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Toward Clinically Applicable Biomarkers in Bipolar Disorder: Focus on BDNF, Inflammatory Markers, and Endothelial Function

Benjamin I. Goldstein, MD, PhD[1,2] and **L. Trevor Young, MD, PhD**[1]

[1]Department of Psychiatry, University of Toronto, 2075 Bayview Avenue, FG-53; Toronto, ON; M4N-3M5; Canada

[2]Sunnybrook Health Sciences Centre, 250 College Street, Suite-835; Toronto, ON; M5T-1R8 Tel: 416-979-6948 ltrevor.young@utoronto.ca

Abstract

The importance of biomarkers to many branches of medicine is illustrated by their utility in diagnosis and monitoring treatment response and outcome. There is much enthusiasm in the field of mood disorders on the emergence of clinically relevant biomarkers with several potential targets. While there are generally accepted criteria to establish a biomarker, such approaches are premature for our field as we acquire evidence on the most relevant candidates. A number of components of the inflammatory pathway are supported by published data together with an increasing focus on brain derived neurotrophic factors (BDNF). These factors may have measurable impacts on endothelial function which may be particularly amenable to study in clinical samples. The adolescent population is a key focus since identifying biomarkers before the onset of comorbid medical conditions and which may help direct early intervention seem especially promising. A systematic approach to biomarker development in mood disorders is clearly warranted.

Keywords

Bipolar disorder; biomarkers; inflammation; inflammatory; neurotrophic; brain-derived neurotrophic factor; cardiovascular; endothelium; endothelial function

Introduction

Biomarker development is a multi-stage process in which improvements in clinical care are evaluated at later stages. In cardiology, for example, these stages have been defined as: 1) proof of concept, 2) prospective validation in independent populations, 3) documentation of incremental information when added to standard risk markers, 4) assessment of effects on patient management and outcomes, and 5) cost-effectiveness.[1] Five similar stages have

Tel: 416-480-5328; Fax: 416-480-6878 benjamin.goldstein@sunnybrook.ca (corresponding author).

Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

This article contains preliminary data based on a sub-sample of the Course and Outcome of Bipolar Illness among Youth (COBY) study (MH59929, B. Birmaher PI), in which Dr. Goldstein is a co-investigator. That study was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent.

been outlined for cancer biomarkers.[2] Biomarkers have a variety of potential applications including diagnosis, monitoring of disease burden, prognosis, and prediction of treatment response.

Bipolar disorder (BD) is a severe recurrent mood disorder that affects 2-5% of adolescents and adults (prevalence estimates among children are less certain).[3, 4] To date, assessment and monitoring of the symptoms of BD has relied exclusively on evaluating subjective clinical variables, since there are not yet any clinically applicable biomarkers. Although other psychiatric illnesses also follow an episodic course, the frequency of symptomatic recurrences in BD may enhance our ability to discover biomarkers of illness activity and course. Similarly, there is an enormous burden of premature and excessive medical illness in BD, which accounts for much of the increased mortality in BD.[5] Mortality due to cardiovascular disease (CVD), already the leading cause of death in the general population, is doubled in BD.[5] This may be due largely to premature onset of CVD.[6] The burden of manic/hypomanic symptoms appears to contribute to CVD mortality among people with BD.[7] An important and critical next step is to determine whether these two core issues in BD, namely the highly symptomatic course and excessive cardiovascular risk, may be explained by shared biological substrates.

Previous rigorous reviews provide a broad and detailed perspective regarding the current state of BD biomarkers in general[8], and in relation to illness activity specifically.[9] This current report will focus on pro-inflammatory markers (PIMs) and brain-derived neurotrophic factor (BDNF), in light of growing evidence to suggest that these markers are salient to both the symptomatic episodes of BD[10, 11] and the excessive cardiovascular burden in BD.[12] This article selectively summarizes the extant literature regarding PIMs and BDNF in relation to BD, and the relevance of these markers to cardiovascular risk among people with mood disorders. Next, the article reviews some very recent data which illustrates the potential relevance of some of these markers in the adolescent population. Finally, we conclude by highlighting several future directions through which peripheral biomarkers may impact our understanding of the pathophysiology of BD, diagnosis and assessment, and novel therapeutic approaches.

Bipolar Disorder and Inflammation

Putative mechanisms of the association between mood disorders and inflammation include glucocorticoid resistance, blood-brain barrier disruption, altered neurotransmitter metabolism, impaired functional connectivity, increased oxidative stress, astrocyte and microglia activation, neuronal damage and degeneration, and reduced neurotrophic support. In adult BD, increased frontal cortical inflammation has been observed[13], and PIM genotypes have been implicated.[10] Peripheral PIMs are elevated during mania[14-17] and depression[16-18], whereas PIMs during euthymia appear similar to controls in most studies.[17, 19, 20] The majority of studies examine circulating PIMs, although stimulation techniques yield similar findings.[20, 21] Short-term (≤10 weeks) treatment with lithium, valproate, and/or anti-psychotics is associated with significant reduction of PIMs in some[20, 22-24] but not all studies.[14, 25, 26] Few studies report differences in PIMs between mania and depression in BD. Levels of c-reactive protein (CRP)[27] may be higher during mania whereas IL-6 may be higher during depression[16], however it is premature to draw conclusions regarding polarity-specific differences. Preliminary evidence suggests that symptomatic severity is proportional with levels of PIMs, or that changes in PIMs and mood symptoms are highly correlated.[15, 17, 19]

In 2013, three meta-analyses incorporating somewhat different methodologies yielded generally convergent findings.[28-30] In one report, Munkholm and colleagues examined 13 studies (using non-stimulated in-vivo studies only) published through January 2012 (n=566

BD, n=767 controls) and found that levels of TNF-α, soluble TNF receptor type 1 (sTNF-R1) and soluble interleukin-2 receptor (sIL-2R) were significantly elevated among manic BD patients vs. controls. In addition, sTNF-R1 and TNF- were elevated among manic BD patients vs. euthymic BD patients. Some studies demonstrated statistical trends toward increased levels of TNF-α and IL-6 among depressed BD patients vs. controls, and increased IL-6 in bipolar depression vs. bipolar mania, however these findings were not significant in the meta-analysis. Only sTNF-R1 was significantly higher among euthymic BD patients vs. controls.

In their subsequent meta-analysis, including articles up to January 2013, Munkholm and colleagues examined 18 studies (non-stimulated, in-vivo; n=761 BD, n=919 controls).[29] They examined all BD subjects together, including those who were manic, depressed, or euthymic, and found that sIL-2R, TNF-, sTNFR1, sIL-6R, and IL-4 (an anti-inflammatory cytokine) were higher among BD patients vs. controls.

Finally, Modabbernia and colleagues examined 30 studies published through December 2012 (n=1351 BD, n=1248 controls).[30] The larger number of studies is owing to the inclusion of studies using mitogen-stimulation, in addition to those examining only circulating levels of PIMs. They found that IL-4, IL-6, IL-10, sIL-2R, sIL-6R, IL-1RA, TNF-α, and sTNFR1 were significantly elevated in manic BD patients vs. controls. Non-significant trends were observed for IL-1β and IL-6. Heterogeneity of findings was mitigated in subgroup analyses based on mitogen stimulation methodology. There were trends toward higher TNF-α and IL-10 levels among depressed BD patients vs. controls. Among BD patients, IL-6 tended to be higher during mania than depression.

Bipolar Disorder and BDNF

BDNF is important for neurogenesis, synaptic plasticity and dendritic growth.[11] Although BDNF is pleiotropic, increasing BDNF expression in the hippocampus and prefrontal cortex produces antidepressant effects.[31, 32] Macrophages, lymphocytes, vascular endothelial cells, and smooth muscle cells are sources of BDNF; however, much of circulating BDNF originates from central nervous system neurons and glia.[33, 34] BDNF can cross the blood-brain barrier in both directions.[35, 36] Preclinical models demonstrate high positive correlation between serum BDNF levels and cortical and hippocampal BDNF expression.[35, 37] N-acetyl aspartate (NAA) levels, reflecting neuronal integrity, have been positively correlated with serum BDNF.[38] The BDNF val66met polymorphism, associated with reduced function, may be implicated among children and adolescents with BD and among adults with early-onset BD[39, 40], and may contribute to prefrontal cortical morphometric and metabolic abnormalities in BD.[41, 42]

Multiple studies have found reduced circulating BDNF protein levels during mania and depression.[43-47] A recent meta-analysis including 13 studies and 1113 subjects found effect sizes of −0.81 for mania and −0.97 for depression.[48] Consistent differences between euthymic BD patients and controls are not evident.[48-51] Studies have also found negative associations between BDNF levels and manic (r=−0.37 to −0.78) and depressive (r=−0.30) symptoms [46, 47], although there are also contradictory findings from small studies.[52] Most studies include participants taking psychotropic medications, however convergent findings were reported among untreated participants.[46] BDNF reductions are greater in BD vs. MDD[45], particularly among BD participants with history of exposure to traumatic events.[53]

A recent systematic review and meta-regression analysis (n=548 BD, n=565 controls) reported reduced BDNF with large effect sizes (ES) for mania (ES −0.81) and depression (ES −0.97) vs. controls.[48] In contrast, differences in BDNF levels among euthymic BD

patients vs. controls were not significant and of modest magnitude (ES −0.20). There was substantial variability in findings in the euthymic phase, and both age and illness duration significantly contributed to this variability. Despite the fact that there were only three studies (N=36 total) of manic patients with BD that included repeated measures of BDNF, there was a significant increase in BDNF following treatment for acute mania (ES −0.63). Among these, one study of first-episode BD (N=14) ascertained BDNF levels at baseline, and after 1, 6, and 12 months.[54] BDNF levels were decreased at baseline, and normalized with time and treatment. However, neither repeated measures of mood symptom severity nor the association between mood and BDNF over time was reported. Two studies in the meta-analysis examined changes in BDNF following pharmacologic treatment and no significant differences were observed. However, the authors highlighted that the two studies examined effects of treatment with risperidone and mifepristone. Changes following other pharmacologic treatments may differ. Since this meta-analysis was published, one additional study examined changes in BDNF among 25 BD patients (n=17 depressed, n=8 manic/mixed), initially unmedicated, following treatment with extended release quetiapine.[55] That study found an increase in BDNF following treatment of depression, contrasting a decrease in BDNF following treatment of manic/mixed episodes.

Endothelial Dysfunction and Mood Disorders

CVD is the leading cause of death in BD, with a standardized mortality ratio of 1.5-2.5.[5, 56] Adults with BD have a 5-fold increased risk of CVD, and manifest CVD 14 years earlier than adults without mood disorders.[6] The prevalence of CVD among adults with BD is doubled as compared to adults with MDD.[6] ED predicts CVD morbidity independent of multiple other CVD risk factors.[57, 58] Several studies have reported an association between depressed or negative mood and ED,[59-66] although discordant findings exist.[67] Sparse data are available on this topic in BD specifically. In a controlled study, adults with MDD or BD demonstrated ED during a depressive episode and remission.[64] Recent findings from the Collaborative Depression Study cohort indicated that after controlling for age, gender, and smoking, there was an association between hypo/manic symptoms and poorer endothelial function, whereas this association was not observed for depressive symptoms.[68]

Inflammation and BDNF are Relevant to Cardiovascular Risk and Vascular Endothelium

Studies have repeatedly associated PIMs with incident CVD and with CVD risk factors.[12, 69, 70] PIMs have also been implicated in ED.[71, 72] PIMs among adults with depression are inversely associated with endothelial integrity.[73] In addition to any association with brain and mood, BDNF may be relevant to CVD.[74-76] Reduced BDNF levels have been observed among adults suffering from acute coronary syndrome.[77] Deficiency of BDNF may be implicated in reduced endothelial integrity and increased endothelial cell apoptosis.[78] One postulated mechanism of these effects is that BDNF serves the important function of maintaining the clustering of β-catenin, an adherens junctional molecule, to endothelial cell-cell contacts. [78] Vascular levels of BDNF mRNA expression are comparable to those in the brain. BDNF and endothelial function may share a bidirectional association, as vascular endothelial cells produce BDNF.[79] In preclinical models, BDNF modulates the coupling of neurogenesis and vasculogenesis.[80]

Summary of Extant Literature

PIMs and BDNF have shown promise for potential clinical applications in BD; however, two central limitations constrain previous findings. First, few studies have examined both PIMs and BDNF, limiting the conclusions that can be drawn regarding their overlapping, independent, and interactive associations with mood symptoms. Second, minimal longitudinal data are available. Longitudinal studies of PIMs have been limited to two

measurements, and follow-up is generally <3 months. Longitudinal studies of BDNF have ≤20 BD subjects each, and are limited to two concurrent measurements of BDNF and mood symptoms. Previous studies have not examined the predictive value of BDNF or PIMs on the subsequent course of BD, although promising findings have been reported in other disorders.[81, 82] Endothelial dysfunction, a proxy for CVD risk, is associated with mood disturbance, and this association may be explained by differences in PIMs and BDNF.

Toward Clinically Applicable Biomarkers in Adolescent Bipolar Disorder

Although inflammation may be particularly salient in early-onset BD[19, 50], little is known regarding inflammation among adolescents with BD. A high-risk study of children of adult probands with BD identified an aberrant inflammatory gene expression signature which was present in 88% of BD offspring with mood disorders vs. 19% of control adolescents.[83] In recently-presented data, untreated manic children and adolescents (N=22) have higher circulating levels of TNF-α and IL-1β vs. healthy controls (N=21).[84]

The single study, to our knowledge, of children and adolescents with BD found that both platelet BDNF levels and lymphocyte BDNF mRNA levels were decreased among unmedicated manic or mixed BD participants vs. controls, and normalized following 8 weeks of treatment.[85] There was a significant positive association (r=0.45) between the change in BDNF mRNA and change in mania symptoms.

We recently conducted a preliminary study regarding PIMs, BDNF, and mood symptoms among 30 adolescents ages 13-19 years with BD-I (N=18), BD-II (N=1), or BD-not otherwise specified (N=11) [86]. Manic symptom severity was significantly associated with hsCRP (r=0.37, p=0.04), but not IL-6. Forty percent of participants had levels of hsCRP that are considered at-risk for CVD among adults (≥2ug/ml)[87], and mean hsCRP (3.1±4.6ug/ml) was 3-fold higher than normal and nearly as high as in acute juvenile rheumatoid arthritis.[88] Preliminary analyses of 3-month follow-up data (N=28) indicate that compared to participants who were asymptomatic throughout the follow-up interval, participants who were symptomatic demonstrated higher baseline levels of hsCRP (3.76±5.18 vs. 1.09±1.01, p=0.03) and IL-6 (1.37±0.83 vs. 1.02±0.21, p=0.08), whereas BDNF levels did not differ. IL-6 and hsCRP had medium correlations with subsequent number of weeks with depressive symptoms (r=0.44, p=0.02 and r=0.32, p=0.10, respectively). However, this preliminary study was constrained by several limitations including: lack of repeated measures, lack of controls, lack of within-subject comparisons for BD participants, and non-fasting blood-draws across various times of day.

Similar to the limited data regarding PIMs and BDNF among adolescents with BD, CVD risk among adolescents with BD is a major concern that has been the subject of comparatively little research to date.[89-93] The American Heart Association concluded that non-invasive imaging of endothelial dysfunction (ED), including vascular ultrasound and peripheral arterial tonometry, can improve detection and risk-stratification of subclinical atherosclerosis in childhood and adolescence, when “hard” endpoints (e.g. myocardial infarction) are fortunately rare.[58] However, research regarding ED and mood among adolescents is lacking. A study of adolescent females found a cross-sectional association between depressive symptoms and ED that is not explained by lifestyle or obesity, and replicated this association over repeated visits during 2.5 years of follow-up.[94]

Conclusion

Recent meta-analyses confirm that BDNF is decreased and PIMs are increased among adults with BD, particularly during acute manic and depressive episodes. Although constrained by a small number of studies with few subjects, there is also preliminary evidence that these

markers change over time and in response to treatment. The extant literature strongly suggests that there is ample justification to continue research regarding these markers as potential clinical biomarkers in BD. For BDNF and PIMs to realize their full potential will require the consistent application of several methodologic approaches. These include larger sample sizes, repeated measures and within-subject comparisons, incorporation of important covariates (e.g. age, sex, BMI, stressors), and sub-group analyses (e.g. BD subtype, sex, family history of BD). Sensitivity, specificity, positive and negative predictive value, and overall classification accuracy are statistical properties of any medical test, including biomarkers, that will be crucial to examine in order to determine the value of incorporating these or other markers into clinical practice. To date, these statistics are rarely described in regard to putative biomarkers in BD. Few studies have examined both BDNF and PIMs, or even examined the classification and predictive metrics of considering multiple PIMs simultaneously.[95] Such an approach may serve to optimize the value of these markers. Studies to date do not sufficiently clarify whether study staff (including laboratory staff conducting the assays) are blind to patient status, which is a key aspect of biomarker validation. Preliminary data suggest that age and stage of illness may contribute to heterogeneity in findings.[50, 96] As such, it will be important for the field to consider the possibility that there are developmental and/or stage-related differences in the relationship of these markers to symptoms, course, and treatment of BD. Validation of PIMs and BDNF would justify further investigation into whether explicitly attempting to modify levels of these markers, using anti-inflammatory and/or neurotrophin-based interventions[97-100], can yield benefits in terms of mood stabilization. Similarly, future studies are needed to examine whether BDNF and PIMs can inform our understanding, treatment, and prevention of two core non-mood aspects of BD, namely CVD and cognitive dysfunction.[101, 102] Does explicitly modifying BDNF and/or PIMs mitigate the excessive cardiovascular risk and cognitive dysfunction associated with BD and its treatments?

The need for biomarkers in psychiatry is widely acknowledged by clinicians, researchers, and patients alike. This need is arguably greatest for BD, characterized by numerous presentations in terms of mood polarity and exceedingly high rates of comorbidity. The articles reviewed here provide promising signals and potential applications for BDNF and PIMs as clinically relevant biomarkers in BD. Progressing further along the stages of biomarker validation will require increasing expense, precision, rigor, and scrutiny in order to ensure that these markers are ready for the clinic. The potential impact on diagnostics, prognostication, novel therapeutic approaches, and stigma reduction suggests that the effort required to achieve this progress is well warranted.

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