Inflammation and the Phenomenology, Pathophysiology, Comorbidity, and Treatment of Bipolar Disorder: A Systematic Review of the Literature

Benjamin I. Goldstein, M.D., Ph.D.; F.R.C.P.C., David E. Kemp, M.D.; Joanna K. Soczynska, H.B.Sc.; and Roger S. McIntyre, M.D., F.R.C.P.C.

Objective: To review extant literature implicating inflammation in the pathophysiology of bipolar disorder. Furthermore, we review evidence regarding the anti-inflammatory actions of mood-stabilizing medication, the putative reciprocal association of inflammation with behavioral parameters and medical burden in bipolar disorder, and the potential role of anti-inflammatory agents in the treatment of bipolar disorder.

Data Sources: MEDLINE and PubMed searches were conducted of English-language articles published from 1950 to April 2008 using the search terms *bipolar disorder*, *manic*, or *mania*, cross-referenced with *inflammation*, *inflammatory*, *interleukin*, *cytokine*, *C-reactive protein*, or *tumor necrosis factor*. The search, which was conducted most recently on August 20, 2008, was supplemented by manually reviewing reference lists from the identified publications.

Study Selection: Articles selected for review were based on adequacy of sample size, the use of standardized experimental procedures, validated assessment measures, and overall manuscript quality.

Data Extraction: Studies were reviewed for statistical comparisons of cytokines among persons with and without bipolar disorder, during symptomatic and non-symptomatic intervals and before and after pharmacologic treatment. Significant and nonsignificant findings were tabulated.

Data Synthesis: Available evidence indicates that bipolar disorder and inflammation are linked through shared genetic polymorphisms and gene expression as well as altered cytokine levels during symptomatic (i.e., mania and depression) and asymptomatic intervals. However, results are inconsistent. Several conventional mood stabilizers have anti-inflammatory properties. The cyclooxygenase-2–selective anti-inflammatory celecoxib may offer antidepressant effects. Inflammation is closely linked with behavioral parameters such as exercise, sleep, alcohol abuse, and smoking, as well as with medical comorbidities including coronary artery disease, obesity and insulin resistance, osteoporosis, and pain. Methodological limitations precluding definitive conclusions are heterogeneity in sample composition, cytokine assessment procedures, and treatment regimens. The inclusion of multiple ethnic groups introduces another source of variability but also increases the generalizability of study findings.

Conclusion: Inflammation appears relevant to bipolar disorder across several important domains. Further research is warranted to parse the reciprocal associations between inflammation and symptoms, comorbidities, and treatments in bipolar disorder. Studies of this topic among youth are needed and may best serve this purpose.

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Received June 29, 2008; accepted Aug. 22, 2008. *From the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pa. (Dr. Goldstein); the Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio (Dr. Kemp); the Mood Disorders Psychopharmacology Unit, University Health Network, and the Institute of Medical Science, University of Toronto, Ontario, Canada (Dr. McIntyre and Ms. Soczynska); and the Departments of Psychiatry and Pharmacology, University of Toronto, Ontario, Canada (Dr. McIntyre).*

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Corresponding author and reprints: Benjamin I. Goldstein, M.D., Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 16213 (e-mail: goldsteinbi@upmc.edu).

The macrophage theory of depression was articulated nearly 20 years ago in an effort to consolidate several related observations, including a growing recognition that pro-inflammatory cytokines can precipitate depressive symptoms among healthy volunteers and that depression commonly occurs in illnesses associated with inflammation, such as coronary artery disease and rheumatoid arthritis.[1] Since that time, accumulating evidence indicates that alteration in inflammation is salient to the pathogenesis and possibly treatment of major depressive disorder (MDD).[2,3] Studies have also examined the role of inflammation in other neuropsychiatric illnesses, such as schizophrenia[4] and Alzheimer's disease.[5] There is evidence that provocation of

a pro-inflammatory response among healthy volunteers is accompanied by increased levels of affective symptoms and decreased neurocognitive performance.[6]

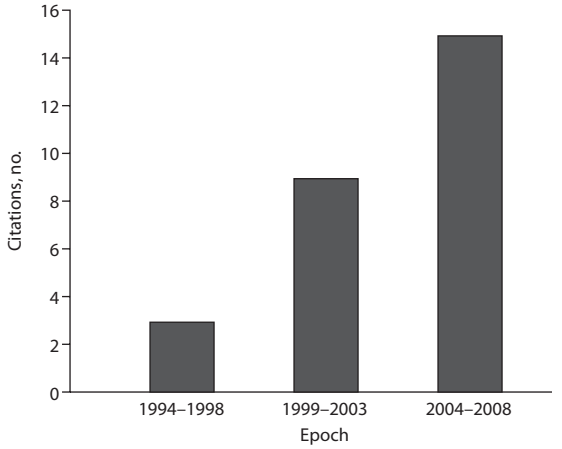
Taken together, studies regarding inflammation in MDD suggest that pro-inflammatory cytokines may subserve depressive symptomatology by activation of the hypothalamic-pituitary-adrenal (HPA) axis and by affecting central monoaminergic systems[2,3] The interactions between cytokines, the HPA axis, and monoamines are complex, however, and are thought to involve multiple factors, including glutamate, calcium, and protein kinase C, among others.[7] Activation of astrocytes and microglia cells and disruption of the blood-brain barrier have similarly been implicated in the role of cytokines in psychiatric disorders.[8] The role of inflammation in neuronal damage and degeneration is well established[9,10] and may be particularly pronounced among those with disturbances in other interacting metabolic networks.[11]

Until recently, however, few studies had examined the potential role of inflammation in bipolar disorder (Figure 1). Bipolar disorder is a severe and impairing neuropsychiatric illness with onset that is frequently early in life and whose diagnosis and treatment are often delayed by more than 10 years.[12–14] In addition to frequent psychiatric comorbidity of bipolar disorder[15,16] co-occurring medical conditions are also common.[17] In a recent editorial, Miller and Manji[18] concluded that "the relevance of inflammatory processes to disorders of the brain and body may thus serve as an important touchstone for increasing integration of psychiatry and medicine." Indeed, previous authors[19] have hypothesized that systemic inflammation may be associated with early natural death in bipolar disorder. Given these findings and observations, we set out to examine the topic of inflammation as it relates to bipolar disorder. Our primary objective was to systematically review the literature regarding the association between inflammation and bipolar disorder. Our secondary objective was to selectively examine evidence implicating anti-inflammatory actions of conventional pharmacotherapy in bipolar disorder, putative reciprocal associations of inflammation with behavioral parameters and medical burden in bipolar disorder, and the potential role of conventional anti-inflammatory agents as possible therapeutic avenues in bipolar disorder.

METHOD

MEDLINE and PubMed searches were conducted of English-language articles published between 1950 and April 2008 using the following search terms: *bipolar disorder*, *manic*, or *mania*, cross-referenced with *inflammation*, *inflammatory*, *interleukin* (IL), *cytokine*, *C-reactive protein* (CRP), or *tumor necrosis factor* (TNF). Articles selected for review were based on adequacy of sample size, the use of standardized experimental procedures, validated assessment measures, and overall manuscript quality. In addition, reference lists from the identified publications were then manually reviewed. The search was conducted most recently on August 20, 2008.

Figure 1. Citations Regarding Bipolar Disorder and Inflammation by 5-Year Epochs



INFLAMMATION AND BIPOLAR DISORDER

The central findings from the 27 studies identified are summarized in Table 1. Table 2 depicts the findings regarding individual cytokines during mania, depression, and euthymia and as they relate to treatment and/or changes in symptoms. Consistent themes in these findings are highlighted below. Cytokines are small proteins released by cells that play a role in inflammation via specific effects on the interactions and communications between cells. ILs, CRP, and TNF-α are examples of cytokines. For parsimony, the appellation *pro-inflammatory markers* (PIMs) is used here to describe factors associated with increased inflammation. Cytokines ascertained via in vitro exposure of macrophages or plasma to mitogen, lipopolysaccharide, or phytohemagglutinin are described as *stimulated*.

Inflammation During Mania or Depression

Taken together, findings regarding PIMs during mania generally provide evidence for increased PIMs, particularly CRP, soluble IL-2 receptor (sIL-2R), IL-6, and TNF-α. Findings regarding anti-inflammatory markers (such as IL-4, IL-10), or imbalance between pro- and anti-inflammatory markers, are less consistent. For example, 2 studies have found increased levels of IL-4 among subjects with mania compared to controls,[31,39] whereas a third study[37] found that subjects with bipolar disorder demonstrated significantly higher levels of IL-6 and TNF-α, significantly lower levels of IL-4, and significantly greater ratios of pro- vs. anti-inflammatory cytokines versus controls. Relatively fewer studies have examined inflammation during bipolar depression, although elevations in several PIMs appear to

Table 1. Characteristics and Findings of Studies Regarding Inflammatory Markers and Bipolar Disorder

Study	Country	Participants	Measures	Findings
Rapaport,[20] 1994	United States	26 euthymic BD-I and -II, 34 controls	Stimulated IL-2[a], sIL-2R	Between-group difference NS; trend toward higher levels in BD males vs females
Maes et al,[21] 1995	United States	10 manic BD-I, 14 SCZ, 21 controls	IL-6, sIL-6R, sIL-2R	sIL-6R and SIL-2R in mania > controls. Reduced PIMs in SCZ after antipsychotics; no change in BD after valproate
Hornig et al,[22] 1998	United States	103 BD-I and -II, 46 MDD, 22 controls	CRP	CRP > 6mg/L in 8.9% BD-I, 0% BD-II, 23.9% MDD, 4.5% controls; NS. No difference between currently depressed vs euthymic; 0/5 of currently hypo/manic were CRP+; lower rates of CRP+ if taking lithium
Rapaport et al,[23] 1999	United States	17 rapid-cycling BD-I and -II, 18 controls	IL-2, IL-4, IL-6, IL-10; sIL-2R, sIL-6R; IFN-γ	Most undetectable. sIL-2R and sIL-6R increased in BD, normalized with lithium. Lithium treatment increased IL-2, sIL-2R, and sIL-6R in controls. No association between mood and PIMs. No association with demographic or clinical variables
Tsai et al,[24] 1999	Taiwan	23 BD-I manic then remitted; 23 controls	Stimulated IL-2R, sIL-6R	sIL-2R higher in mania vs remission and vs controls. Decreased sIL-2R with decreased manic severity. Remitted vs controls, NS
Tsai et al,[25] 2001	Taiwan	31 BD-I manic, 31 matched controls	sIL-2R, sIL-6R	sIL-2R higher in mania vs remission and vs controls; proportional with manic symptoms r = 0.34; change in mania and change in sIL-2R highly correlated r = 0.61. No association with other clinical variables
Kim et al,[26] 2002	Korea	25 BD-I manic, 34 MDD, 43 SCZ, 85 controls	IL-12	MDD > controls; other comparisons NS; IL-12 decreased after treatment, but not associated with smoking, age, BMI, or other variables
Su et al,[27] 2002	Taiwan	20 BD-I manic, 15 controls	Stimulated sIL-2R, IL-10, IFN-γ	IFN-γ in BD mania and BD remission < controls; no difference in IL-10; no association with clinical variables. In mania, IFN-γ and IL-10 did not differ between medicated and medication-free subjects
Wadee et al,[28] 2002	South Africa	45 BD-I manic, 45 controls	CRP	CRP greater in manic group (11.4 vs 4.7), but NS
Breunis et al,[29] 2003	The Netherlands	172 BD-I and -II, 66 matched controls	sIL-2R	sIL-2R in BD euthymic, manic, depressed > controls; manic > depressed
Boufidou et al,[30] 2004	Greece	BD-I and -II, 40 lithium-treated euthymic, 10 medication-naive, 20 controls	Stimulated IL-2, IL-6, IL-10, IFN-γ	PIMs among lithium-treated BD < controls. Decreased PIMs among medication-naive following treatment. Finding observed for lithium responders and nonresponders. No in vitro effect of lithium among BD subjects or volunteers
Kim et al,[31] 2004	Korea	70 BD-I manic (baseline and 8 wk), 96 controls	IFN-γ, IL4	Both markers higher in BD. Change during treatment NS. No association with demographic or clinical variables
Liu et al,[32] 2004	Taiwan	29 BD-I manic, 20 controls	Stimulated IL-1RA, IL-2, IL4, IL-10, IFN-γ	IL-1RA higher in acute mania and remission; IFN-γ lower in mania and remission. IL-2, IL4, and IL-10, NS
O'Brien et al,[33] 2006	Ireland	21 BD (9 depressed, 12 manic); 21 controls	IL-6, IL-8, IL-10; TNF-α, sIL-6R	BD depression and mania had greater IL-8 and TNF-α vs controls; trend toward increased IL-6 in BD; significant for mania only. No significant association with symptomatic severity
Knijff et al,[34] 2006	The Netherlands	54 BD-I and -II, 19 controls	Stimulated IL-2R with dexamethasone suppression	Dexamethasone suppression in BD < control, especially at low concentration of dexamethasone (18.9% vs 35.8% suppression); no association between circulating and stimulated IL-2R; no association with demographic or clinical characteristics or mood symptoms
Dickerson et al,[35] 2007	United States	122 BD-I and-II, 165 controls	CRP	Within BD sample, CRP associated with mania symptoms, younger age at onset, female sex, and nonwhite race. CRP only independent predictor of mania symptoms. BD > controls only if YMRS > 6. No association with depression symptoms or clinical characteristics
Huang and Lin,[36] 2007	Taiwan	13 BD-I manic, 23 MDD, 31 controls	hsCRP	hsCRP in BD, MDD > controls; after adjusting for age, only BD > controls
Kim et al,[37] 2007	Korea	37 BD-I manic, 74 controls	Stimulated IL-2, IL-4, IL-10, TNF-α, and IFN-γ	IL-6 and TNF-α BD > controls; IL-4 BD < controls. Pro: Anti-inflammatory ratios greater in BD; IL-6 decreased at 6 weeks. No association with demographic or clinical variables

(continued)

Table 1 (continued). Characteristics and Findings of Studies Regarding Inflammatory Markers and Bipolar Disorder

Study	Country	Participants	Measures	Findings
Knijff et al,[38] 2007	The Netherlands	80 BD-I and-II, 59 controls	IL-1β, IL-6	Decreased IL-1β: IL-6 ratio among nonlithium–treated subjects. IL-1β increased and IL-6 decreased with lithium treatment. In vitro lithium decreased IL-1β, minimal effect on IL-6
Ortiz-Dominguez et al,[39] 2007	Mexico	20 unmedicated BD-I (10 manic, 10 depressed), 33 controls	IL-1β , IL-2, IL-4, IL-6; TNF-α	Vs controls: BD-depression had > IL-6, TNF-α, < IL-2. BD-mania had > IL-4, TNF-α, < IL-1β, IL-2 Mania vs depression: > IL-4, < IL-1β, IL-6
Cunha et al,[40] 2008	Brazil	80 BD-I (30 manic, 30 depressed, 20 euthymic), 32 controls	hsCRP	hsCRP increased in mania vs BD depressed or euthymic, or controls. No significant correlation with manic or depressive symptoms

[a]Where not otherwise indicated, PIM levels were ascertained only from serum/plasma without stimulation.
Abbreviations: BD = bipolar disorder, BMI = body mass index, CRP = C-reactive protein, hsCRP = high-sensitivity CRP, IFN = interferon, IL = interleukin, IL-1RA = interleukin-1 receptor antagonist, MDD=major depressive disorder, NS = not significant, PIMs = pro-inflammatory markers, SCZ = schizophrenia, sIL-2 = soluble interleukin-2, sIL-2R = soluble interleukin-2 receptor, sIL-6R = soluble interleukin-6 receptor, TNF = tumor necrosis factor, YMRS = Young Mania Rating Scale.

overlap with those elevated during mania, including sIL-2R, IL-6, IL-8, CRP, and TNF-α (see Table 1; e.g., Kim et al.,[31] Papiol et al.,[44] and Middle et al.[47]). Finally, there is preliminary evidence of increased IL-1β and IL-6 during depression versus mania, and increased sIL-2R, IL-4, and CRP during mania versus depression.[44,55,56]

Changes in Inflammation After Treatment and/or Symptomatic Improvement

Most studies that have tested for associations between PIMs and treatment and/or resolution of symptoms have not reported significant findings. The nature of this association may vary between cytokines. Several studies regarding sIL-2R and IL-6 suggest that changes in these PIMs are associated with treatment and/or symptom resolution.[29,45,54] In contrast, although several studies[49,53,55] have found increased levels of TNF-α during mania and bipolar depression, significant associations with treatment and/or symptom resolution have not been reported.

Inflammation During Euthymia

Few studies have reported findings regarding inflammation during euthymia. Breunis and colleagues[29] found that sIL-2R is elevated among euthymic bipolar disorder subjects versus controls, similar to findings during mania and depression. Although no significant findings have been reported regarding the anti-inflammatory cytokine IL-10 during mania or depression, one study[30] reported decreased levels of IL-10 among euthymic subjects with bipolar disorder under lithium treatment. The same study also found decreased levels of IL-2, -6, and -10 during euthymia. A preliminary Canadian study[41] examined serum cytokines in relation to cognitive performance among 20 euthymic subjects with bipolar disorder. The researchers found that TNF-α is associated with intrusions on California Verbal Learning Test (CVLT), that IL-8 is associated with repetitions on CVLT, and that recollection deficits are negatively associated with IFN-γ. Finally, IL-1RA was significantly associated with self-reported cognitive deficits. There were no significant cytokine differences between cognitively impaired (≥ 1 SD below the norm on the CVLT) versus non-impaired subjects, and there was no significant association of CRP with cognitive performance.

Lack of Association Between Cytokines and Demographic or Clinical Variables

Several studies[34,46,50] examined whether cytokines are associated with a variety of clinical variables other than changes in symptoms, such as duration of illness, age at bipolar disorder onset, smoking, and obesity. Similarly, many studies[34,46,50] examined whether cytokines are associated with demographic variables such as age and sex. However, to date, no demographic or clinical correlates of inflammation among subjects with bipolar disorder have been reported. As acknowledged in the Summary section below,

Table 2. Summary of Findings Regarding Inflammatory Markers and Bipolar Disorder[a]

Cytokine	Mania vs Controls	Mania vs Euthymia	Depression vs Controls	BD (various mood states) vs Controls	Mania (M) vs Depression (D)	Internally Confirmatory Findings[b]
IL-1RA	↑	↑				
IL-1-β	↓				D > M	+
IL-2	↓		↓	↓		+
sIL-2R	↑↑↑↑	↑↑	↑	↑	M > D	+++
IL-4	↑↑↓				M > D	
IL-6	↑↑		↑	↓	D > M	+++
sIL-6R	↑			↑		+
IL-8	↑		↑			
IL-10				↓		+
IL-12						+
CRP	↑↑	↑	↑		M > D	+
TNF-α	↑↑↑		↑↑			
IFN-γ	↑↓↓	↓↓		↓		+

[a]Each arrow signifies a study that found statistically significant between-group differences. Relative increases are noted with a ↑, whereas decreases are noted with a ↓.
[b]Including correlation with symptom severity and/or change in levels following treatment; each separate study denoted by +.
Abbreviations: BD = bipolar disorder, CRP = C-reactive protein, IFN = interferon, IL = interleukin, IL-1RA = interleukin-1 receptor antagonist, sIL-2R = soluble interleukin-2 receptor, sIL-6R = soluble interleukin-6 receptor, TNF = tumor necrosis factor.

the literature is constrained by important methodological limitations, and these limitations may explain in part the lack of association with demographic or clinical variables. In particular, modest sample sizes and heterogeneity in sample characteristics and methodologies may be contributory.

Evidence for Glucocorticoid Resistance

A recent study[34] from the Netherlands examined the impact of dexamethasone suppression on stimulated sIL-2R expression among 54 subjects with bipolar disorder and 29 controls. At low concentrations of dexamethasone, sIL-2R was reduced by 35.8% among subjects with bipolar disorder as compared with an 18.9% reduction among controls. That a significant difference in suppression was observed at low, but not high, concentrations of dexamethasone suggests relative resistance. This finding is noteworthy given the evidence that cytokines may lead to glucocorticoid resistance through direct effects on glucocorticoid receptor expression and function.[42,43] No demographic variables or clinical variables such as mood state, duration of illness, or duration of treatment were significantly correlated with dexamethasone suppression. Of note, although serum sIL-2R concentrations were elevated among subjects with bipolar disorder compared to controls, this difference disappeared after 72-hour in vitro culture. This observation suggests the possibility that subjects with bipolar disorder had a pro-inflammatory in vivo milieu.

Inflammation-Related Genetic Polymorphisms and Expression

Papiol and colleagues,[44] from Spain, examined a polymorphism in the promoter region of the *IL1B* gene and the variable nucleotides tandem repeat (VNTR) polymorphism of the *IL1RA* gene among 88 subjects with bipolar disorder, 78 subjects with schizophrenia, and 176 controls. They found a significant excess of the haplotypic combination among subjects with bipolar disorder and schizophrenia compared to controls. The highest prevalence of this haplotype was observed among subjects with bipolar disorder with family history of bipolar disorder, schizophrenia, or MDD. The authors concluded that *IL1* cluster genetic variability may comprise shared genetic susceptibility for bipolar disorder and schizophrenia. In contrast, Kim and colleagues,[45] from Korea, examined the *IL1RA* VNTR polymorphism among 83 subjects with bipolar disorder, 269 subjects with schizophrenia, and 297 controls and found a significant association with schizophrenia but not with bipolar disorder.

Another study[46] from Korea examined the *TNFA* 308 polymorphism among 89 subjects with bipolar disorder and 125 controls. The *TNF2* allele was significantly more common among subjects with bipolar disorder in comparison to controls (21.3% vs 7.2%). In contrast, a previous United Kingdom study of women with BD with (N = 116) or without (N = 56) puerperal psychosis, compared to healthy controls (N = 72), found no significant association between either bipolar disorder or puerperal psychosis and the *TNFA* 308 polymorphism.[47] Meira-Lima and colleagues,[48] from Brazil, similarly found no significant association between this polymorphism and bipolar disorder (N = 161), although this variant was more common among subjects with schizophrenia (N=186) versus controls (N = 657).

Padmos and colleagues [49] identified a signature of 19 aberrantly expressed messenger RNAs for inflammatory genes. Subjects included 42 adults with bipolar disorder, 25 adult controls, 54 adolescent or young adult offspring of parents with bipolar disorder (of whom 16 had a mood disorder at baseline or during follow-up), and 70 adolescent

or young adult controls. The pro-inflammatory signature was observed among 52% of bipolar disorder adults, 18% of control adults, 88% of bipolar disorder offspring with mood disorder, 45% of bipolar disorder offspring without mood disorder, and 19% of control adolescents. The *IL6* gene was among the strongest variables distinguishing bipolar disorder adults from controls. *IL6* differed significantly between the bipolar disorder offspring (with and without mood disorders) and controls, and between bipolar disorder offspring with versus without mood disorder.

In summary, genetic findings suggest that bipolar disorder is associated with *IL1* and *IL6* genetic polymorphisms and that there have been contradictory findings for *TNFA* polymorphisms. Moreover, aberrant expression of inflammatory genes may comprise an endophenotype or biologic marker for bipolar disorder, although replication studies are needed.

Inflammation and Mood Stabilizers

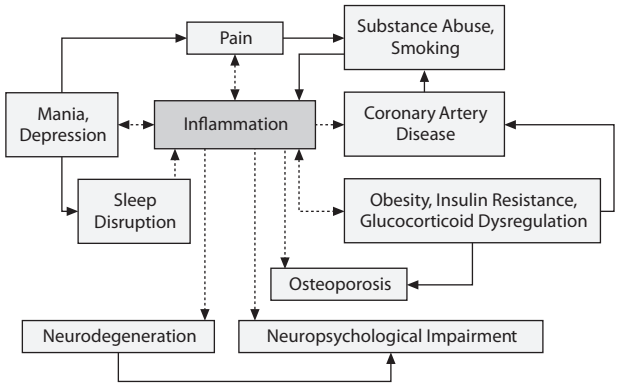
Several clinical and pre-clinical studies suggest that the mechanism of action of mood stabilizing medications (e.g., antipsychotics, carbamazepine, lamotrigine, lithium, and valproate) may include cyclooxygenase 2 (COX-2) inhibition and reduction in inflammatory cytokines.[50–59] Several studies have also examined the association between lithium treatment and markers of inflammation among subjects with bipolar disorder, although some of these studies have included subjects taking other medications as well.

Hornig and colleagues[22] found that significantly fewer subjects taking lithium were considered CRP-positive as compared to subjects not taking lithium. There was a similar trend among subjects taking lithium in addition to an antidepressant. Rapaport and colleagues[23] found that lithium treatment resulted in increased IL-2, sIL2R, and soluble IL-6R (sIL6R) among healthy controls. There were trends toward significant diagnosis-by-treatment interaction ($p < .10$) for both sIL2R and sIL6R. The authors speculated that, in healthy controls, lithium may stimulate these inflammatory markers by decreasing the levels of cyclic adenosine monophosphate, which has an inhibitory effect on cytokines such as *IL6*.

Knijff and colleagues[38] found that in vitro addition of lithium to monocytes from healthy subjects dose-dependently down-regulated lipopolysaccharide and stimulated IL-1β production but did not influence IL-6 production. A recent study[30] from Greece examined IL-2, IL-6, IL-10, and IFN-γ among 50 euthymic subjects with bipolar disorder (N = 40 taking long-term lithium, N = 10 medication-naive) and 20 controls. Lithium-treated subjects with bipolar disorder had significantly lower levels of IL-2, IL-6, IL-10, and IFN-γ compared to controls. Subsequent treatment of medication-naive subjects with bipolar disorder with lithium results in decreased cytokine production after 3 months of treatment, and this decrease in production was observed in all of the cytokines examined. In vitro stimulation with lithium did not have a significant effect among subjects with bipolar disorder or controls. Finally, Padmos and colleagues[49] found that treatment with lithium and antipsychotics down-regulated expression of most inflammatory genes examined.

In summary, it appears that lithium attenuates the pro-inflammatory milieu in bipolar disorder, although the opposite effect may be observed among nonbipolar disorder subjects. Although studies of bipolar disorder have examined changes in inflammation following medication treatment, to our knowledge, none have examined whether inflammation is a moderator or mediator of treatment response. Preliminary data from MDD indicate that treatment response may be predicted by certain baseline IL-6 levels, whereas TNF-α levels correlate with changes in depression symptoms during treatment.[60] It remains to be determined whether the same correlations are true in bipolar disorder.

Figure 2. Putative Role of Inflammation in Bipolar Disorder



MEDICAL BURDEN IN BIPOLAR DISORDER

The excessive burden of medical conditions in bipolar disorder is increasingly recognized.[17] Examples of medical conditions that are both prevalent in bipolar disorder and related to inflammation include cardiovascular illness, obesity and insulin resistance/diabetes, pain, arthritis, and headache. Similarly, alcohol use disorders (AUDs) are both prevalent in bipolar disorder and related to inflammation. A conceptual framework for understanding the inter-relationships between all of these factors is depicted in Figure 2.

Cardiovascular Illness

For over 25 years, studies have demonstrated increased mortality due to cardiovascular disease in bipolar disorder,[61–63] with the most recent estimates suggesting standardized mortality ratios of 1.9 and 2.6 for men and women, respectively.[64] The onset of cardiovascular illness may also be earlier than in the general population.[65] Inflammation is an antecedent of cardiovascular disease among men[66] and women[67] and

may independently predict mortality among persons experiencing acute coronary syndromes.[68,69] Fortunately, reducing inflammation may improve cardiac outcomes independent of other factors such as cholesterol.[70] For this reason, measurement of inflammatory markers has become part of the clinical biomarker armamentarium in cardiology.[71]

Obesity and Insulin Resistance/Diabetes

The majority of adults with bipolar disorder are overweight or obese,[72,73] and epidemiologic data suggest mutually increased prevalence of bipolar disorder and obesity.[74,75] Similarly, the prevalence of diabetes is elevated in bipolar disorder,[76,77] even after controlling for psychotropic medications.[78,79] Inflammatory markers, particularly *CRP*, IL-6, and TNF-α, are elevated in obesity.[80] Most research has been cross-sectional[81]; however, there is evidence for a bidirectional association between inflammation and obesity. Subcutaneous fat releases inflammatory markers such as IL-6,[82] but stress-induced inflammation may also lead to obesity.[83] There may also be an association between inflammation and diabetes/insulin resistance independent of obesity.[84] Evidence of genetic inflammatory diathesis has been reported for obesity[85] and type II diabetes.[86] A recent review concluded that increased TNF-α is a consequence, rather than a cause, of antipsychotic-induced weight gain.[87] To our knowledge, however, cytokines such as IL-6 have yet to be examined as they relate to medication-induced weight gain.

Antidiabetic agents may also provide future treatment options. A recent study found that rosiglitazone, a thiazolidinedione, results in rapid and significant reduction in CRP levels independent of its effect on glycemia, and that this change was associated with regression of carotid artery intima-media thickness.[88] Studies are currently underway that examine the impact of these medications on mood disorders.[89,90]

Pain, Arthritis, and Headache

There is evidence for elevated burden of several pain conditions, including arthritis, backache, and headache, in bipolar disorder.[91–94] There is abundant evidence that pathologic pain is mediated by cytokines, particularly IL-1β, IL-6, and TNF-α.[95] Similarly, inflammation has been implicated in migraine headaches,[96,97] rheumatoid arthritis,[98] and osteoarthritis.[99]

Smoking and Alcohol Use

In addition to these medical comorbidities, comorbid AUDs (i.e., alcohol abuse or dependence) are prevalent among the majority of individuals with bipolar disorder at some point during their lifetime. Alcohol is the most common substance of abuse in bipolar disorder, and bipolar disorder is arguably the Axis I psychiatric disorder most strongly associated with AUDs.[100,101] Epidemiologic data indicate that the lifetime prevalence of daily smoking among adults with bipolar disorder is 82.5%, more than twice as high as that of adults with no mental illness (39.1%) and higher than that of adults with lifetime major depression (59%).[102] Unfortunately, the cessation rate for adults with bipolar disorder (16.6%) is substantially lower than for adults with no mental illness (42.5%) or those with lifetime major depression (38.1%).[102] Both cigarette smoking[103] and heavy alcohol use[104] are associated with increased systemic inflammation.

Other Factors

Other factors that relate to the association between inflammation and bipolar disorder include osteoporosis, physical activity, and sleep. Little is known about osteoporosis and bipolar disorder, but the illness is thought to have a direct effect on bone density in addition to the effects of lithium (disturbed calcium metabolism and parathyroid hormone secretion), anticonvulsants (increased vitamin D catabolism), and antipsychotic medication (hyperprolactinemia).[105] Accordingly, inflammation is a recognized factor in the pathophysiology of osteoporosis.[106] Recent findings that inflammation contributes to decreased bone mass among premenopausal women with depression may extend to bipolar disorder as well.[107]

In addition to medication-related weight gain, decreased physical activity is one factor that has been implicated in the high rates of obesity.[108–111] It is therefore worthwhile noting that, in addition to any direct impact on obesity, physical fitness has been associated with smaller inflammatory responses to acute mental stress.[112]

Finally, sleep is a variable that is closely linked with bipolar disorder and inflammation. Even during euthymia, the majority of patients with bipolar disorder experience significant sleep difficulties including impaired sleep efficiency[113] and variability in sleep duration and night wake time.[114] Sleep disturbances result in significantly increased IL-6[115,116] and TNF-α, as well as increased transcription of messenger RNA for these variables.[116]

In summary, comorbid medical illnesses, smoking, and excessive alcohol use, which differentially affect individuals with bipolar disorder, are also associated with altered inflammatory networks. The same is true of decrements in physical activity and sleep parameters. In some cases, such as obesity, there is a bidirectional association between inflammation and comorbidity. In other cases, such as smoking and alcohol use, inactivity, and sleep disturbance, inflammation is generally a consequence rather than a cause. Nonetheless, the latter behavioral parameters are inherent to bipolar disorder and may contribute significantly to the cumulative burden of inflammation in bipolar disorder.

POTENTIAL ROLE FOR ANTI-INFLAMMATORY MEDICATIONS IN BIPOLAR DISORDER

The potential role of anti-inflammatory agents in the treatment of psychiatric illness has been suggested by results from several recent studies. For example, celecoxib has

shown promise as an adjunctive treatment in bipolar disorder, MDD, and schizophrenia.[117–120]

A recent 6-week, double-blind, randomized, placebo-controlled study[117] examined the efficacy of adjunctive celecoxib 400 mg/day for the treatment of depressive or mixed episodes among adults with bipolar disorder.[117] The celecoxib-treated subjects evinced a greater numerical improvement when compared to the placebo-treated subjects in the first week of therapy using intention-to-treat analysis. Amongst individuals who completed the full duration of treatment, celecoxib-treated subjects exhibited a significantly greater improvement from baseline to endpoint. However, the small sample size (N = 28) increases the probability of a type II error. Moreover, 64% of the sample had comorbid substance use disorders indicative of a more complex illness presentation.

A separate 6-week, double-blind, randomized, placebo-controlled study examined the efficacy of celecoxib 400 mg/day as an adjuvant to reboxetine (4–10 mg) for the treatment of MDD among 40 subjects (93% inpatients) with MDD.[118] Celecoxib-treated subjects demonstrated a significantly greater decrease in depressive symptoms compared to placebo-treated subjects. The advantage of celecoxib was also apparent on secondary outcome measures (e.g., response rates).

Adjunctive celecoxib (in addition to atypical antipsychotics) has also shown promise in the treatment of schizophrenia. Two studies have found that celecoxib-treated (400 mg/day) subjects exhibited a reduction in overall positive and negative symptoms when compared to placebo, and that celecoxib was well tolerated.[119,120] A third negative study was reported that included continuously ill outpatients (versus acutely ill inpatients) who were older when compared to the positive studies.[121] Attempts to identify predictors of response indicated that celecoxib responders exhibited increased sIL-2R after 5 weeks of treatment and lower pretreatment levels of TNF-α receptor.[122] Data regarding cytokines from the Rapaport study suggest that celecoxib combined with olanzapine may result in a transient increase in TNF-α and IL-2.[123]

Taken together, the findings regarding celecoxib suggest that the principal benefit of adjunctive treatment may be the acceleration of treatment response among acutely ill patients at early stages of the illness. Larger controlled studies are warranted to corroborate and extend these findings. Future studies of celecoxib and other anti-inflammatory medications are need to identify predictors of response such as age, duration of illness, comorbidity, inflammation-related genotypes, and cytokine levels in order to maximize the risk-benefit ratio of these medications. Similarly, studies are needed to evaluate whether changes in cytokine levels mediate treatment response.

Neuroprotection

Neuroprotective effects of celecoxib against macrophage toxicity toward motor neurons have been reported,[124] as have neuroprotective effects of rofecoxib against induced excitotoxicity of cholinergic neurons.[125] COX-2 inhibitors may also have neuroprotective effects in brain regions that are more directly related to bipolar disorder. A study of celecoxib in a rat model of depression found that celecoxib treatment was associated with significantly lower hypothalamic IL-1β and IL-10 concentrations. Celecoxib treatment also resulted in significantly lower prefrontal cortical TNF-α and IL-1β and higher IL-10.[126] Another preclinical study found that celecoxib normalizes age-related increase of hippocampal TNF-α and IL-1β, as well as corticosterone.[127] These foregoing changes paralleled reduced aversive behavior in a conflict situation and improved cognitive ability in a spatial learning test.

"Somatoprotection"

Given the vastly increased burden of medical illness in bipolar disorder,[17] it is important to consider the potential impact of new medications on medical problems that are common in this population. Indeed, recent studies suggest that celecoxib may have tumoricidal and anti-angiogenic properties,[128–130] in addition to analgesic and anti-arthritic properties.[131] Celecoxib also enhances glucocorticoid receptor function.[132] This fact is important in light of glucocorticoid dysregulation in manic, depressed, and euthymic phases of bipolar disorder,[133] the known effects cytokines have on glucocorticoid receptor expression and function,[32,42] and the impact that glucocorticoid dysregulation has on allostatic load.[134,135] It remains to be determined how celecoxib's analgesic, anti-inflammatory, and other medically beneficial properties relate to its putative benefits in psychiatric illness. Nonetheless, treatment with celecoxib is not without risks. Although it does not appear that celecoxib shares the same propensity for cerebrovascular events as does rofecoxib, all nonsteroidal anti-inflammatories, including celecoxib, carry a "black-box" warning contained in the product insert underscoring the cardiovascular risks.

Other Anti-Inflammatory Treatments

TNF-α has been proposed as a possible pharmacologic target in bipolar disorder.[136] For example, the TNF antagonist etanercept has U.S. Food and Drug Administration approval for the treatment of rheumatoid arthritis in both pediatric and adult populations. There have been no studies to date regarding its effect in the treatment of mood disorders per se. However, preliminary findings related to its mood-modulating properties have been reported from a large placebo-controlled trial (N = 618) for psoriasis.[137,138] Although the study excluded patients with diagnosed psychiatric illness, subjects treated with etanercept demonstrated a significant reduction in Beck Depression Inventory (bipolar I disorder) and Hamilton Rating Scale for Depression (HAM-D) scores. Moreover, the proportion of bipolar I disorder responders (55% vs. 39%) and the proportion of subjects with minimal depressive symptoms (84% vs.

75%) were significantly greater in the etanercept group vs. placebo. Similar significant differences were observed with the HAM-D. Effect sizes for bipolar I disorder and HAM-D were 0.22 and 0.25, respectively.[138] As with other anti-inflammatory medications, etanercept has been associated with treatment-emergent mania.[139] In addition, etanercept is being evaluated for possible increased risk of lymphoma among children and young adults.[140]

Another treatment option relating to inflammation is omega-3 fatty acids. Multiple studies have found that omega-3 fatty acids have beneficial effects in acute and chronic inflammatory conditions and that they alter cytokine production ex vivo.[141] This alteration may explain in part the known benefits of omega-3 fatty acids on cardiovascular and endocrine-metabolic parameters.[140,142] Placebo-controlled studies have yielded both positive[143,144] and negative[145] findings in bipolar disorder. A small trial[144] (N = 30) found that a combination of ethyl-eicosapentanoic acid (EPA) 6.2 g/day and docosahexaenoic acid 3.4 g/day resulted in significantly longer duration of remission versus placebo. A larger study[143] of bipolar depression found that treatment with ethyl-EPA 1 to 2 g/day (N = 49) resulted in significant improvements in HAM-D scores and Clinical Global Impression scale (CGI) scores versus placebo (N = 26). No significant differences were observed between subjects receiving 1 g/day (N = 24) or 2 g/day (N = 25) of ethyl-EPA. Indeed, Keck and colleagues[145] hypothesized that the negative findings in their study of bipolar depression and rapid-cycling bipolar disorder (N = 116) may have been explained by the high ethyl-EPA dose of 6 g/day, which exceeded the 1–3 g/day effective dose in dose-ranging studies of MDD and schizophrenia.

In addition to examining anti-inflammatory medications, the effects of exercise on the association between inflammation and mood in bipolar disorder merit investigation. Recent findings suggest that exercise may attenuate inflammatory responses to acute mental stress in the general population,[112] although it has yet to be shown that exercise affects inflammatory mediators in bipolar disorder.

SUMMARY

The articles reviewed in this article provide early evidence that inflammation may explain, in part, the phenomenology, comorbidity, pathophysiology, and treatment response in bipolar disorder. However, it is important to acknowledge that, similar to other nascent areas of investigation, inferences and interpretations that can be drawn from the literature are constrained by several important limitations, which include heterogeneity in mood state, bipolar disorder subtype, cytokine ascertainment, nationality, and concurrent medications. Additionally, sample sizes are generally modest. The discrepancies of study findings may be explained in part by these methodological differences. Further, most studies do not control for known confounds, such as obesity and smoking. Studies that did include these variables did not find that they were significantly associated with inflammation. Previous authors have suggested that these variables may account in large part for the association between severe mental illness—including bipolar disorder—and inflammation.[146] Again, the methodological limitations may explain why, to date, studies of bipolar disorder have not found these variables to be associated with inflammation. Finally, studies to date have excluded subjects with comorbid medical disorders and substance use disorders. Given the high prevalence of these disorders in bipolar disorder,[147] these exclusion criteria limit the generalizability of the reviewed findings.

Despite the methodological limitations, the extant literature provides sufficient data to support the working hypothesis that altered inflammatory networks are salient to the pathophysiology and treatment of bipolar disorder. For example, there is evidence for either increased PIMs or an imbalance between pro- and anti-inflammatory markers in bipolar disorder. Second, genetic findings suggest that bipolar disorder may be associated with *IL*11 and *IL6* genes, whereas findings for *TNFA*α polymorphisms are conflicting. There is preliminary evidence for aberrant expression of inflammatory genes in bipolar disorder, which may comprise a susceptibility marker for bipolar disorder. Third, medications such as lithium may serve to modulate the inflammatory milieu in bipolar disorder, and this effect may indeed be specific to persons with bipolar disorder. Fourth, regardless of the direction of the associations, the high prevalence of comorbid medical illnesses, smoking, and excessive alcohol use, combined with decrements in physical activity and sleep parameters, contribute to a pro-inflammatory milieu in bipolar disorder. Finally, conventional anti-inflammatory therapies may possess symptom-alleviating effects among acutely ill patients at early stages of their illness.

Future Directions: Focus on Youth and Early Adversity

At present, there is insufficient evidence to support a recommendation for ascertainment of cytokines as part of the usual clinical management of bipolar disorder. Further studies are needed to demonstrate the potential clinical utility of including cytokines as part of the diagnostic or monitoring armamentarium in bipolar disorder. For example, no study to date has examined whether changes in cytokines may precede the onset of mood episodes. Longitudinal studies are needed to evaluate whether inflammatory dysregulation may be a predictor of important clinical outcomes such as relapse, recurrence, or polarity switches.

Similarly, no previous study has specifically examined inflammation among children or adolescents with bipolar disorder (although the study by Padmos and colleagues[49] did include some adolescent offspring of parents with bipolar disorder). Many of the studies from adults with bipolar disorder reviewed above included subjects with 20-year

courses of illness. Drawing definitive conclusions from subjects with prolonged illnesses is problematic because of the possibility that long-term symptom burden and pharmacologic treatment alter the association between bipolar disorder and inflammation. Indeed, inflammation may potentially play a larger role early in the disease process. Testing this hypothesis has treatment implications, as the relative risks and benefits of adjunctive anti-inflammatory medication may differ for youth. Youth are extremely prone to weight gain and metabolic effects conferred by mood stabilizers and antipsychotics, particularly when used in combination.[148] Therefore, the possibility of using anti-inflammatories as weight-neutral adjunctive treatments is particularly appealing in this population. Another advantage of examining this topic among youth is that this offers greater opportunity to detect differences between subjects with bipolar disorder and controls, as inflammation is extremely low among healthy youth.[149] Findings from Padmos and colleagues[49] suggest that offspring of parents with bipolar disorder are more than twice as likely to express an aberrant inflammation-related messenger RNA signature compared to offspring of controls. Future longitudinal studies are needed to examine whether inflammatory diathesis may predict subsequent mood disorders in this high-risk population.

Another question that arises is how to delineate persons with pro-inflammatory diathesis for genotypic, phenotypic, and therapeutic investigations. An emerging risk factor for increased inflammation among adults with MDD is childhood maltreatment.[150,151] Unfortunately, childhood abuse is reported by approximately 50% of adults with bipolar disorder and is associated with increased illness severity as evidenced by substance abuse, rapid cycling, and suicide attempts.[152,153] Future studies of bipolar disorder should examine the possibility that inflammation in part mediates the impact of childhood maltreatment on illness severity in bipolar disorder.

CONCLUSION

Inflammation has been hypothesized to signal the brain to produce neurochemical, neuroendocrine, and neuroimmune changes in the face of stress.[154] Indeed, it is precisely the brain's response to stress that is central to the kindling theory which suggests that psychosocial stress and recurrent mood episodes combine to leave a cumulative "residue" of biochemical and anatomical vulnerabilities in mood disorders.[155] Recent work regarding allostatic load has extended the evidence that stress and recurrent mood episodes leave a residue of vulnerabilities on both the brain and the body.[134,156] The association of inflammation with bipolar disorder, psychosocial stress, sleep, neurotoxicity, obesity, and insulin resistance provides evidence that inflammation may comprise an integral part of both the neuropsychiatric and metabolic residues of bipolar disorder. In addition to the potential importance of inflammation to the pathophysiology and treatment of bipolar disorder, its putative role in the increased medical burden and premature mortality of bipolar disorder lends further urgency to progress on this topic.

Drug names: carbamazepine (Carbatrol, Equetro, and others), celecoxib (Celebrex), dexamethasone (Maxidex and others), etanercept (Enbrel), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), rosiglitazone (Avandia), valproate (Depacon and others).

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