. A systematic review and meta-regression analysis, based on 3 studies with repeated BDNF measurements, found that BDNF levels increase after treatment for acute mania [68]. A more recent meta-analysis attempted to combine data from treatment studies in major depressive disorder (21 studies) and bipolar disorder (7 studies), but reported that there were insufficient data to quantitatively assess for BDNF changes in BD treatment and analysis was limited to qualitative evaluation [69]. The qualitative analysis did suggest a trend toward an increase in peripheral BDNF (both plasma and serum levels) in BD patients who respond to treatment while peripheral BDNF levels seem not to change in non-responders [69]. One study of epigenetic regulation of BDNF suggested a trend toward lower BDNF promoter methylation levels in BD patients taking mood stabilizers (trending toward control levels of promoter methylation), which suggests a mechanism by which mood stabilizers regulate BDNF expression and thereby stabilize mood [70].

Lithium increases BDNF expression in cultured rodent neurons [71], and this has been proposed as one mechanism by which lithium may prevent some neurodegenerative aspects of bipolar disorder. Additionally, platelet BDNF mRNA increases with 8 weeks of medication treatment for BD (lithium, valproate, or atypical antipsychotic) [61]. However, lithium and valproate may produce different effects on astrocytes versus neurons; in cultured human astrocytoma cell lines, valproate increased extracellular BDNF levels while lithium reduced BDNF release [72]. Both the potential direct and indirect effects of medication on BDNF expression need to be considered in the interpretation of studies in which BDNF levels are measured in medicated patients, because many studies group together results from patients treated with various mood stabilizers which may exert differing effects on BDNF levels.

There is evidence to suggest that BDNF expression might be a downstream target of antidepressants and mood stabilizers, and that BDNF itself exerts antidepressant activity in animal models of depression [51]. Boulle et al. reported that chronic stress promotes hippocampal BDNF expression in a mouse model of depression, and the antidepressant drug agomelatine restored BDNF expression to the levels observed in non-stressed mice [73]. Chang et al. demonstrated that chronic administration of mood stabilizers (carbamazepine and lamotrigine) increased BDNF mRNA expression and protein concentrations in rat frontal cortex [74].

Pillai reported a mean decrease of BDNF mRNA levels by 36% in antipsychotic-naive patients with a trend towards significance in the DLPFC of BD samples from the Stanley Brain Collection. No significant association was found between antipsychotic use at time of death and BDNF mRNA expression. The potential effects of antipsychotic medications on levels of BDNF were examined in the frontal cortex of rats treated with haloperidol and olanzapine. Haloperidol treated rats showed significant reductions in BDNF mRNA and protein levels. In contrast, olanzapine treated rats showed a significant increase in BDNF mRNA expression and protein concentrations when compared to vehicle-treated rats [75].

One group has made a significant effort to evaluate the effects of lithium on gene expression across species and cell types, and reported that the neurotrophin signaling KEGG pathway was the most highly enriched, despite the fact that many included studies had no relationship to bipolar disorder whatsoever [76]. This suggests that the relationship between lithium treatment response and neurotrophin signaling may be distinct from the effect of lithium on psychiatric symptoms. Another set of data that dampens enthusiasm for BDNF somewhat is a meta-analysis and meta-regression of 11 studies of patients in depressive mood episodes (including MDD and BD) showing that ECT caused an increase in BDNF independent of clinical response [77].

There has been much interest in the role of the BDNF Val66Met polymorphism in neuropsychiatric disease risk and treatment response. The polymorphism has been linked with risk of depression in Alzheimer disease [31], cognitive impairment in Parkinson's disease [34], neurotic personality traits [25], schizophrenia [23], but not postpartum depression [24], with mixed findings in bipolar disorder [43,78,79] and anxiety disorders [25,27]. A large meta-analysis of BDNF polymorphisms, including Val66Met, and antidepressant efficacy in depressed patients (largely MDD or MDE diagnoses) found little evidence to support Val66Met involvement in treatment response [80]. A handful of studies have looked at the polymorphism in relationship to lithium response in bipolar disorder with mixed results [66,81,82]. One study found a co-association of the Val66Met polymorphism with a polymorphism in a serotonin transporter gene and lithium response [83], highlighting the complicated nature of how genetics contributes to treatment response. In terms of negative treatment outcomes, the BDNF Val66Met polymorphism is associated with both increased markers of metabolic syndrome and obesity in BD patients treated with atypical antipsychotics [84], suggesting that BDNF may be important in modulating side effects of treatment.

Overall, there is significant data to suggest that BDNF may become a useful biomarker of treatment response; it often increases with successful treatment. Additionally, BDNF appears to be a potential "state" marker, that is, BDNF is generally lower

during mood episodes in bipolar disorder, and may normalize during euthymia. However, it is less clear on an individual patient basis that pre-treatment BDNF levels predict response to a specific intervention, which limits our current ability to use BDNF levels clinically for making treatment decisions. One possible way to clarify this issue would be to randomize subjects in treatment trials into specific arms based on baseline pre-treatment BDNF levels, and then observe whether a person's pre-treatment BDNF level alone predicts treatment response.

Other neurotrophins

Only a few studies have attempted to determine potential relationships between bipolar disorder and other neurotrophins. Two studies reported that serum neurotrophin-3 (NT3) concentration was higher in BD during both depression and mania [85–87], which did not differ between medicated and drug-free patients [86]. Kapczinski et al. reported that serum NT-3 levels were elevated during euthymia and depression and reduced during mania [87]. However, Walz et al. reported that both lithium and valproate increased NT3 levels in serum and hippocampus of rats with amphetamine-induced hyperactivity, one animal model of mania [88]. This research group found in a separate study that serum neurotrophin-4/5 was higher than controls in all phases of bipolar disorder, including euthymia, with no differences in levels between mood states [89]. Loch et al. also reported increased plasma levels of both NT-3 and NT-4/5 in acutely depressed BD subjects compared to healthy controls; however, they did not find significant differences in NT-3 and NT-4/5 levels after lithium treatment [90]. Contrary to other reports, Barbosa et al. reported decreased NT-4/5 plasma levels in BD patients with mania in comparison with controls without significant differences in NT-3 plasma levels between BD patients and controls [91].

Other growth factors

Glial-derived growth factor (GDNF, a member of the TGFβ growth factor family) levels are increased in cultured glial cells when chronically exposed to antidepressants [92], valproate [93,94], and antipsychotics [95], suggesting that GDNF may be altered by psychotropic medications. This raises the possibility that GDNF levels may serve as a predictor of treatment response, that GDNF may be a biological mediator of treatment response, or perhaps both. However, results regarding GDNF levels in BD patients have been variable, which may be partially attributable to fewer studies addressing this growth factor, as well as small sample sizes. Takebayashi and colleagues observed lower whole blood GDNF levels in both euthymic and "partially remitted" bipolar disorder subjects, independent of both lithium and antidepressant treatment, suggesting that GDNF levels did not correspond to specific treatments [96]. However, no patients in that study were medication-free, and therefore, no conclusions can be drawn about whether GDNF was lower secondary to medication or illness. Another study in a Chinese Han population found that serum GDNF concentrations were reduced in unmedicated BD patients in both depressive or manic episodes compared to healthy controls, and GDNF levels increased with 8 weeks of medication treatment [97]. In the Zhang et al. study, medications included mood stabilizers, antipsychotics, and antidepressants; no specific conclusions could be drawn about the effect of any specific medication class compared to another. More recently, Tunca and colleagues found no correlation between serum GDNF concentrations and either mood state or medication response in a mixed sample of BD-I and BD-II patients, though serum lithium levels in patients did predict higher serum GDNF levels in mania and lower levels in euthymia [49]. Interestingly, in a very small sample of bipolar depressed patients, lower serum levels of GDNF were correlated with poor ECT response, and ECT-triggered switch into mania was correlated with higher serum GDNF levels after treatment [98]. The variability in results regarding GDNF levels may be related to genetic factors, differences in methods for detecting and quantitating levels (although most used ELISA for serum samples), and medication effects on GDNF (not all patients in all studies were taking similar medications at similar doses).

Vascular endothelial growth factor (VEGF) has been previously implicated in the pathophysiology of mood disorders and is believed to be the target of several antidepressants. In cultured lymphocytes from healthy controls, both lithium and valproate treatment downregulated VEGF-A expression [99]. Similarly, Kikuchi et al. reported that VEGF mRNA levels are decreased in leukocytes of lithium-treated bipolar patients compared with unmedicated healthy controls, and the authors suggested that VEGF mRNA expression may be useful as a peripheral marker of the effects of lithium [100]. However, because there was no comparison with VEGF levels in unmedicated bipolar patients, or patients on other types of medication, a nonspecific effect of lithium on leukocyte VEGF levels can't be ruled out based on either of these studies. Liu and colleagues investigated the levels of many growth factors in a relatively large sample of unmedicated manic patients, and found that VEGF levels were not different between unmedicated manic patients and controls, though levels of nerve growth factor (NGF), fibroblast growth factor 2 (FGF-2), and insulin-like growth factor 1 (IGF-1) were elevated in mania [101]. Given the lack of published data scrutinizing differences in VEGF between treated and untreated bipolar patients, more work is required to determine if peripheral VEGF is linked to treatment administration, response, or outcomes.

Transforming growth factor beta 1 (TGFβ1) is the growth factor for which the TGFβ superfamily of ligands was named; this superfamily includes not only TGFβs, but also activins, bone morphogenic proteins (BMPs), and anti-müllerian hormone, among others. These growth factors are critical in a wide variety of cellular functions including cell growth, differentiation, apoptosis, and embryogenesis. There is relatively little known about how it may function in mood disorders, but postmortem studies suggest TGFβ1 may be downregulated in frontal cortex in bipolar disorder [102]. However, the few studies investigating peripheral TGFβ1 levels in bipolar disorder have yielded disparate results. Kim et al. [103] reported that plasma TGFβ1 levels were significantly lower in manic patients, and increased significantly after mood stabilizer treatment. However, Li et al. reported that plasma TGFβ1 concentrations were initially higher in manic patients who went on to respond to lithium plus quetiapine combination treatment, and that TGFβ1 levels decreased in those same individuals with treatment [104]. Lee et al. reported that no relationship between TGFβ1 levels and clinical response to treatment with open-label valproate with or without adjunctive medications [105]. In many of these studies, TGFβ1 levels did not correlate with clinical outcome measures, which may be due to small sample sizes and lack of statistical power, or it may be that TGFβ1 levels are influenced by medications regardless of efficacy.

Overall, there is great appeal in the idea of using serum growth factors as biomarkers for treatment response (Table 1), but their clinical predictive value is still unknown. The most well-studied is BDNF, which does appear to vary with both mood state and treatment, and it is possible that a few well-designed clinical trials could clarify whether it can be used for prognostic or treatment planning purposes. Other growth factors, such as GDNF, VEGF, and TGFβ1, are of interest as well but there are too few data at this point to suggest whether any of these will prove to be clinically useful.

Table 1
Growth factor changes in bipolar disorder with a focus on treatment response. Many growth factors are altered in bipolar disorder mood episodes, as well as in euthymia. Studies that analyzed growth factor changes before and after specific treatment in the same subject group are marked with an asterisk.

Growth factor	Study	Subjects	Source	Treatment	Result		Notes
					Mania	Depression	
Supports Biomarker for Treatment Response							
BDNF	[52]	BD-I patients (32 manic, 21 depressed, 32 euthymic); 32 HC	Serum	Mood stabilizers, antipsychotics, benzodiazepines, antidepressants (clinician's choice)	↓ in episode	↓in episode	BDNF levels in euthymic patients were comparable to levels in HC
BDNF*	[63]	BD-I (n = 10) and BD-II (n = 4) in depressed episode	Plasma	Antidepressants or mood stabilizers (baseline meds) ± atypical antipsychotic augmentation (intervention)		↑BDNF in responders but not in non-responders	Only 6 patients responded to atypical antipsychotic augmentation intervention
BDNF	[98]	BD-I and II patients (33 manic, 26 depressed, 37 euthymic), 61 HC	Serum	Lithium, valproate, or atypical antipsychotics	↓BDNF during mania compared to euthymia; BDNF in euthymia is not different from HC	↓BDNF during depression	Lithium doses differed between groups (manic > depressed > euthymic), but lithium blood levels did not correlate with dosages (euthymic > manic > depressed); Lithium level correlated with BDNF; not assessed in same subjects pre- and post-treatment
BDNF*	[282]	BD patients (n = 64; 46 BD-I and 18 BD-II or BD-NOS; 19 manic, 16 mixed, 29 depressed at study entry); 64 HC	Serum	Quetiapine XR open-label monotherapy trial OR clinicians-choice treatment (lithium, valproate, antidepressants, benzodiazepines)	No change in BDNF with treatment; baseline BDNF was higher in non-responders compared with responders and controls; baseline BDNF was a predictor of clinical response in multivariate regression model		Did not report results stratified by mood episode at study entry; BDNF was consistently lower in clinician's choice arm compared to quetiapine arm
BDNF	[283]	BD-I (39 manic, 24 depressed), MDD (n = 40), 78 HC	Serum	Mood stabilizer, antipsychotic, or antidepressant, alone or in combination	↓BDNF compared to HC	↓BDNF compared to HC	Bipolar depressed and unipolar depressed patients were combined into one "depressed" group; BDNF level did not correlate with medication class but did negatively correlate with YMRS and HAMD
BDNF*	[61]	Pediatric drug-naïve BD-I in mixed/manic episode (n = 26); 21 HC	Lymphocytes	8 weeks mood stabilizer (lithium or valproate) or atypical antipsychotic	↓BDNF at baseline compared to HC; BDNF normalized after treatment		Change in BDNF level with treatment correlated with change in YMRS score
BDNF*	[284]	BP (most likely BP-I) n = 14; drug-free	Plasma	Mood stabilizers (lithium or "other"), typical and atypical antipsychotics (clinician's choice) for one year	↓BDNF at onset of first psychotic episode, and ↑BDNF with treatment		Subjects in study presumed BP-I because they were recruited during a first psychotic episode; study did not state whether patients were manic or depressed
BDNF	[285]	BD-I (n = 280); 288 HC	Peripheral blood genomic DNA	Lithium or valproate monotherapy	miR-206 SNP in combination with a BDNF SNP correlated with ↓ treatment response to mood stabilizers		Treatment response was assessed retrospectively with medical records; did not report data stratified by mood episode/valence
BDNF*	[286]	BD-II, depressed episode (n = 232)	Lymphocyte DNA	Open label valproate (500–1000 mg/day) with randomized placebo-controlled memantine (5 mg/day)	Val66Met patients had reduced response to add-on memantine (assessed by HAMD scores)		Patients were diagnosed with BD-II after only 2 days of hypomania instead of the standard 4-day criterion
TGFβ1*	[104]	BP-I manic n = 41 (28 drug-naïve, 13 drug-free); HC 36	Plasma	8 weeks of lithium (titrated to serum level ⩾ 0.6 mmol/L) plus quetiapine (600–750 mg/day); permitted short-acting benzodiazepine as needed	↑TGFβ1 baseline levels in treatment responders		26/41 patients achieved remission
NT-3*	[287]	Patients in depressed episode (2 BD, 9 MDD, 4 MDE)	Serum	Unilateral ECT or medication (venlafaxine or mirtazapine for an average of 4 weeks)		NT-3 did not change with unilateral ECT, and did not differ from medication management alone; NT-3 levels did correlate with HAMD score at discharge	Data from different mood disorder diagnoses were not separated in paper
GDNF	[283]	BD-I (39 manic, 24 depressed), MDD (n = 40), 78 HC	Serum	Mood stabilizer, antipsychotic, or antidepressant, alone or in combination	↑GDNF compared to HC	No change	Bipolar depressed and unipolar depressed patients were combined into one "depressed" group; GDNF level did not correlate with any

(*continued on next page*)

Table 1 (*continued*)

Growth factor	Study	Subjects	Source	Treatment	Result		Notes
					Mania	Depression	
							specific medication class in BD subjects
GDNF*	[97]	BD-I (22 manic, 18 depressed), 50 HC; subjects unmedicated for 2–5 weeks prior to study	Serum	Medications included mood stabilizers, antipsychotics, antidepressant (specific names not specified), 8-week treatment period	↓GDNF in mania, which normalizes within 8 weeks of treatment	↓GDNF in depression, which normalizes within 8 weeks of treatment	No specific information provided about numbers of patients on each medication class, but GDNF levels didn't vary with medication class; in general, YMRS scores decreased in manic subjects and HAMD decreased in depressed subjects
VEGF*	[288]	Patients in depressive episode (21 MDD, 13 BD), off antidepressants at study start	Plasma	Medications included antidepressants, mood stabilizers, hypnotics, anxiolytics, and/or antipsychotics in 4-week period		No significant differences in VEGF with treatment group or response, but there was a trend toward ↑baseline VEGF in non-responders	In regression analysis, baseline VEGF was a predictor of post-treatment MADRS score
Does Not Support Biomarker for Treatment Response							
BDNF	[53]	24 euthymic MDD (3 on meds), 17 euthymic BD-I (6 on meds), 11 euthymic BD-II (2 on meds), 11 MDD in episode (4 on meds), 22 HC	Serum	BD patients were on lithium, valproate, or carbamazepine	↓BDNF levels compared to HC, independent of medication	↓BDNF levels compared to HC, independent of medication	Most subjects were untreated; not assessed in same subjects pre- and post-treatment
BDNF*	[289]	BD patients in manic episode (n = 68); 30 HC	Serum	Haloperidol (10–30 mg/day) plus quetiapine (100–900 mg/day) (n = 46) OR above regimen plus ECT (n = 22)	↓BDNF levels in mania at baseline; ↓BDNF further after ECT; nonsignificant ↓BDNF with medication alone		BDNF levels not related to actual treatment response
BDNF*	[290]	BD patients (manic n = 12; depressed n = 6); 20 HC	Plasma	Risperidone 2–6 mg/day	No difference between BDNF levels at baseline or with treatment compared to HC	BDNF levels were lower at baseline in depressed patients, did not increase with treatment	Risperidone had no effect on BDNF levels
BDNF*	[67]	BD-I manic patients (n = 26); 56 HC	Serum	4 weeks of mood stabilizer (lithium (n = 9) or valproate (n = 12)) ± antipsychotic (typical or atypical); could also receive lorazepam or zolpidem	No difference in baseline BDNF compared to HC, no change in BDNF with treatment		20 patients were classified as treatment responders
BDNF*	[291]	BD-I manic episode (n = 116); 123 HC	Medium from whole blood cultures	Mood stabilizers (lithium, valproate) and/or antipsychotics (clinician's choice)	No difference in BDNF at baseline compared to HC, no change after treatment		Majority of patients were drug-naïve or drug-free at study start
BDNF*	[292]	BD (type not specified) n = 25, depressed, one-week off antidepressants prior to study	Serum	Single ketamine infusion (0.5 mg/kg); subjects maintained on home regimens of mood stabilizers and/or antipsychotics		Ketamine responders had no change in BDNF (did not compare baseline levels to a control population)	Approximately 50% of patients were classified as ketamine responders; ↓BDNF after infusion in nonresponders
BDNF*	[287]	Patients in major depressive episode (2 BD, 9 MDD, 4 MDE)	Serum	Unilateral ECT or medication (venlafaxine or mirtazapine for an average of 4 weeks)		No change with unilateral ECT, and also did not differ from medication management alone	Data from different mood disorder diagnoses were not separated in paper; BDNF level did not correlate with treatment response
BDNF*	[293]	BD-II depressed episode (n = 117), all medication-naïve	Plasma	12-week open-label treatment with valproate 500–1000 mg/day		↓BDNF with treatment, but did not correlate with treatment response (assessed by YMRS and HAMD)	Patients were diagnosed with BD-II after only 2 days of hypomania instead of standard 4-day criterion
BDNF	[237]	BD-I (n = 49; 9 euthymic, 16 depressed, 21 manic/hypomanic, 3 mixed), BD-II (n = 45; 22 euthymic, 17 depressed, 4 hypomanic, 1 mixed); 52 HC	Peripheral blood mononuclear cells	Most patients were on mood stabilizers, atypical antipsychotics; small group of patients were on gabapentin, pregabalin, and/or antidepressants (SSRI, SNRI, TCA)	↓BDNF promoter methylation when manic/hypomanic/mixed patients were grouped (driven mostly by BD-II group)	No difference in BDNF promoter methylation	No statistical differences noted when stratified by mood episode valence unless BD-I and BD-II groups were combined; did not report whether promoter methylation was related to treatment outcome/response

TrkB*	[67]	BD-I manic patients (n = 26); 56 HC	Serum	4 weeks of mood stabilizer (lithium (n = 9) or valproate (n = 12)) ± antipsychotic (typical or atypical); could also receive lorazepam or zolpidem	No baseline difference in TrkB overall compared with HC; no change in TrkB with treatment		TrkB was higher in mania in females at baseline
NT-3*	[292]	BD (type not specified) n = 25, depressed episode, one-week off antidepressants prior to study	Serum	Single ketamine infusion (0.5 mg/kg); subjects maintained on home regimens of mood stabilizers and/or antipsychotics		No change with treatment (did not compare baseline levels to a control population)	Approximately 50% of patients were classified as ketamine responders
NT-3	[86]	BD-I (n = 10 in each group: unmedicated manic, unmediated depressed, medicated manic, medicated depressed); 20 HC	Serum	Mood stabilizers (90% of patients), antipsychotics (70%), antidepressant (30%)	↑NT-3 in mania compared to HC, which did not differ between medicated and unmedicated subjects	↑NT-3 in depression compared to HC, which did not differ between medicated and unmedicated subjects	HAMD and YMRS scores were not different between unmedicated and medicated patients; suggests possibly all subjects were treatment nonresponders
NT-3	[91]	BD-1 (manic n = 22, euthymic n = 18); 25 HC	Plasma	Lithium, anticonvulsants, atypical antipsychotics	No difference in NT-3 levels between BD (manic or euthymic) and HC		NT-3 levels were not associated with any specific medication class nor YMRS/HAMD score
NT-3*	[90]	BD-I depressed episode (n = 8); BD-II depressed episode (n = 15); all subjects unmedicated; HC = 28	Serum	Lithium (450–900 mg/day)		↑NT-3 at baseline compared to HC, did not change with lithium treatment	NT-3 levels did not correlate with clinical response as assessed by HAMD
NT-4*	[292]	BD (type not specified) n = 25, depressed, one-week off antidepressants prior to study start	Serum	Single ketamine infusion (0.5 mg/kg); subjects maintained on home regimens of mood stabilizers and/or antipsychotics		No change with treatment (did not compare baseline levels to a control population)	Approximately 50% of patients were classified as ketamine responders
NT-4/5	[89]	BD-I (manic n = 54, depressed n = 61, euthymic n = 39); 30 HC	Serum	Lithium, other mood stabilizers, antipsychotics, antidepressants, benzodiazepines	↑NT-4/5 regardless of medication class, not different from euthymia	↑NT-4/5 regardless of medication class, not different from euthymia	NT-4/5 levels similar across all mood states in BD patients, which was higher than HC; no differences between pts. on different meds
NT-4/5	[91]	BD-1 (manic n = 22, euthymic n = 18); 25 HC	Plasma	Lithium, anticonvulsants, atypical antipsychotics	↓NT-4/5 levels mania compared to HC, no difference in NT-4/5 in mania compared to euthymia		NT-4/5 levels were not associated with any specific medication class nor YMRS/HAMD score
NT-4/5	(90)	BD-I depressed episode (n = 8); BD-II depressed episode (n = 15); all BD subjects unmedicated; 28 HC	Serum	Lithium (450–900 mg/day)		↑NT-4/5 at baseline compared to HC, no change with lithium treatment	NT-4/5 levels did not correlate with clinical response as assessed by HAMD
GDNF	[96]	BD-1 (n = 9); BD-II (n = 8); 56 HC	Total blood GDNF	Antidepressants and/or mood stabilizers (clinician's choice)	↓GDNF in BD patients compared to HC despite most patients being in remission		Data not stratified by mood episode valence; GDNF level was not associated with antidepressants or lithium
GDNF*	[292]	BD (type not specified) n = 25, depressed, one-week off antidepressants prior to study start	Serum	Single ketamine infusion (0.5 mg/kg); subjects maintained on home regimens of mood stabilizers and/or antipsychotics		No change with treatment (did not compare baseline levels to a control population)	Approximately 50% of patients were classified as ketamine responders
GDNF	[49]	BD-I and II patients (33 manic, 26 depressed, 37 euthymic), 61 HC	Serum	Lithium, valproate, or atypical antipsychotics	GDNF does not vary across mood states	GDNF does not vary across mood states	Lithium doses differed between groups (manic > depressed > euthymic), but lithium blood levels did not correlate with dosages (euthymic > manic > depressed); not assessed in same subjects pre- and post-treatment; Lithium level correlated negatively with GDNF level

(*continued on next page*)

Table 1 (*continued*)

Growth factor	Study	Subjects	Source	Treatment	Result		Notes
					Mania	Depression	
TGFβ1*	[105]	BP-II (n = 117), drug-naïve	Plasma	12 weeks of open-label valproic acid (500–1000 mg daily) with lorazepam (⩽8 mg/day) or fluoxetine (⩽20 mg/day)	No relationship between TGFβ1 and treatment response as assessed by HAMD and YMRS		Did not report numbers of patients by mood valence
TGFβ1 and TGFβ2	[96]	BD-1 (n = 9); BD-II (n = 8); 56 HC	Blood	Antidepressants and/or mood stabilizers (clinician's choice)	Total blood TGFβ1 and TGFβ2		No difference between TGFβ1 and TGFβ2 levels between BD subjects and HC
All		patients were in partial or full remission; Data not stratified by mood episode valence; TGFβ1 and TGFβ2 levels not associated with antidepressants or lithium					
Biomarker Inconclusive for Treatment Response							
BDNF*	[62]	BD-I manic patients (n = 10); HC n = 10	Serum	Lithium with or without antipsychotic; benzodiazepines and ECT also included	↓BDNF levels at baseline, which ↑ after treatment	n/a	All treatment responders had ↑BDNF post-treatment; however, authors stated BDNF level itself did not correlate with improvement in YMRS, HAMD, GAF
BDNF*	[65]	BD patients (n = 25; 17 depressed and 8 manic/mixed)	Serum	Open-label quetiapine XR 300 mg/day	↓ after treatment (in manic and mixed episodes)	↑ after treatment	BDNF levels did not correlate with treatment response (assessed by CGI, HAMD, YMRS)
BDNF*	[46]	BD-I manic patients (n = 10)	Plasma	Lithium monotherapy (4 weeks)	↓BDNF levels in mania at baseline which ↑ after treatment		Change in BDNF did not correlate with YMRS score
BDNF*	[294]	BD-I or BD-II (n = 309, included manic and depressed patients); 123 HC	Plasma	Valproate (open-label) ± dextromethorphan (randomized/blinded); other meds allowed included lorazepam, risperidone, fluoxetine, anticholinergics	↑BDNF levels in higher dose dextromethorphan group, which did not correlate with treatment response as assessed by YMRS or HAMD scores		Did not differentiate between mood episodes or diagnoses in data reporting
TGFβ1*	[103]	BP-I mania (n = 70), drug-naïve or medication-free at least 4 months; 96 HC	Plasma	8 weeks of medication (lithium, valproate, typical or atypical antipsychotics, or combination thereof)	↓TGFβ1 at baseline, and ↑TGFβ1 after treatment		TGFβ1 levels did not correlate with YRMS or BPRS

Abbreviations: BD-I = bipolar disorder type I; BD-II = bipolar disorder type II; BDNF = brain-derived neurotrophic factor; BD-NOS = bipolar disorder not otherwise specified; CGI = Clinical Global Impression; ECT = electroconvulsive therapy; ELISA = enzyme-linked immunosorbent assay; GAF = global assessment of functioning; GDNF = glial-derived growth factor; HAMD = Hamilton Depression Rating Scale; HC = healthy control; HDL = high-density lipoprotein; HgA1c = hemoglobin A1c; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; MDE = major depressive episode; miR = micro-RNA; NT-3 = neurotrophin-3; NT-4 = neurotrophin-4; OCD = obsessive compulsive disorder; PCR = polymerase chain reaction; qPCR = quantitative polymerase chain reaction; rtPCR = real-time polymerase chain reaction; SAD = schizoaffective disorder; SCZ = schizophrenia; SNP = single nucleotide polymorphism; SNRI – selective norepinephrine reuptake inhibitor; SSRI – selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TrkB = tropomyosin-related kinase B; XR = extended release; YMRS = Young Mania Rating Scale.

Energy metabolism

Mitochondrial dysfunction

Mitochondrial energy production via oxidative phosphorylation is essential to meet the brain's high demands for energy. Some of the earliest suggestions that mitochondrial dysfunction occurs in BD came from magnetic resonance spectroscopy (MRS) studies of BD patients. These demonstrated increased phosphomonoesters in the frontal regions of manic patients, which were attributed to accumulations of inositol monophosphate, suggesting altered energy metabolism [106]. Further studies have expanded on these observations and have provided additional evidence that BD is associated with mitochondrial dysfunction [107–111]. A reduction in complex I activity in the mitochondrial electron transport chain (ETC) causes increased production of reactive oxygen species [112], leading to increased oxidative stress [113]. Mertens et al. reported an upregulation in mitochondrial gene expression in hippocampal dentate gyrus-like neurons derived from iPSCs of patients with bipolar disorder relative to healthy controls, even though mitochondria were observed to be approximately 60% smaller in bipolar samples. Treatment with lithium significantly down-regulated several mitochondrial genes and also increased mitochondrial size [114], suggesting that lithium might be diminishing the hyperactivity of bipolar neurons. An analysis of mitochondrial complex I obtained from postmortem PFC of bipolar patients found increased protein levels of 24-kDa and 51-kDa subunits relative to controls. This might be expected in hyperactive tissues; however, the mitochondrial complex I subunits were not affected by antipsychotic treatment in a pooled sample of schizophrenic and bipolar subjects [110]. Another study found decreased mitochondrial gene expression in hippocampal tissue from bipolar patients compared to controls, but was unable to establish whether the down-regulation was secondary to antipsychotics or mood stabilizers [115]. Whether mitochondrial dysregulation contributes to or is a consequence of BD remains to be clarified.

Oxidative stress

Oxidative stress is a disturbance in the equilibrium between production of reactive oxygen species and cellular capacity to remove these oxygen species or repair the damage they cause. Growing evidence suggests that oxidative stress plays an important role in the pathophysiology of BD [116,117]. Oxidative stress alters multiple cell functions, including increasing intracellular lipid peroxidation. Byproducts of this lipid degradation include thiobarbituric acid reactive substances (TBARS) which can serve as a measure of the damage of oxidative stress. A meta-analysis

Table 2
Studies of energy metabolism biomarkers for treatment response in bipolar disorder.

Biomarkers	Reference	Sample Source	Population (n)/Age/Sex	Treatment response
S100B TBARS SOD GSH-Px CAT	[119]	Human serum	Bipolar N = 84 Mania N = 32 (56.3%); 40.1 ± 12.6 Depression N = 21 (35.0%); 43.4 ± 8.0 Euthymic N = 31 (62.5%); 40.3 ± 11.3 Controls N = 32 (34.4%); 40.7 ± 12.1	S100B elevated in depression and mania; SOD elevated in depression and mania; GSH-Px elevated in euthymia; TBARS elevated in depression, mania, euthymia. No difference in S100B levels regardless of lithium treatment
NO SOD	[120]	Human serum	Bipolar Mania N = 29 (48.3%); 33.1 ± 9.6 Controls N = 30 (46.7%); 29.73 ± 7.24	No significant difference of NO or SOD between treatment groups, (ECT vs. non-ECT, atypical antipsychotics vs. non-atypical antipsychotics, mood stabilizers vs. non-mood stabilizers, classical antipsychotics vs. non-classical antipsychotics) at 1st and 30th days
NO SOD	[122]	Human serum	Bipolar Depressed N = 29 (48.3%); 32.79 ± 12.16 Controls N = 30 (53.3%); 29.73 ± 7.24	NO levels normalize with treatment (ECT, antidepressant); SOD levels increase with treatment (ECT, antidepressant)
TBARS SOD CAT NSE	[125]	Human plasma	Bipolar Manic N = 45 Unmedicated N = 30 (76.7%); 26 ± 4 Lithium N = 15 (73.3%); 26.2 ± 6 Controls N = 30	Acute treatment with lithium showed a significant reduction in both SOD/CAT ratio and TBARS levels
SOD GSH-Px CAT MDA NO	[126]	Human erythrocytes	Psychiatric inpatients N = 30 (46.7%); 39.8 ± 13.1 Bipolar type I N = 18 (16 manic, 2 depressed) MDD N = 6 Schizoaffective bipolar subtype N = 6 Controls N = 21	"Treatment as usual" caused no change in erythrocyte CAT or SOD or NO, or MDA, but GSH-Px increased almost to normal
mRNA and protein levels of the 24-kDa and 51-kDa subunits of ETC complex I	[110]	Human postmortem samples	Bipolar N = 15 (40%); 42.3 ± 11.7 MDD N = 15 (40%); 46.4 ± 9.3 Schizophrenia N = 14 (42.9%); 45.6 ± 12.9 Controls N = 15 (40%); 48.1 ± 10.7	Medication did not affect the significance between the groups in mRNA and in protein levels in the prefrontal or ventral parietooccipital cortices
Neuroanatomical Pattern of Mitochondrial Complex I Pathology	[295]	Human Postmortem samples	Bipolar N = 15 (40%); 42.3 ± 11.7 Schizophrenia N = 15 (40%); 44.5 ± 13.1 MDD N = 15 (40%); 46.4 ± 9.3 Controls N = 15 (40%); 48.1 + -10.7	No significant difference was observed between the two subgroups in mRNA or protein levels comparing no antipsychotic (8 bipolar/3 schizophrenic) with antipsychotic (7 bipolar/12 schizophrenia)

Abbreviations: thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT), nitric oxide (NO), neuron-specific enolase (NSE), glutathione peroxidase (GSH-Px), malondialdehyde (MDA).

of oxidative stress markers (TBARS and nitric oxide) and antioxidant enzymes in 16 studies of BD patients [118] found significantly increased TBARS and nitric oxide (NO), suggesting pronounced oxidative damage in BD, without significant change in levels of antioxidant enzymes. These findings were corroborated by other studies demonstrating elevated TBARS in BD patients during manic [87,119], depressive [87,119], and euthymic states [119]. They suggested that damage to lipid structures from oxidative stress may be consistent throughout the course of BD.

Other laboratories reported increased levels of the oxidant nitric oxide (NO) in BD patients, associated with different mood states and treatments. Serum levels of NO and the protective enzyme superoxide dismutase (SOD) were measured in BD patients over 30 days of inpatient treatment for mania [120]. Significant elevations of NO and reductions of SOD activity in bipolar patients were observed. Other studies have replicated significant increases in plasma NO during manic episodes [121]. These same significantly elevated NO levels and decreased SOD levels have been noted in serum from depressed BD patients during inpatient treatment [122], and also in euthymic BD patients [123]; the level of serum NO positively correlated with the number of past episodes of mania. These findings reinforce the hypothesis that oxidative stress mechanisms are altered across all mood states in BD, and that NO might be a biomarker for BD, though its usefulness is hampered by assay difficulties.

Oxidative stress pathways may be altered by pharmacological treatment. A case study of bipolar twins compared oxidative stress markers in the presence and absence of pharmacological mood stabilization, and found that after six weeks of treatment, TBARS and SOD returned to healthy control levels, but remained unchanged in the untreated twin [124]. The effect of lithium mood stabilization on reducing oxidative stress biomarkers (TBARS and SOD) has been confirmed in a larger study of manic patients [125]. Pharmacological treatment has also been shown to improve blood levels of glutathione peroxidase (GSH-Px) following treatment for mood episodes in BD patients [126].

In summary, several putative energy metabolism biomarkers for treatment response have been proposed (Table 2). Oxidative stress is both implicated in, and affected by, inflammation. This is important because inflammatory markers are more easily measured biomarkers which could be used to follow treatment response, assess disease severity, or act as prognostic indicators. Oxidative stress is postulated to activate redox-sensitive transcription factors, which then increase expression of genes related to inflammation, such as those encoding cytokines, which themselves have intercellular signaling effects [127].

Inflammatory markers

Cytokines

Cytokines are proteins associated with the immune system and both pro-inflammatory and anti-inflammatory cytokines have been characterized. Pro-inflammatory cytokines have also been intensively studied in recent decades in major depression and to a lesser extent in bipolar disorder. In MDD, the majority of studies have reported increases in peripheral concentrations of proinflammatory cytokines [128–132]. Concentrations of cytokines in various phases of bipolar disorder, including mania, depression and euthymia have been studied [87,133–138].

There are several studies that have evaluated various inflammatory markers in relation to treatment response in bipolar disorder (Table 3). The limitations of these studies include a limited number of patients per study and not all studies evaluated the same inflammatory markers. In one of the studies, Kim and colleagues [134] found that elevated levels of IL-6 were only increased in the acute manic phase and these levels subsequently decreased after 6 weeks of using a mood stabilizer (either lithium, valproate sodium, or a combination of both). This same group found that IL-12 levels also decreased significantly for those with bipolar disorder after 8 weeks of either lithium or valproate sodium [139].

Su and colleagues also evaluated lithium treatment response, but they focused on interferon-gamma (IFN-ɣ) and IL-10. They did not find any difference in IFN-ɣ or IL-10 levels in patients who had been medicated with lithium compared to those who were unmedicated [140]. Boufidou and colleagues investigated cytokine production in isolated peripheral blood lymphocytes in 40 euthymic bipolar patients maintained on chronic lithium treatment. However, unlike Su, they found a significant reduction in the number of cells that secreted IL-2, IL-6, IL-10 and interferon (IFN)-ɣ in those taking lithium compared to healthy controls [141].

Guloksuz and colleagues also studied bipolar patients treated with lithium and found increased levels in TNF-α and IL-4 in euthymic bipolar patients treated with lithium, but no differences in TNF-α levels were found in medication free euthymic bipolar patients compared to healthy controls [142]. Hornig and colleagues evaluated transferrin (TFN), a negative acute phase protein, but

Table 3
Studies of inflammatory markers regarding treatment response in bipolar disorder.

Study	Biomarker	Population: N/sex/age	Treatment	Treatment Response
[134]	IL-2, IL-4, IL-6, TNF-α, IFN-γ	37 BD patients in mania/ 14 M, 23 F/37.8 ± 12.0	Lithium, valproate sodium	After 6 weeks of treatment, levels of IL-6 were significantly decreased. No significant changes in IL-2, IL-4, TNF-α, IFN-γ.
[141]	IL-2, IL-6, IL-10, IFN-γ	40 BD patients in euthymia/ 20 M, 20 F/42.8 ± 14.7	Lithium	Patients with chronic lithium treatment had decreased IL-2, IL-6, IL-10, IFN- γ versus healthy controls.
[139]	IL-12	25 BD/12 M, 13 F/28.6 ± 8.0	Lithium, valproate sodium	After 8 weeks, IL-12 values decreased significantly for those with bipolar disorder.
[140]	IFN-γ, IL-10	20 BD/8 M, 12 F/31.7 ± 9.9	Lithium	No significant changes in IFN-γ or IL-10.
[144]	IL-2, IL-4, IL-6, Il-10, IFN- γ, sIL-2R, sIL-6R	17 BD patients with rapid cycling/8 M, 9 F/38.8 ± 13.0	Lithium	Rapid cycling BD patients had increased sIL-2R and sIL-6R, which normalized with lithium treatment after 30 days.
[143]	CRP, TFN	79 BD-I/36 M, 43 F/ 51.5 ± 14.3 24 BD-II/6 M, 18F/ 42.3 ± 13.0	Lithium	Elevated CRP was less likely in those with lithium monotherapy as well as those taking lithium and an antidepressant. No significant changes in TFN levels.
[145]	IL-6, sIL-6R, sIL-2R	10 BD patients in mania/3 M, 7 F/40.5 ± 13.4	Valproate	No significant change in IL-6, sIL-6R, sIL-2R with valproate treatment.

*Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; sIL-2R, soluble IL-2 receptor; soluble IL-6 receptor; CRP, C-reactive protein; TFN, transferrin.

found there was no change in TFN levels when patients were treated with lithium. However, they did find that patients taking lithium were less likely to have an elevated C-reactive protein (CRP) [143].

Two studies evaluated the soluble IL-2 (sIL-2R) and IL-6 (sIL-6R) receptors. Patients with rapid cycling bipolar had normalization of the sIL-2R and sIL-6R levels with the use of lithium treatment after 30 days [144]; however, no significant change was detected following treatment with valproate [145].

Human leukocyte antigen (HLA)

The HLA system consists of numerous genes that are responsible for encoding proteins that reside on the surface of cells in the body. These genes and their proteins are responsible for regulating the immune system. Over the last three to four decades, there has been interest of how antigens associated with the HLA system may be markers for affective disorders, including bipolar disorder and unipolar depression.

Unfortunately, studies to date have shown mixed results and the ability to replicate positive findings has been minimal. Bersani et al. found an increased frequency of HLA-B37 in those with bipolar disorder; however, this result lost significance when accounting for multiple comparisons. Shapiro et al. found increased frequencies in HLA-A3, HLA-Bw16, and HLA-B7 in a bipolar sample [146,147]. However, Beckman et al. found decreased frequencies of HLA-B7 in those with bipolar [148]. Smeraldi et al. investigated 91 patients with affective disorders and found that HLA-A29 and HLA-Bw22 frequencies were increased while HLA-A10 and HLA-A30 were decreased in the overall sample compared to controls. However, these frequencies were not different between the unipolar and bipolar patients [149]. Ucok et al. found increased frequencies of HLA-A10, HLA-A29, HLA-B7, HLA-B16, and HLA-B21 in bipolar patients compared to healthy controls [150]. A more recent study using exon microarrays by Morgan et al. found that HLA-DPA1 and CD74 were decreased in the anterior cingulate cortex in patients with bipolar disorder [151]. Overall, more research is needed to better understand how the HLA system may be used as a biomarker for bipolar disorder.

There are a few studies that have investigated HLA type and its association with lithium response. Smeraldi et al. evaluated patients on long-term lithium therapy and found that those with higher frequencies of HLA-B5 had lower rates of relapse [149]. Perris et al. found that increased rates of HLA-A3 were associated with lithium non-response. This finding was replicated by Del Vecchio et al. [152] and Maj et al. [153].

Overall, more research is needed to better understand how cytokines and other inflammatory markers respond to treatment. Current studies are relatively small and have contradictory findings. Confounding factors may include the type of mood stabilizer used for treatment and the phase (mania, depression, or euthymia) in which the patient presents. Future studies with more consistent methodology may help elucidate inflammatory processes in bipolar disorder.

Neuroendocrine markers

Hypothalamic-pituitary-adrenal (HPA) axis

Dysregulation of the hypothalamic-pituitaryadrenal (HPA) axis has been implicated in the pathophysiology of bipolar disorder [154–156], depressive and manic episodes [157–160], suicidal behavior [161–166], and first episode and risk states for psychosis [167–171]. The HPA axis regulates the hypothalamic secretion of corticotropin-releasing hormone (CRH), anterior pituitary secretion of adrenocorticotrophic hormone (ACTH), and adrenocortical secretion of cortisol, which then provides negative feedback at the hypothalamus, pituitary, and higher CNS areas including the hippocampus [172]. It has long been postulated that chronic stress results in HPA hyperactivity due to excessive release of CRH, resulting in failure in the normal negative feedback of cortisol on glucocorticoid receptors (GR) in the hypothalamus and the pituitary, resulting in increased vulnerability to psychiatric disorders [173–175].

Cortisol

Cortisol levels have been proposed as a measure of HPA activity in affective disorders. Single sample or serial measurements of basal cortisol are assumed to capture secretion in the unstressed, resting state. A recent meta-analysis of HPA axis activity in BD was conducted by Belvederi Murri et al., in which 41 case-control studies were compared consisting of 1069 bipolar patients and 1836 healthy controls. The meta-analysis showed that bipolar patients had higher basal cortisol than controls at awakening, morning, afternoon and night hours. Cortisol levels assessed over 12 or 24 h were also significantly higher in bipolar patients than controls [154]. Another meta-analysis comparing 19 case-control studies examining single measures of morning cortisol levels in bipolar patients compared to controls also reported increased morning cortisol levels in BD, with greater morning cortisol levels found in non-manic outpatients [176]. Becking et al. reported that cortisol levels and C-Reactive Protein (CRP) levels were jointly associated with lifetime manic episodes, where depressed men with high levels of both diurnal cortisol slope and CRP had a 5-fold increased odds of having a lifetime (hypo)manic episode compared to men with low levels of both measurements [159]. Elevated bedtime cortisol levels have also been associated with a past history of suicide attempt in bipolar patients [165].

Endocrine challenge tests

Several endocrine challenge tests have been proposed as biomarkers to assess HPA axis in mood disorders. In the dexamethasone suppression test (DST), the synthetic glucocorticoid dexamethasone (Dex) is administered, which suppresses plasma concentrations of adrenocorticotropic hormone (ACTH) and cortisol in healthy subjects. Non-suppression has been frequently reported in unipolar and bipolar depression [177–179], mania [158,180], and suicide risk [181,182]. A meta-analysis of morning post-dexamethasone cortisol levels revealed that patients with BD had significantly higher cortisol levels than controls [154].

The Dex/CRH combination test is believed to be a more sensitive measure of HPA axis activity, reflecting both feed-back and feed-forward mechanisms [183]. Several studies using the combined DEX/CRH test have showed a higher response in ACTH and cortisol levels in BD in mixed medicated and medication-free patients [184–186]. Medications may increase dexamethasone clearance, potentially producing false-positive DST results. For example, Watson et al. found that patients taking carbamazepine had lower dexamethasone levels, higher delta cortisol levels and were more likely to respond to the dex/CRH test than those not taking carbamazepine. However, dexamethasone levels and delta cortisol did not differ based on treatment with CYP3A4-inhibiting drugs, lithium or selective serotonin reuptake inhibitors [184]. Rybakowski and Twardowska showed that the cortisol levels following the DEX/CRH test were significantly elevated in bipolar patients compared with unipolars and control subjects and that a decrease in HPA activity, as measured with the DEX/CRH test before and after the course of antidepressant treatment, may confirm a stabilizing effect of antidepressant treatment [160].

Glucocorticoid receptors

Altered GR signaling has also been reported in BD [187–190], and peripheral blood biomarkers targeting GR proteins and genetic variants [188,191–194], mRNA expression [195–197], or function [155] have been proposed. Other studies suggested that reduced GR function was related to the dysregulation of GR co-factors such as FKBP5/FKBP51, BAG1, PTGES3, and HSP70 [191,198–203].

Thyroid function

Several neuroendocrine markers that measure thyroid function have been proposed as candidate biomarkers for BD. BD patients are 2.55 times more likely to experience thyroid dysfunction than controls [204]. Several studies have reported elevated thyroid-stimulating hormone (TSH) levels [205–207], elevated thyroxine (T4) levels [208–210], as well as an exaggerated TSH response to thyrotropin-releasing hormone (TRH) [211–213]. Wysokinski and Kloszewska reported that patients with bipolar disorder have higher levels of TSH compared to patients with unipolar depression, and that patients with bipolar depression had the highest level of TSH, while the lowest level was found in patients with bipolar mania [207]. Valle et al. reported that in lithium-naive subjects, bipolar II patients have significantly higher TSH levels compared to bipolar I patients [214]. The anti-thyroid effects of lithium have been well documented and may evoke an exaggerated TSH response to TRH [215]. Gyulai et al. studied the response of medication-free rapid-cycling BD patients to thyrotropin-releasing hormone (TRH) compared to controls before and after 4 weeks of lithium treatment. Although baseline thyroid function tests did not differ between patients and controls, patients had significantly higher ΔTSH after TRH stimulation following lithium treatment, suggesting that patients with rapid-cycling BD may be sensitive to the anti-thyroid properties of lithium [216].

Genetic biomarkers

Peripheral gene expression

Alterations of gene expression as potential biomarkers of therapeutic response in BD has been posited. Genetic changes may also help to unravel the etiology of BD. An obvious limitation of peripheral gene expression biomarkers is that gene expression in the brain is not necessarily linked to expression patterns in blood. For example, Middleton et al. reported conflicting directionality of gene expression in lymphocytes compare to brain tissue in BD and SZ [217]. Despite this limitation, there is increasing evidence in the literature that peripheral markers are robust and many are able to produce comparable outcomes to those from postmortem studies. Although gene transcription profiles are not completely concordant between blood and brain, several studies have provided evidence that there are similarities in expression patterns, further supporting the use of whole blood and its components (lymphocytes, peripheral blood mononuclear cells) for the detection of treatment response biomarkers.

The peripheral blood transcriptome shares more than 82% homology with the brain [218]. The peripheral gene expression profiles of several biological processes are equivalent to those seen in the prefrontal cortex [219]. Rollins et al. [220] demonstrated corresponding gene expression between peripheral blood and brain within individuals. Sullivan et al. [219] reported a substantial correlation between peripheral gene expression and CNS gene expression, with roughly half of the genes tested having similar expression in both the periphery and CNS. Peripheral biomarkers are an excellent alternative to traditional tissue biopsy-derived RNA and are the most logical proxy for the brain. Peripheral gene expression profiling has been successfully used to examine treatment response for a variety of genetically complex medical disorders [221–230]. Sugawara et al. studied gene expression changes induced by lithium and valproate in order to elucidate the common molecular effect of therapeutic concentrations of these drugs on lymphoblastoid cell cultures derived from healthy subjects. Genome-wide gene expression profiling identified 44 and 416 genes that were regulated by lithium and valproate, respectively. Eighteen genes were commonly altered by both drugs which include VEGFA, PFDN4, DPY19L2P2, PCMT1, KIAA0947, RNMT, SS18, NF1, SLC35D1, E2F4, PIK3CD, MTF1, FAM21A/B/C/D, VAMP3, C9orf16, IKBKG, STX11, and PSMD1 [99].

Valproic acid is associated with the epigenetic regulation of gene expression through inhibition of histone deacetylase [231,232]. Valproic acid significantly alters DNA methylation [233] Treatment with valproic acid in cultured rat cortical neurons resulted in up-regulation of 726 genes including BDNF and down-regulated in 577 genes including genes involved in the development of GABAergic inhibitory neurons [234]. Another genome-wide gene expression analysis found significant up-regulation of 145 genes and significant down-regulation of Plec1 in Brown Norway rats treated with valproic acid [235]. Wang et al. demonstrated that valproic acid regulates mRNA levels of neuroligin-1 and neuregulin-1 post-synaptic cell adhesion molecules and neuronal pentraxin-1and thrombospondin-3 extracellular matrix molecules in primary rat astrocyte cultures [236]. Treatment with valproate significantly reduces DNA methylation in BDNF promoter [237]. Valproic acid also strongly upregulates sepiapterin reductase (SPR) gene transcription [238]. SPR plays an important role in the biosynthesis of neurotransmitters.

Clelland et al. examined whether the residual effects of antipsychotic and mood stabilizer medication drives peripheral gene expression differences between patients and controls. A peripheral gene expression biomarker panel was developed based on global leukocyte gene expression changes in first-episode and never-medicated BPD patients compared to currently medicated BPD patients and matched healthy controls. The 10-gene model exhibited a diagnostic accuracy of 84% (89% sensitivity and 75% specificity; $p < 0.001$) [239]. Lowthert et al. (2012) reported that 127 genes were differentially expressed in lithium responders versus non-responders in depressed BD patients after 8 weeks of treatment, with an upregulation of apoptosis regulatory genes [240].

Padmos et al. reported that inflammatory gene expression patterns vary with mood state of the patients. During a manic episode, the mRNA expression of *MAPK6* and *CCL2* was significantly increased in monocytes of manic vs. euthymic bipolar patients; during depressive episodes, expression of these mRNAs was raised in addition to increases in *IL6*, *PTX3*, *EMP1*, and *BCL2A1*. Except for *CCL2* and *EMP1*, mRNAs were significantly higher in euthymic bipolar patients compared with healthy controls [137]. Padmos et al. reported a monocyte gene expression signature of 19 atypically expressed genes involved in inflammation and inflammation-related processes in 42 bipolar patients compared to 25 healthy controls. A positive signature test was detected in 55% of the bipolar patients compared to 18% of the healthy controls. Dysregulated gene expression in bipolar patients included inflammatory genes (PDE4B, IL1B, IL6, TNF, TNFAIP3, PTGS2, and PTX3), chemokinesis/-motility genes (CCL2, CCL7, CCL20, CXCL2, CCR2, and CDC42), MAPK pathway genes (MAPK6, DUSP2, NAB2, and ATF3), and the cell survival/apoptosis genes (BCL2A1 and EMP1). All were overexpressed in the monocytes of bipolar patients, except for CCR2 which was under expressed. Lithium and antipsychotic treatment was shown to decrease the expression of most of these inflammatory genes. [137].

Genetic markers of treatment response

Evidence from candidate gene studies

There is abundant evidence that the serotonin-transporter-linked polymorphic region (5-HTTLPR) is a biomarker for antidepressant response. Homozygotes for the long variant (l/l) of the 5-HTTLPR have a better response than homozygotes for the short variant (s/s) to fluvoxamine [241], clomipramine [242], bupropion [243] and pindolol [244]. However, patients carrying the s/s allele in Asian populations reportedly have a better response than the patients carrying the l/l allele in fluvoxamine [245], fluoxetine or paroxetine [244], suggesting ethnic differences in antidepressant response. Several studies suggest that the serotonin-transporter-linked polymorphic region (5-HTTLPR) modulates pharmacological response to lithium [83,246–248]. A prospective study conducted by Serretti et al. reported that subjects with the s/s variant had a worse lithium response compared to those with the l/s or l/l variants [246]. An epistatic interaction between the short (s) 5-HTTLPR allele and the Val/Val genotype BDNF polymorphism were reported in lithium nonresponders compared with responders. [249]. The 5-HTTLPR s allele has also been associated with antidepressant induced mania [250,251], early side effects of risperidone and poorer early response of psychosis symptoms to risperidone [252].

Other candidate genes are promising genetic biomarkers for lithium response in BD. Significant associations have been reported between TPH [253], ACCN1 [254], GSK-3beta [255], and GADL1 [256] genes and lithium response. In addition, a repeat in PLCG1-5 associated with lithium response has been reported in two studies [257,258]. It is important to note that these are relatively small studies. Additional longitudinal studies with larger sample sizes are needed to replicate these findings.

Evidence from genome-wide association studies (GWAS)

Fabbri et al. identified several SNPs associated with long-term treatment outcome in bipolar disorder based on depressive and/or (hypo)manic episode recurrence during follow-up from the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) genome-wide dataset. Notable associations with episode recurrence were found in BD susceptibility genes DFNB31 and SORCS2 as well as novel associations in the TRAF3IP2-AS1, NFYC, DEPDC6 and RNLS genes.

It has long been reported that patients with a good response to lithium treatment also have a positive family history of BD [259], suggesting that underlying genetic factors play a crucial role in lithium response in BD. Song et al. performed genome-wide association studies (GWAS) to identify genetic variants influencing lithium response in BD. Genes implicated in lithium response included genes encoding a neural adhesion molecule (CNTN5), a cell recognition and cell adhesion molecule (NRXN3), and a protein involved in receptor-differentiation, proliferation and apoptosis (NOTCH4). Also implicated were 2 ncRNAs, and 3 intergenic regions. A variant in SESTD1 involved in regulation of phospholipids, a target of lithium treatment, was significantly associated with risk for lithium-responsive BD. Variants in LAMP3 involved in dendritic cell function and adaptive immunity, as well as TCF3 involved in inflammation were also implicated [260]. A previous linkage mapping study provided evidence of lithium response to chromosomal regions 15q14, 7q11.2 as well as suggestive loci on chromosomes 6 and 22 [261]; however, these regions do not overlap with the results reported by Song et al., highlighting a need for further validation and replication in larger longitudinal studies.

Several GWAS have been performed with specific focus on response to serotonin reuptake inhibitors in major depressive disorder [262], response to citalopram treatment [263,264], as well as associated side effects [265,266]. GWAS have also identified genes associated with antipsychotic response to olanzapine (DRD2, SLC26A9, HUNK, GPR137B, ANKS1B) [267], Risperidone (PRKCZ, ZFP90, CNTNAP5, TRPM1) [267,268], Ziprasidone (EHF) [267,268], Quetiapin (MAP3K9, PIO1, ANKs1B, ADGRL3, ANKRD33) [268] and response to haloperidol in psychosis (EIF2AK4) [269]. Gene associations of side effects including metabolism of psychotropic drugs [270], tremors caused by antipsychotics [271], metabolic side effects [272], and QT prolongation [273] have also been identified. While these results are potentially applicable to treatment response for BD, these results must be evaluated and validated specifically in BD patients.

Epigenetic biomarkers

Epigenetic modifications have been proposed as biomarkers for treatment response in BD [274–278]. Lee et al. reported alterations in histone H3 methylation and acetylation in the leptin receptor gene (Lepr) following Li and VPA treatment in Brown Norway rats [235]. An investigation of VPA treatment in a rat serotonergic cell line (RN46A) revealed an upregulatory effect of the sepiapterin reductase (SPR) gene involved in the tetrahydrobiopterin (BH4) synthetic pathway. BH4 is an essential cofactor for neurotransmitter biosynthesis. VPA treatment increased the acetylated histone mark H3K9/K14ac at the Spr promoter [238]. Future studies are

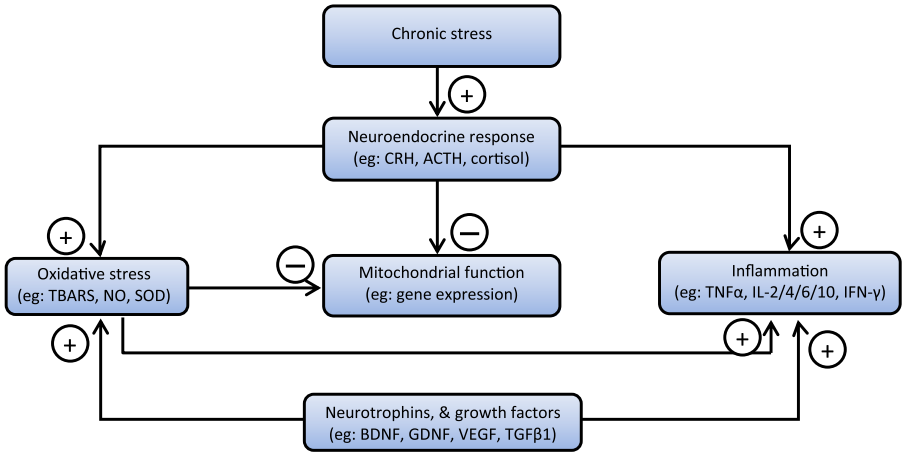

Fig. 1. Putative biological pathway interactions affecting treatment response in bipolar disorder. (TBARS: Thiobarbituric acid reactive substances; NO: nitric oxide; SOD: superoxide dismutase; BDNF: Brain-derived neurotrophic factor; GDNF: Glial cell-derived neurotrophic factor; VEGF: Vascular endothelial growth factor; TGFβ1: transforming growth factor beta 1; TNFα: Tumor necrosis factor alpha; IL-2/4/6/10: Interleukin- 2/4/6/10; IFN-γ: Interferon gamma).

needed to further elucidate the effects of epigenetic regulation of therapeutic action.

Conclusions

Given the complex nature of data collected from human subjects, traditional data analysis may miss subtler relationships between variables, or the emergent properties revealed by combining multiple datasets. This complexity may partially explain why no single biomarker emerges as being strongly predictive of treatment response in bipolar disorder, and yet, there do appear to be some relationships between biomarkers that are worth exploring (see Fig. 1). Machine learning offers a creative and potentially powerful solution to the problem of the large and complicated datasets generated by the biomarker studies reviewed here. There are many machine learning and statistical learning methods by which scientists could mine large datasets for patterns that may be missed by traditional supervised and hypothesis-driven data analysis methods. Although it is outside the scope of this review to examine these approaches in detail, a recent review by Iniesta and colleagues [279] highlights several machine and statistical learning algorithms and how they might be useful for analyzing large datasets in psychiatry. Some efforts have already been made to use machine learning to understand complicated data relationships. For example, Guilloux and colleagues [280] used a machine learning approach to examine relationships between peripheral gene expression and likelihood of non-response to citalopram in patients with comorbid depression and anxiety, and were able to identify a panel of 13 genes which predict with 76–79% accuracy which patients will not remit with citalopram treatment. These methods are not always superior to logistic regression and other supervised methods of analysis (see [281]) but they do represent an opportunity to study relationships that might otherwise be overlooked.

In summary, there is a significant need for developing specific peripheral biomarkers for monitoring treatment response in patients with bipolar disorder. Ideally, future biomarkers should be obtained in a general psychiatric or primary care clinic to ensure broad applicability and utility. Current promising areas of study include biomarkers for cell growth, cell survival, synaptic plasticity, energy metabolism, inflammation, stress/neuroendocrine response, and peripheral gene expression, although others are sure to be identified in future. Further investigation into these biomarkers may yield not only useful data for clinical treatment planning, but may even shed light on potential pharmaceutical targets and mechanisms of disease. More research is needed to identify specific and reliable circulating biomarkers to predict treatment response in bipolar disorder. While the data on biomarkers for treatment response is encouraging, many of these results have not been broadly validated and lack threshold cutoffs that would allow straightforward interpretation in a clinical setting. In addition, prospective validation of treatment response biomarkers integrated into clinical trials is needed in order to prove their utility in the clinic. It is clear that bipolar disorder is a complex disease involving multiple molecular mechanisms; therefore, a panel of biomarkers may be more appropriate from a clinical perspective. This may generate a more comprehensive portrait of the underlying pathophysiology of the disease in order to facilitate treatment decisions and reduce health costs.

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