JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 21, Number 5, 2011

Pp. 479–484
DOI: 10.1089/cap.2011.0009

Brief Report

Preliminary Findings Regarding Proinflammatory Markers and Brain-Derived Neurotrophic Factor Among Adolescents with Bipolar Spectrum Disorders

Benjamin I. Goldstein, M.D., Ph.D., FRCPC,[1,2] Katelyn A. Collinger, M.A.,[1]
Francis Lotrich, M.D., Ph.D.,[2] Anna L. Marsland, R.N., Ph.D.,[3] Mary-Kay Gill, M.S.N.,[2]
David A. Axelson, M.D.,[2] and Boris Birmaher, M.D.[2]

Abstract

Mood symptoms in adult bipolar disorder are associated with increased proinflammatory markers and decreased brain-derived neurotrophic factor (BDNF). We examined serum interleukin-6, high-sensitivity C-reactive protein (hsCRP), and BDNF among 30 bipolar disorder adolescents. Hypomanic/manic symptoms were positively associated with hsCRP. BDNF levels were negatively associated with interleukin-6. Forty percent had cardiovascular high-risk hsCRP levels. Larger longitudinal studies are warranted.

Introduction

There has been increasing emphasis on peripheral biomarker research in bipolar disorder (BP) in recent years (Kapczinski et al. 2009), particularly proinflammatory markers (PIMs) (Goldstein et al. 2009b) and brain-derived neurotrophic factor (BDNF) (Post 2007). PIMs interact with most pathophysiologic processes invoked in BP, including 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 (Banks et al. 1995; Allan and Rothwell 2001; Banks et al. 2002; Knijff et al. 2006; Aktas et al. 2007; Harrison et al. 2009; Miller et al. 2009; Rao et al. 2010; Wersching et al. 2010). PIMs may be particularly salient in early-onset BP (Dickerson et al. 2007). Although the extant literature is not yet definitive, several studies have found that PIMs such as interleukin-6 (IL-6) and C-reactive protein (CRP) are elevated during mania and depression, and may improve with pharmacologic treatment, with limited evidence for elevated PIMs in euthymia (O'Brien et al. 2006; Kim et al. 2007; Ortiz-Dominguez et al. 2007; Brietzke et al. 2009; Goldstein et al. 2009). BDNF is important for neurogenesis, synaptic plasticity, and dendritic growth (Post 2007), and the BDNF val66met genetic polymorphism has been associated with pediatric BP (Geller et al. 2004) and may contribute to prefrontal cortical morphometric and energy metabolism abnormalities in adult BD (Frey et al. 2007; Matsuo et al. 2009). Recent findings suggest that BDNF polymorphisms may be associated with circulating BDNF protein levels in humans (Lang et al. 2009; Elzinga et al. 2010). Adult BP studies have reported that levels of BDNF are markedly reduced during mania and depression, whereas it is not clear whether BDNF levels are lower among euthymic patients with BP than among controls (Lin 2009; Post 2007). One study examined the association between BDNF and PIMs among adults with BD (Kauer-Sant'Anna et al. 2009), finding that BDNF levels were negatively associated with TNF-α levels and positively associated with IL-6 levels.

Few studies regarding BP have examined peripheral markers of inflammation or BDNF among children or adolescents. A single study examined inflammation among adolescent and young-adult offspring of parents with BP: pro-inflammatory gene expression signature was more prevalent among BP offspring compared with control offspring, particularly among offspring with mood disorders (Padmos et al. 2008). To our knowledge no studies have examined BDNF serum protein levels among BP youth, although a study found decreased lymphocyte BDNF gene expression and platelet BDNF protein levels among manic youth versus controls (Pandey et al. 2008).

We examined this topic among adolescents with BP, hypothesizing that depressive and manic symptom severity would be positively associated with IL-6 and CRP levels and negatively associated with BDNF protein levels. In light of evidence that PIMs may be neurotoxic (Wersching et al. 2010), we further hypothesized that levels of IL-6 and high-sensitivity CRP (hsCRP) would be negatively associated with BDNF levels. We further sought to examine descriptively the prevalence of hsCRP levels that are considered high-risk for cardiovascular disease (CVD), as CVD is highly prevalent among adults with BP and hsCRP may comprise a shared biomarker among these conditions (Osby et al. 2001; Goldstein et al. 2009a, Greenland et al. 2010).

[1]Department of Psychiatry, Sunnybrook Health Sciences Centre, Faculty of Medicine, University of Toronto, Toronto, Canada.
[2]Western Psychiatric Institute and Clinic, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.
[3]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Methods

Subjects

Subjects included 30 participants aged 12–19 years enrolled in the Course and Outcome of Bipolar Youth (COBY) (Axelson et al. 2006; Birmaher et al. 2009) study with BP-I ($n = 18$), BP-II ($n = 1$), or BP not otherwise specified (BP-NOS) ($n = 11$). Consecutive COBY subjects presenting for follow-up assessments were invited to participate in this study. Details regarding the COBY methodology, including the operationalized diagnosis of BP-NOS and its longitudinal validation, have been previously reported (Axelson et al. 2006; Birmaher et al. 2009). Exclusion criteria were infectious illness within 14 days, known inflammatory or auto-immune illness, use of steroidal medication or insulin during the past month, and self-reported alcohol or illicit drug use within 24 hours (two subjects who smoked cigarettes regularly were included). These exclusion criteria were determined based on known associations with PIMs (Lovell et al. 2000; Imhof et al. 2001; Pacifici et al. 2003; Joe et al. 2007; Wright et al. 2010). Two potential subjects (not among the 30 included subjects) were excluded due to insulin-dependent diabetes mellitus; none of the other exclusion criteria was invoked.

Psychiatric and anthropometric measures

Both the categorical BP diagnosis and continuous measures of mood symptoms were assessed by the mood disorder sections of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present Episode, fourth revision (K-SADS-P) plus additional items from the Mania Rating Scale (MRS) (Chambers et al. 1985; Axelson et al. 2003). Hypomanic/manic symptomatic severity was determined based on MRS total scores, and depressive symptomatic severity was determined based on K-SADS-P depression section total scores. Nonmood diagnoses were determined using the, K-SADS Present and Lifetime version (K-SADS-PL) (Kaufman et al. 1997). The primary caretaker was interviewed about the psychiatric status of the subject's first- and second-degree relatives using the Family History Screen, a method that has acceptable reliability and validity (Weissman et al. 2000). This method provides psychiatric history for all 1st and 2nd degree relatives across the major diagnostic categories; however, the present study focused specifically on first degree family history of hypomania/mania. Height and weight were measured using a Tanita scale and stadiometer. Obesity was defined as age- and sex-adjusted body mass index $\geq$95th percentile according to Center for Disease Control body mass index norms.

Biochemical assays

Twenty milliliters of blood were drawn from each subject by antecubital venipuncture into anticoagulant-free vacuum tubes. Blood draw times ranged between 9:35 a.m. and 3:45 p.m. Blood samples were immediately centrifuged at 3,000 *g* for 5 minutes, and stored at -80°C until assayed. Serum IL-6 levels ($n = 29$) were determined using a high sensitivity quantitative sandwich enzyme linked immune sorbent assay kit according to the manufacturer's instructions (R&D Systems). Serum levels of hsCRP ($n = 30$; Alpco) and BDNF ($n = 30$; R&D Systems) were also determined using enzyme linked immune sorbent assay in a similar fashion to IL-6.

Statistical analyses

Statistical analyses were performed using the Statistical Package or the Social Sciences Version 14 (SPSS). Statistical significance was set at $\alpha = 0.05$ (two-tailed). Given the dearth of information regarding PIMs and BDNF in this population, these analyses were not adjusted for multiple comparisons. Rank correlation coefficients (Spearman's *r)* were computed to examine the association between mood symptoms, inflammatory cytokines, and BDNF. To examine for associations with categorical demographic and clinical characteristics, exploratory paired *t*-tests were used for BDNF and IL-6, and Mann–Whitney was used for hsCRP owing to non-normal distribution. Effect sizes (Cohen's *d*) are presented in Table 2.

Results

Demographic and clinical characteristics are presented in Table 1. Nineteen participants (63%) were in the midst of a full-threshold or clinically significant sub-threshold symptomatic interval (7 manic or hypomanic, 5 depressed, 7 mixed). Levels of hsCRP (3.1 ± 4.6 μg/mL), IL-6 (1.3 ± 0.7 μg/mL), and BDNF (25.8 ± 5.8 ng/mL) were detectable for all subjects.

Comparability with overall COBY sample

Subjects in the present study were more likely to have a first-degree family history of hypomania/mania compared with the overall COBY sample (60% vs. 35%) and were more likely to be male (80% vs. 53%).

Association between symptoms, PIMs, and BDNF

Manic symptom severity was significantly associated with hsCRP ($r = 0.37$, $p = 0.04$), but not IL-6 ($r = 0.03$, $p = 0.90$).

Table 1. Descriptive Demographic and Clinical Characteristics

Age	15.5 ± 2.3 years
Male	$n = 24$, 80%
Caucasian	$n = 23$, 77%
Socioeconomic status[a]	3.07 ± 1.10
Lives with both biological parents	$n = 11$, 37%
Obese	$n = 12$, 40%
BP sub-type:	
BP-I	$n = 18$, 60%
BP-II	$n = 1$, 3%
BP-NOS	$n = 11$, 37%
Episode:	
Hypomanic/manic	$n = 7$, 23%
Depressed	$n = 5$, 17%
Mixed	$n = 7$, 23%
Euthymic/minimal symptoms	$n = 11$, 37%
Mania symptom severity[b]	10.5 ± 10.0
Depression symptom severity[c]	10.3 ± 8.8
First-degree family history of hypomania/mania	$n = 18$, 60%
History of physical or sexual abuse	$n = 9$, 30%
Second-generation antipsychotic	$n = 18$, 60%
Lithium or divalproex sodium	$n = 9$, 30%
Psychostimulant	$n = 12$, 40%
Antidepressant	$n = 7$, 23%

[a]Determined via Hollingshead scale (possible scores 1–5).
[b]Determined via Mania Rating Scale (MRS) total score.
[c]Determined via Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present Episode, fourth revision (K-SADS-P) depression section total score.

BP-I, Bipolar I disorder; BP-II, bipolar II disorder; BP-NOS, BP not otherwise specified.

Depressive symptom severity was not significantly associated with hsCRP ($r = 0.10$, $p = 0.61$) or IL-6 ($r = 0.23$; $p = 0.23$). BDNF was not significantly associated with manic ($r = 0.00$) or depressive ($r = 0.14$) symptom severity. Of note, all 3 subjects with hsCRP levels $>10\,\mu$g/mL had mania symptom scores >20 on the MRS. In contrast, high MRS scores were not necessarily indicative of high hsCRP levels as there were 3 subjects with MRS scores >20 who had hsCRP levels $<1\,\mu$g/mL. BDNF levels were significantly negatively associated with IL-6 ($r = -0.37$, $p = 0.048$), whereas the negative association between BDNF and hsCRP ($r = -0.26$, $p = 0.17$) was not significant.

Association between other clinical characteristics, PIMs, and BDNF

There were no significant differences between subjects with BP-I versus BP-NOS with respect to IL-6, hsCRP, or BDNF. However, compared with nonobese subjects ($n = 18$), obese subjects ($n = 12$) had significantly higher levels of hsCRP (4.9 ± 5.2 vs. $2.0 \pm 3.8\,\mu$g/mL; Mann–Whitney $U = 45$, $p = 0.008$) and IL-6 (1.6 ± 0.8 vs. $1.1 \pm 0.6\,\mu$g/mL; $t = 2.2$, $p = 0.04$). Associations between PIMs, BDNF, and other demographic and clinical variables, including medications, are reported in Table 2. Although *a priori* multivariable analyses were not undertaken due to sample size constraints, sensitivity analyses using analysis of covariance were computed to control for obesity. After controlling for obesity, the association between manic symptom severity and hsCRP was reduced to a trend ($t = 1.91$, $p = 0.066$), as was the association between IL-6 and BDNF ($t = 1.92$, $p = 0.066$).

Cardiovascular risk

Forty percent of participants had levels of hsCRP that are considered at-risk for CVD among adults ($\geq 2\,\mu$g/mL) (Ridker et al. 2008).

Discussion

This is the first study to our knowledge that examines both PIMs and BDNF among adolescents with BP. Our preliminary findings suggest a positive association between hypomanic/manic symptom severity and hsCRP levels, and a negative association between BDNF and IL-6 levels. These associations may underlie the mood symptoms and neuropsychological dysfunction associated with adolescent BP. Forty percent of participants had levels of hsCRP that are considered at-risk for CVD among adults (Ridker et al. 2008). Moreover, mean hsCRP was threefold higher than normal and nearly as high as levels reported in acute juvenile rheumatoid arthritis (Lovell et al. 2000). These findings raise concern that adolescents with BP may already be accumulating risk for premature CVD and other medical problems (Goldstein et al. 2009a; Kapczinski et al. 2010).

The association between hsCRP levels and hypomanic/manic symptom severity converges with findings from adults (Dickerson et al. 2007). In addition, present findings provide a tentative signal that, similar to adults, hsCRP may be more strongly associated with manic symptoms, whereas IL-6 may be more strongly associated with depressive symptoms of BP (Goldstein et al. 2009b). A previous study found that BDNF levels were negatively associated with TNF-α levels and positively associated with IL-6 levels (Kauer-Sant'Anna et al. 2009). However, those analyses were collapsed

Table 2. Association of Proinflammatory Markers and Brain-Derived Neurotrophic Factor with Demographic and Clinical Variables

	hsCRP (μg/mL)	*IL-6 (μg/mL)*	*BDNF (ng/mL)*
Age	r[a] $= -0.1$	$r = 0.1$	$r = 0.0$
Morning versus afternoon blood draw	3.3 ± 5.0 vs. 2.4 ± 3.6 d[b] $= 0.2$	1.4 ± 0.9 vs. 1.2 ± 0.7 $d = 0.2$	24.9 ± 4.1 vs. 26.2 ± 6.6 $d = 0.2$
Male versus female	3.5 ± 5.0 vs. 1.8 ± 1.0 $d = 0.4$	1.2 ± 0.7 vs. 1.6 ± 0.8 $d = -0.1$	26.4 ± 6.2 vs. 23.5 ± 3.3 $d = 0.5$
White versus non-White race	2.8 ± 4.3 vs. 4.4 ± 5.5 $d = -0.3$	1.3 ± 0.8 vs. 1.2 ± 0.6 $d = 0.0$	25.4 ± 5.9 vs. 27.1 ± 5.6 $d = -0.3$
Obese versus nonobese	4.9 ± 5.2 vs. 2.0 ± 3.8 $d = 0.6$	1.6 ± 0.8 vs. 1.1 ± 0.6 $d = 0.7$	24.6 ± 4.3 vs. 26.6 ± 6.6 $d = -0.3$
Abuse history[c]	3.6 ± 4.9 vs. 3.0 ± 4.5 $d = 0.1$	1.6 ± 0.8 vs. 1.2 ± 0.7 $d = 0.6$	25.9 ± 6.5 vs. 25.7 ± 5.6 $d = 0.0$
Family history of hypomania/mania[c]	4.1 ± 5.6 vs. 1.8 ± 1.5 $d = 0.5$	1.3 ± 0.8 vs. 1.3 ± 0.7 $d = 0.0$	25.1 ± 4.1 vs. 26.8 ± 7.8 $d = 0.3$
BP-I versus BP-NOS	1.9 ± 2.0 vs. 4.1 ± 6.0 $d = -0.5$	1.1 ± 0.4 vs. 1.5 ± 1.0 $d = -0.6$	25.1 ± 5.1 vs. 27.2 ± 7.0 $d = -0.4$
Second-generation antipsychotic[c]	2.4 ± 3.7 vs. 4.2 ± 5.6 $d = -0.4$	1.3 ± 0.7 vs. 1.3 ± 0.9 $d = 0.0$	25.0 ± 5.7 vs. 27.0 ± 6.0 $d = -0.3$
Lithium and/or divalproex sodium[c]	1.2 ± 1.0 vs. 4.0 ± 5.2 $d = -0.7$	1.1 ± 0.4 vs. 1.4 ± 0.8 $d = -0.5$	26.2 ± 7.0 vs. 25.6 ± 5.4 $d = 0.1$
Psychostimulant[c]	1.0 ± 1.1 vs. 4.6 ± 5.4 $d = -0.5$	1.1 ± 0.7 vs. 1.4 ± 0.8 $d = -0.4$	26.6 ± 7.2 vs. 25.3 ± 4.9 $d = 0.2$
Antidepressant[c]	1.0 ± 0.6 vs. 3.8 ± 5.0 $d = -0.7$	1.1 ± 0.4 vs. 1.4 ± 0.8 $d = -0.5$	28.1 ± 6.6 vs. 25.1 ± 5.5 $d = 0.5$

[a]Spearman's r correlation coefficient.
[b]Cohen's d effect size.
[c]Present versus absent.
hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin; BDNF, brain-derived neurotrophic factor.

across early- and late-stage BP, which were found in that study to differ with regard to these biomarkers. Future studies are therefore needed to examine for stage-related differences in the associations between PIMs and BDNF. Reasons for the lack of associations between BDNF and mood symptoms in this preliminary study are uncertain, and may be due to confounding as described below.

This study included exploratory analyses regarding potential covariates for future studies. Present findings suggest that psychiatric medications, sex, obesity, history of abuse, BP subtype, and family history of BP are important covariates to consider in future studies. With regard to medications, these preliminary analyses suggest that traditional mood-stabilizers and antidepressants have medium effect sizes in terms of PIMs, and antidepressants have a medium effect size in terms of BDNF. Present findings therefore appear to converge in part with prior evidence regarding these medications (Rapaport and Manji 2001; Bosetti et al. 2002, 2003; Rapoport and Bosetti 2002; Frey et al. 2006; Sen et al. 2008; Yasuda et al. 2009).

The high levels of hsCRP are concerning from a CVD risk perspective. High hsCRP is a risk factor for CVD independent of traditional risk factors (Greenland et al. 2010). A previous study found that adults with BP have a fivefold increased risk of CVD compared with the general population, and manifest CVD 14 years earlier than adults without mood disorders (Goldstein et al. 2009a). Indeed, recent studies suggest that increased risk for CVD in BP may begin in childhood and adolescence (Goldstein et al. 2008; Evans-Lacko et al. 2009; Jerrell et al. 2010). Medications, particularly second-generation antipsychotics and/or concurrent use multiple mood-stabilizing medications, may contribute to weight gain and other metabolic disturbances (Correll 2007). However, it not clear whether these medications contribute to premature CVD mortality despite their clear association with CVD risk factors (Tiihonen et al. 2009). Moreover, the association between BP and CVD was observed before the availability of these medications (Kraepelin 1921; Tsuang et al. 1980; Weeke et al. 1987). Further research is warranted regarding the associations between psychotropic medications, inflammation, and CVD risk among youth.

This study's primary limitation, similar to biomarker research in BP in general, relates to variability in domains such as mood states, obesity, medication regimens, comorbid conditions, history of abuse, and family psychiatric history. Detailed information regarding lifestyle variables such as sleep, nutrition, and exercise was not ascertained. Given the associations of these variables with PIMs and/or BDNF (Irwin et al. 2006; Hamer and Steptoe 2007; Tang et al. 2008; Gorgulu and Caliyurt 2009; Rasmussen et al. 2009), these factors may have contributed to residual confounding. The robustness of these findings is uncertain, as the sample size does not provide sufficient statistical power to control for the above covariates. Similarly, we elected not to correct for multiple comparisons; however, findings would no longer have been statistically significant had we done so. Finally, the present study is constrained by the absence of healthy controls and the cross-sectional methodology.

Conclusions

Despite its limitations, this study provides novel evidence regarding these biomarkers among adolescents with BP, and findings are largely convergent with those from adults with BP. Larger-scale longitudinal studies are needed to examine the temporal relationship between these biomarkers and the symptoms and associated medical comorbidity of BP. Studies of adults are constrained by decades of exposure to BP symptoms and their associated physiological strain, which may exhaust and alter natural adaptive homeostatic mechanisms that are salient to the association between these biomarkers and BP (McEwen 1998; Kapczinski et al. 2008). Parsing the association between these biomarkers and the symptoms, course, and comorbidity of BP among adolescents may therefore be advantageous.

Clinical Significance

Extending this line of research by employing longitudinal methods and repeated assessments has the potential to inform clinical monitoring and treatment of BP in the future. For now, the unequivocal medical risks associated with high levels of PIMs invoke urgency toward mitigating the inflammatory burden of BP. These preliminary findings suggest that first-line medications for BP may not exacerbate inflammatory burden and may have a salutary effect.

Disclosures

The authors have the following disclosures: Dr. Birmaher is a consultant for Schering-Plough, participated in a forum sponsored by Forest, has or will receive royalties for publications from Random House, Inc., and Lippincott Williams and Wilkins.

Dr. Goldstein has received honoraria from Purdue Pharma and grant support from Pfizer. The other authors have no personal affiliations or financial relationships with any commercial interest to disclose relative to this article.

Acknowledgments

This study was supported by a generous donation from the Order of the Eastern Star of Ontario (Goldstein), and by NIMH R01 59929 (Birmaher). Findings were presented in part at the 8th Annual NIMH Pediatric BP Conference, Boston, March 2010, and were selected as a Finalist for best poster presentation at the 65th Annual Meeting of the Society of Biological Psychiatry, New Orleans, May 2010.

References

Aktas O, Ullrich O, Infante-Duarte C, Nitsch R, Zipp F: Neuronal damage in brain inflammation. Arch Neurol 64:185–189, 2007.

Allan SM, Rothwell NJ: Cytokines and acute neurodegeneration. Nat Rev Neurosci 2:734–744, 2001.

Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M: Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 63:1139–1148, 2006.

Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, Ryan N: A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J Child Adolesc Psychopharmacol 13:463–470, 2003.

Banks WA, Farr SA, Morley JE: Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation 10:319–327, 2002.

Banks WA, Kastin AJ, Broadwell RD: Passage of cytokines across the blood-brain barrier. Neuroimmunomodulation 2:241–248, 1995.

Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Houck P, Ha W, Iyengar S, Kim E, Yen S, Hower H, Esposito-Smythers C, Goldstein T, Ryan N, Keller M: Four-year longitudinal course of children and adolescents with bipolar spectrum disorders:

The Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry 166:795–804, 2009.

Bosetti F, Rintala J, Seemann R, Rosenberger TA, Contreras MA, Rapoport SI, Chang MC: Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E(2) concentration in rat brain. Mol Psychiatry 7:845–850, 2002.

Bosetti F, Weerasinghe GR, Rosenberger TA, Rapoport SI: Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and −2 in rat brain. J Neurochem 85:690–696, 2003.

Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, Chies JA, Kapczinski F: Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 116:214–217, 2009.

Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, Davies M: The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. Arch Gen Psychiatry 42:696–702, 1985.

Correll CU: Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: A systematic review and pooled analysis of short-term trials. J Am Acad Child Adolesc Psychiatry 46:687–700, 2007.

Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R: Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 31:952–955, 2007.

Elzinga B, Molendijk M, Oude Voshaar R, Bus B, Prickaerts J, Spinhoven P, Penninx B: The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. Psychopharmacology 214:319–328, 2010.

Evans-Lacko SE, Zeber JE, Gonzalez JM, Olvera RL: Medical comorbidity among youth diagnosed with bipolar disorder in the United States. J Clin Psychiatry 70:1461–1466, 2009.

Frey BN, Andreazza AC, Cereser KMM, Martins MR, Valvassori SS, Reus GZ, Quevedo J, Kapczinski F: Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. Life Sci 79:281–286, 2006.

Frey BN, Stanley JA, Nery FG, Monkul ES, Nicoletti MA, Chen H-H, Hatch JP, Caetano SC, Ortiz O, Kapczinski F, Soares JC: Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: An *in vivo* 1H MRS study. Bipolar Disord 9 Suppl 1:119–127, 2007.

Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH, Jr.: Linkage Disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 161:1698–1700, 2004.

Goldstein BI, Birmaher B, Axelson DA, Goldstein TR, Esposito-Smythers C, Strober MA, Hunt J, Leonard H, Gill MK, Iyengar S, Grimm C, Yang M, Ryan ND, Keller MB: Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. J Clin Psychiatry 69:1953–1959, 2008.

Goldstein BI, Fagiolini A, Houck P, Kupfer DJ: Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord 11:657–662, 2009a.

Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS: Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry 70:1078–1090, 2009b.

Gorgulu Y, Caliyurt O: Rapid antidepressant effects of sleep deprivation therapy correlates with serum BDNF changes in major depression. Brain Res Bull 80:158–162, 2009.

Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr., Taylor AJ, Weintraub WS, Wenger NK: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. JACC 56:2182–2199, 2010.

Hamer M, Steptoe A: Association between physical fitness, parasympathetic control, and proinflammatory responses to mental stress. Psychosom Med 69:660–666, 2007.

Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD: Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry 66:407–414, 2009.

Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W: Effect of alcohol consumption on systemic markers of inflammation. Lancet 357:763–767, 2001.

Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S: Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med 166:1756–1762, 2006.

Jerrell JM, McIntyre RS, Tripathi A: A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder. J Clin Psychiatry 71:1518–1525, 2010.

Joe K-H, Kim Y-K, Kim T-S, Roh S-W, Choi S-W, Kim Y-B, Lee H-J, Kim D-J: Decreased plasma brain-derived neurotrophic factor levels in patients with alcohol dependence. Alcohol Clin Exp Res 31:1833–1838, 2007.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PVS, Kauer-Sant'Anna M, Klamt F, de Bittencourt Pasquali MA, Quevedo J, Gama CS, Post R: A systemic toxicity index developed to assess peripheral changes in mood episodes. Mol Psychiatry 15:784–786, 2010.

Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vázquez GH, Vieta E, Berk M: The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 33:1366–1371, 2009.

Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, Kauer-Sant'Anna M, Grassi-Oliveira R, Post RM: Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. Neurosci Biobehav Rev 32:675–692, 2008.

Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, Yatham LN: Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol 12:447–458, 2009.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988, 1997.

Kim Y-K, Jung H-G, Myint A-M, Kim H, Park S-H: Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 104:91–95, 2007.

Knijff EM, Breunis MN, van Geest MC, Kupka RW, Ruwhof C, de Wit HJ, Nolen WA, Drexhage HA: A relative resistance of T cells to dexamethasone in bipolar disorder. Bipolar Disord 8:740–750, 2006.

Kraepelin E: Manic-Depressive Insanity and Paranoia. Edinburgh: E.S. Livingstone; 1921.

Lang UE, Hellweg R, Sander T, Gallinat J: The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentrations. Mol Psychiatry 14:120–122, 2009.

Lin P-Y: State-dependent decrease in levels of brain-derived neurotrophic factor in bipolar disorder: A meta-analytic study. Neurosci Lett 466:139–143, 2009.

Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK: Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 342:763–769, 2000.

Matsuo K, Walss-Bass C, Nery FG, Nicoletti MA, Hatch JP, Frey BN, Monkul ES, Zunta-Soares GB, Bowden CL, Escamilla MA, Soares JC: Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder. Neuropsychopharmacology 34:1904–1913, 2009.

McEwen BS: Protective and damaging effects of stress mediators. N Engl J Med 338:171–179, 1998.

Miller AH, Maletic V, Raison CL: Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol Psychiatry 65:732–741, 2009.

O'Brien SM, Scully P, Scott LV, Dinan TG: Cytokine profiles in bipolar affective disorder: Focus on acutely ill patients. J Affect Disord 90:263–267, 2006.

Ortiz-Dominguez A, Hernandez ME, Berlanga C, Gutierrez-Mora D, Moreno J, Heinze G, Pavon L: Immune variations in bipolar disorder: Phasic differences. Bipolar Disord 9:596–602, 2007.

Osby U, Brandt L, Correia N, Ekbom A, Sparen P: Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 58:844–850, 2001.

Pacifici R, Zuccaro P, Pichini S, Roset PN, Poudevida S, Farre M, Segura J, De la Torre R: Modulation of the immune system in cannabis users. JAMA 289:1929–1931, 2003.

Padmos RC, Hillegers MHJ, Knijff EM, Vonk R, Bouvy A, Staal FJT, de Ridder D, Kupka RW, Nolen WA, Drexhage HA: A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch Gen Psychiatry 65:395–407, 2008.

Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN: Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: Effects of treatment and clinical response. J Am Acad Child Adolesc Psychiatry 47:1077–1085, 2008.

Post RM: Role of BDNF in bipolar and unipolar disorder: Clinical and theoretical implications. J Psychiatr Res 41:979–990, 2007.

Rao JS, Harry GJ, Rapoport SI, Kim HW: Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry 15:384–392, 2010.

Rapaport MH, Manji HK: The effects of lithium on *ex vivo* cytokine production. Biol Psychiatry 50:217–224, 2001.

Rapoport SI, Bosetti F: Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder? Arch Gen Psychiatry 59:592–596, 2002.

Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, Secher NH, Pedersen BK, Pilegaard H: Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol 94:1062–1069, 2009.

Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Jr., Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ: Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. N Engl J Med 359:2195–2207, 2008.

Sen S, Duman R, Sanacora G: Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. Biol Psychiatry 64:527–532, 2008.

Tang SW, Chu E, Hui T, Helmeste D, Law C: Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. Neurosci Lett 431:62–65, 2008.

Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J: 11-year follow-up of mortality in patients with schizophrenia: A population-based cohort study (FIN11 study). Lancet 374:620–627, 2009.

Tsuang MT, Woolson RF, Fleming JA: Causes of death in schizophrenia and manic-depression. Br J Psychiatry 136:239–242, 1980.

Weeke A, Juel K, Vaeth M: Cardiovascular death and manic-depressive psychosis. J Affect Disord 13:287–292, 1987.

Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M: Brief screening for family psychiatric history: The family history screen. Arch Gen Psychiatry 57:675–682, 2000.

Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M, Conty M, Minnerup J, Ringelstein EB, Berger K, Deppe M, Knecht S: Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology 74:1022–1029, 2010.

Wright RJ, Newby DE, Stirling D, Ludlam CA, Macdonald IA, Frier BM: Effects of acute insulin-induced hypoglycemia on indices of inflammation: Putative mechanism for aggravating vascular disease in diabetes. Diabetes Care 33:1591–1597, 2010.

Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM: The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. Mol Psychiatry 14:51–59, 2009.

Address correspondence to:
Benjamin I. Goldstein, M.D., Ph.D., FRCPC
Department of Psychiatry
Sunnybrook Health Sciences Centre
Faculty of Medicine
University of Toronto
2075 Bayview Ave.
FG53
Toronto M4N-3M5
Canada

E-mail: benjamin.goldstein@sunnybrook.ca