Personalized Medicine in Psychiatry xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

Putative biological predictors of treatment response in bipolar disorders

Suzanne D. Gonzalez [a,*], Aislinn J. Williams [b], Caren J. Blacker [c], Jennifer L. Vande Voort [c], Kathryn M. Schak [c], Charles B. Nemeroff [d,e], Alik S. Widge [e,f], Mauricio Tohen [e,g]

[a] Department of Biomedical Sciences, Texas Tech University Health Sciences Center, El Paso, TX, USA
[b] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[c] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
[d] Department of Psychiatry and Behavioral Sciences, University of Miami, Miami, FL, USA
[e] The American Psychiatric Association Task Force on Biomarkers and Novel Treatments, USA
[f] Harvard Medical School, Massachusetts General Hospital, Massachusetts Institute of Technology (MIT), Boston, MA, USA
[g] Department of Psychiatry & Behavioral Sciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form 24 November 2016
Accepted 24 November 2016
Available online xxxx

Keywords:
Bipolar disorder
Biomarkers
Neurotrophins
Oxidative stress
Cytokines
Hypothalamic-pituitary-adrenal (HPA) axis

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.

* Corresponding author at: Center of Emphasis in Neurosciences, Department of Biomedical Sciences, Texas Tech University Health Sciences Center, Medical Science Building 3002, 5001 El Paso Drive, El Paso, TX 79905, USA.
E-mail address: suzanne.gonzalez@ttuhsc.edu (S.D. Gonzalez).

http://dx.doi.org/10.1016/j.pmip.2016.11.003
2468-1717/

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

Please cite this article in press as: Gonzalez SD et al. Putative biological predictors of treatment response in bipolar disorders. Personalized Medicine in Psychiatry (2016), http://dx.doi.org/10.1016/j.pmip.2016.11.003