The Bipolar Spectrum and Psychoneuroimmunology: Implications for Diagnosis and Treatment

Moritz Muehlbacher1 and Aye-Mu Myint2

1 Moritz Muehlbacher, MD
University Hospital for Psychiatry and Psychotherapy
Bipolar Outpatient Clinic
Paracelsus Medical University
Christian Doppler Clinic
Ignaz Harrer Strasse 79
5020 Salzburg, Austria
m.muehlbacher@salk.at

2 Dr. Aye Mu Myint
M.B.,B.S.; M.Med.Sc.; PhD.
Laboratory for Psychoneuroimmunology
Psychiatric Hospital, LMU
Nussbaumstrasse 7
D-80336 Munich

Abstract

The potential contribution of chronic inflammation to the development of neuropsychiatric disorders such as bipolar spectrum disorders has received increasing attention during the last years. Elevated biomarkers of inflammation have been found in bipolar patients during acute phases and throughout the course of the disease. Inflammatory cytokines can interact with multiple pathways known to be involved in the development of psychiatric disorders, including monoamine metabolism, neuroendocrine function, circadian rhythms, synaptic plasticity, and neurocircuits relevant to mood regulation. In addition, a number of typical comorbidities seem to share an inflammation-related background and might have mutually aggravating effects. Awareness of these relationships should lead to greater diagnostic vigilance and thorough diagnostic assessment.

Key words: bipolar disorder, inflammation, biomarker, cytokine

Introduction

Bipolar spectrum disorders are severe psychiatric conditions with high prevalence and enormous economic and social burden (1;2). There is enough data presently to advocate a genetic immunological predisposition and a role of various environmental factors with an adverse impact on the immune system as part of the pathophysiological background of bipolar disorders and, possibly, associated comorbidities. Pro-inflammatory alterations of the immune system are closely interrelated with clinical symptoms and may prove to be useful diagnostic or therapeutic markers. Moreover, some inflammatory conditions or (auto-) immune disorders may elicit or worsen symptoms of depression, mania and associated comorbidities. A thorough and diligent investigation of the history and present condition of the patient with regard to possible immunological/inflammatory alterations should therefore always be included in the diagnostic work-up. In addition, new drugs targeting aberrant immunological mechanisms might become a welcome addition to the customary treatment in the future. In the current article, we aim to provide a short overview of the present state of knowledge relating to the immunological background and implications for diagnosis and treatment.

Epidemiological and genetic findings

Bipolar disorders are typical multifactorial disorders with a plethora of known associated genetic and environmental contributors, lacking, however, a readily identifiable single cause. A genetic domain of particular interest implicated in bipolar disorders on chromosome 6p22.1 contains several immunity-related genes (3). Other associated genetic regions include genes for inflammatory cytokines (4). Interestingly, pro-inflammatory and anti-inflammatory cytokines are known to play an important physiological role as regulators of the prenatal development of the central nervous system with substantial influence on neurogenesis and gliogenesis, cell differentiation, migration and synaptogenesis (5). Factors known to be associated with pro-inflammatory changes, like infection during pregnancy and early childhood, birth complications and early childhood traumata, amplify the risk to develop various psychiatric disorders in later life. (6-8). A positive family history of autoimmune disorders also augments the risk and patients who are newly diagnosed with certain autoimmune disorders are prone subsequently to develop bipolar spectrum disorders or psychosis (9). Notably, chronic inflammatory disorders are associated with a high rate of comorbid depression and pro-inflammatory cytokines are known to cause "sickness behaviour" with symptoms resembling those of major depression (10;11). Taken together, these findings corroborate the hypothesis of a bidirectional relationship between immunological/inflammatory processes and a variety of psychiatric disorders, including the bipolar spectrum.

Immunological changes during the course of bipolar disorders
Early Stages

Bipolar disorders and psychotic disorders often present with an initial prodrome of non-specific and variable symptoms, typically during teenage years or in adolescence. An up-regulation of the expression of genes with immunological functions - a "pro-inflammatory signature" – has been found in monocytes during these first stages, even before the development of clear-cut clinical symptoms (12). Twin studies suggest that the better part of these changes is not due to a genetic background but to environmental factors yet unidentified (13). At the same time, there is evidence for an up-regulation of regulatory T-Cell networks, suggestive of an activation of the immune system involving both pro-inflammatory and anti-inflammatory forces in early stages (14). Interestingly, in spite of some overlap, the exact pattern of aberrant gene activation in monocytes seems to show subtle differences between patients who are later diagnosed with schizophrenia, bipolar disorder or recurrent unipolar depression and might be a trait marker (15).

Acute phases

Abnormal cytokine levels, independent of other inflammatory processes, have been found during acute psychotic, depressive and manic episodes. In first episode and acutely relapsed psychotic patients, levels of macrophage-derived cytokines (Interleukin-1β, Interleukin-6, and Tumour necrosis factor α) and TH1- derived cytokines (Interferon-γ, Interleukin-12) are elevated. There is also evidence for an initial counter-regulatory elevation of anti-inflammatory cytokines like Tumour growth factor β and Interleukin-1 Receptor antagonist (16). In major depression, a recent meta-analysis reaffirmed previous findings of an activation of the inflammatory response system, reflected by elevated levels of tumour necrosis factor α and Interleukin-6 (17). Analogous changes with raised levels of pro-inflammatory cytokines were seen both during manic and depressive episodes in bipolar patients (18).

Remission and progression

Several studies report that the levels of pro-inflammatory markers like soluble Interleukin-2 receptor and Interleukin 6 drop to lower or normal levels with remission of the acute phase, while other pro-inflammatory markers (e.g. tumour necrosis factor α) seem to lack this association (19). Although the "pro-inflammatory signature" in monocytes of bipolar patients appears to be retained throughout the course of disease, a counteroffensive T-cell response- often present in younger patients- may be

lost in some subjects, leading to a less favourable outcome with a higher rate of complications (20). Few studies have reported findings regarding inflammation during euthymia or long-term remission. The results were inconsistent. One study comparing early-stage versus late-stage bipolar patients suggests that an initial counter-regulatory reaction with raised levels of the anti-inflammatory Interleukin-10 could be lost throughout the course of the disorder and the level of pro-inflammatory cytokines may rise along with increasing duration of the disorder in later stages. These findings may indicate a deterioration of the inflammatory status as a possible stage marker (21).

Impact of inflammation on bipolar disorders and possible causal connections

Inflammation during acute phases and throughout the course of disease can influence a variety of functions in the central nervous and endocrine system. These mechanisms may, in part, explain clinical symptoms of the disorder and its associated comorbidities.

Tryptophan Metabolism

Tryptophan is an essential amino acid and a precursor molecule of serotonin. Some aspects of its metabolism highlight interesting points to bridge the gap of knowledge about the interrelation between neurotransmission and immunology (22). Pro-inflammatory cytokines, like those seen elevated in acute phases of bipolar disorder, can induce enzymes involved in tryptophan metabolism, causing a shift away from the production of serotonin. The alternative pathway leads to kynurenine and a variety of subsequent neuroactive tryptophan catabolites with multiple functions. Under physiological conditions, some catabolites are used for the production of adenosine triphosphate and nicotinamide adenine dinucleotide, a pathway which is important for glycogen storage/ glycolysis and mitochondrial functioning. An excess of another catabolite, quinolinic acid, can cause excitotoxicity through an agonistic effect at glutamatergic NMDA-receptors, whereas kynurenic acid is an antagonist at the same target. By means of this dichotomy, tryptophan catabolism is closely intertwined with immunological, monoaminergic and glutamatergic functioning. In addition, kynurenic acid also antagonizes 7-nicotinic acetylcholine receptors which play a role in cognitive processes. Lastly, 3-hydroxykynurenine can induce neuronal apoptosis. In summary, inflammatory alterations of the immune system can lead to an imbalance between tryptophan catabolites and may therefore interfere with monoaminergic and glutamatergic transmission, cause cognitive impairment and contribute to cell damage. In agreement with this, disproportionate production of tryptophan catabolites has been shown in psychotic, manic and depressed patients in different patterns. (23-26). As yet, directly targeting these imbalances with pharmacological compounds remains a mere theoretical possibility. However, anti-inflammatory or immunomodulatory drugs with indirect effect on tryptophan catabolism have already been tested and demonstrated some beneficial effects.

Circadian rhythm and synaptic function

Circadian rhythms are endogenous oscillations of biological processes, including not only the sleep-wake cycle but also a variety of other bodily functions. These reiterative patterns are encoded on a genetic level by "clockwork genes". A recognized core feature of bipolar disorders is the desynchronisation of circadian rhythms, which may partly be explained by genetic predisposition. However, the relationship between circadian rhythms, clockwork genes and the immune system is unquestionably bidirectional. On the one hand, the immune response is governed by superordinate regulatory clockwork genes and follows a chronobiological pattern. On the other hand, inflammatory cytokines exert an impact on the activity of clockwork genes and may inflict a loss of proper chronobiological functioning (27). In the light of these findings, it seems reasonable to suggest that the inflammatory alterations documented in bipolar disorders contribute to the typical clinical symptoms of disturbed circadian rhythms. In similar ways, proper functioning of monoaminergic synapses - like synaptic plasticity and synaptic scaling which both regulate synaptic activity in the central nervous system - and inflammatory signals have a reciprocal relationship (28;29). Whenever the balance between pro-inflammatory and anti-inflammatory signals is lost, the stability of synaptic transmission may be endangered (30).

Autoimmune Diseases

A family history of pernicious anaemia is known to be a risk factor for bipolar disorders, and patients with a history of Guillain-Barré syndrome, Crohn's disease and autoimmune hepatitis have a heightened risk of developing bipolar disorders (9). Possibly the most important and most frequent autoimmune disease associated with bipolar disorders is Hashimoto's thyroiditis (31). It seems to be linked to an unfavourable outcome, higher frequency of episodes and rapid cycling. Women are affected more frequently than men. Although lithium treatment may often lead to thyroid hypofunction, it is currently not thought be the sole and exclusive cause. An early diagnosis and treatment of comorbid Hashimoto's thyroiditis is crucial to a good outcome of patients with bipolar disorders. Some other autoimmune disorders are not clearly associated with bipolar disorders per se but may mimic symptoms of mania, depression and psychosis. These include autoimmune connective tissue diseases (32), multiple sclerosis (33), antiphospholipid syndrome (34), Behcet's syndrome (35) and others.

Inflammation-related Comorbidities

A number of somatic diseases known to be frequent comorbidities of bipolar disorders are associated with chronic inflammation (18). For over a quarter of a century, studies have shown increased mortality due to cardiovascular disease in bipolar disorder (36;37). Inflammation is an antecedent of cardiovascular disease and may individually predict mortality. Measurement of inflammatory markers in cardiovascular disorders has become a regular medical procedure in cardiology and reducing inflammation may lead to a better outcome (38). Moreover, epidemiological data suggest a mutually increased prevalence of bipolar disorder, obesity and insulin resistance, even after controlling for psychotropic medication with possible metabolic adverse effects (39;40). Similar findings have emerged from studies on migraine (41;42), cigarette smoking (43), heavy alcohol abuse (44) and impaired sleep efficiency (45;46), which are all frequent among bipolar patients, even during phases of remission. All of these disorders share a pathophysiological background hallmarked by chronic inflammation. There is hope that targeting inflammation as a common denominator both of bipolar disorders and these comorbidities may help to achieve a better overall therapeutic outcome.

Febrile infections

A possible positive impact of febrile infections on the course of affective and psychotic disorders has been acknowledged for over two centuries (47).While, in some cases, bipolar patients may actually recover from an acute episode along with an infection, it should be noted that complex effects of febrile states on drug metabolism for medicated patients may also be expected. Barring non-specific effects on fluid homeostasis, electrolytes and excretion, pro-inflammatory cytokines can directly impair hepatic detoxification pathways and thereby alter pharmacokinetics of various psychotropic drugs (48). The importance of diligent clinical monitoring of bipolar patients and regular laboratory tests of drug plasma levels under febrile conditions is therefore strongly emphasised.

Immunosuppressive drugs with possible negative effects

A variety of psychiatric symptoms, including depression, psychosis and suicidal ideation, are possible adverse effects of immunosuppressive therapy with interferon-α; a history of psychiatric disorders is one of the known risk factors for these adverse events (49). Similarly, systemic high-dose cortisol therapy can be accompanied by psychiatric symptoms. However, in this case, a history of psychiatric disorders does not seem to a particular risk factor (50). While it does not seem justified to deny psychiatric patients the possible benefits of these therapies when needed for severe medical conditions, close monitoring for adverse psychiatric events and regular consultation with specialists are strongly recommended.

Possible future anti-inflammatory and immunomodulatory treatment approaches

At present the main focus of research interest and drug development for mood disorders has predominantly relied on targeting the monoaminergic system. Almost all of the currently available, effective and approved compounds interfere with one or more of the monoamine systems. New drugs targeting aberrant immunological mechanisms might prove to become a welcome addition to customary treatment. Celecoxib is a cyclooxygenase-2 inhibitor licensed for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and for the management of acute pain in adults. Benefits of celecoxib add-on therapy have repeatedly been shown in patients with schizophrenia, major depression and bipolar disorder (51-55). In addition to a reduction of overall symptom severity, celecoxib may also accelerate treatment response and have a positive effect on cognition (56). Future studies are needed to identify predictors of response, like cytokine and tryptophan catabolite levels or inflammation-related genotypes, in order to maximise the risk-benefit ratio of celecoxib treatment. Acetylsalicyc acid (ASA) is available worldwide on a generic basis. Findings from large epidemiological studies as well as controlled clinical trials point towards a favourable influence of low-dose ASA in both unipolar depressive and bipolar patients (57-59). Recently, the tetracycline antibiotic minocycline has gained increasing attention, since it attenuates the inflammatory response of T cells and microglia (60). In psychotic disorders, minocycline shows favourable effects on negative symptoms and executive function and was well tolerated up to 6 months of treatment (61). On a cautionary note, antagonists of pro-inflammatory cytokines have lately also been proposed as possible treatment options (62;63). However, these compounds are potent immunosuppressive agents and their safety and efficacy has not been assessed in psychiatric populations in controlled trials yet.

Discussion

A growing body of evidence points towards a multifaceted interrelationship between bipolar spectrum disorders, the immune system and inflammation. While many findings suggest a certain genetic background, additional environmental factors seem to be of considerable importance. No single environmental cause has been identified unequivocally yet, conceding the possibility that different environmental causes with an impact on the immune system might be responsible in different cases. As inflammatory signals can not only influence a variety of brain functions which are directly connected with mood regulation or psychosis but chronic inflammation is also related to a number of typical comorbidities, knowledge about this shared cause may become crucial for good medical practice.

Potential implications are clear:

- A thorough and diligent investigation of a bipolar patient's history and present condition with regard to possible immunological/inflammatory alterations should always to be included in the diagnostic work-up.

- Auto-immune disorders mimicking bipolar symptoms have to be ruled out as a possible differential diagnosis

- Other frequent comorbid auto-immune disorders with negative impact on the course of the disorder (e.g. Hashimoto's thyroiditis) should always be considered and referred to a consulting specialist. Early treatment may be crucial for a good outcome.

- Bipolar patients in need of immunomodulatory treatment for other serious medical conditions may be at risk of adverse psychiatric events. While it does not seem ethical or necessary to refuse such treatments to bipolar patients, regular clinical and psychiatric monitoring are necessary.

- Many typical comorbidities of bipolar disorders (e.g. cardiovascular disease, obesity, and diabetes) seem to share a common cause: chronic inflammation. Bipolar patients should be treated as "high

risk" patients for these disorders. Some typical "lifestyle" modifications have a direct positive impact on chronic inflammation. These include smoking cessation, reduction of alcohol consumption and establishing a regular sleep/wake pattern.

- In the future, inflammatory or immunological markers may serve as state, trait or staging markers or as predictors for treatment response. Some anti-inflammatory compounds, e.g. celecoxib, have already been tested in bipolar disorders and merit further investigation.

GP Comment

What have I learned from this paper?

I learned of the fascinating links between measurable inflammatory biomarkers and bipolar disorder, with a definite signature in early, acute and remitted disease. It is thus important to rule out an inflammatory differential diagnosis, and especially to watch out for and treat Hashimoto's thyroiditis, as this leads to a poorer outcome unless treated aggressively. Bipolar patients needing immune-modularity treatments need careful monitoring, due to the risk of deterioration. Lifestyle interventions such as smoking cessation, alcohol reduction, and establishing a regular sleep/ wake cycle have an impact on chronic inflammation, and can also reduce co- morbidities; they are important from diagnosis, and should be emphasised in routine care.

Dr John Hague, GP, Suffolk.

References

1. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. Eur J Neurol 2012 Jan;19 (1):155-62.
2. Ferrari AJ, Baxter AJ, Whiteford HA. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. J Affect Disord 2011 Nov;134 (1-3):1-13.
3. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 2009 Aug 6;460 (7256):753-7.
4. Papiol S, Rosa A, Gutierrez B, Martin B, Salgado P, Catalan R, et al. Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J Med Genet 2004 Mar;41 (3):219-23.
5. Deverman BE, Patterson PH. Cytokines and CNS development. Neuron 2009 Oct 15;64 (1):61-78.
6. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004 Aug;61 (8):774-80.
7. Rantakallio P, Jones P, Moring J, Von WL. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. Int J Epidemiol 1997 Aug;26 (4):837-43.
8. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry 2008 Apr;65 (4): 409-15.
9. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. Bipolar Disord 2010 Sep;12 (6):638-46.
10. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008 Jan;9 (1):46-56.
11. Myint AM, Schwarz MJ, Steinbusch HW, Leonard BE. Neuropsychiatric disorders related to interferon and interleukins treatment. Metab Brain Dis 2009 Mar;24 (1):55-68.
12. Drexhage RC, Heul-Nieuwenhuijsen L, Padmos RC, van BN, Cohen D, Versnel MA, et al. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients. Int J Neuropsychopharmacol 2010 Nov;13 (10):1369-81.
13. Padmos RC, Van Baal GC, Vonk R, Wijkhuijs AJ, Kahn RS, Nolen WA, et al. Genetic and environmental influences on pro-inflammatory monocytes in bipolar disorder: a twin study. Arch Gen Psychiatry 2009 Sep;66 (9):957-65.
14. Drexhage RC, Hoogenboezem TA, Cohen D, Versnel MA, Nolen WA, van Beveren NJ, et al. An

activated set point of T-cell and monocyte inflammatory networks in recent-onset schizophrenia patients involves both pro- and anti-inflammatory forces. Int J Neuropsychopharmacol 2011 Jul;14 (6):746-55.
15. Weigelt K, Carvalho LA, Drexhage RC, Wijkhuijs A, de WH, van Beveren NJ, et al. TREM-1 and DAP12 expression in monocytes of patients with severe psychiatric disorders. EGR3, ATF3 and PU.1 as important transcription factors. Brain Behav Immun 2011 Aug;25 (6):1162-9.
16. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011 Oct 1;70 (7):663-71.
17. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010 Mar 1;67 (5):446-57.
18. 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 2009 Aug;70 (8):1078-90.
19. Breunis MN, Kupka RW, Nolen WA, Suppes T, Denicoff KD, Leverich GS, et al. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. Biol Psychiatry 2003 Jan 15;53 (2):157-65.
20. Drexhage RC, Hoogenboezem TH, Versnel MA, Berghout A, Nolen WA, Drexhage HA. The activation of monocyte and T cell networks in patients with bipolar disorder. Brain Behav Immun 2011 Aug;25 (6):1206-13.
21. Kauer-Sant'anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol 2009 May;12 (4):447-58.
22. Myint AM, Schwarz MJ, Muller N. The role of the kynurenine metabolism in major depression. J Neural Transm 2012 Feb;119 (2):245-51.
23. Myint AM, Kim YK, Verkerk R, Park SH, Scharpe S, Steinbusch HW, et al. Tryptophan breakdown pathway in bipolar mania. J Affect Disord 2007 Sep;102 (1-3):65-72.
24. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Disord 2007 Feb;98 (1-2):143-51.
25. Muller N, Myint AM, Schwarz MJ. Kynurenine pathway in schizophrenia: pathophysiological and therapeutic aspects. Curr Pharm Des 2011;17 (2):130-6.
26. Kim YK, Myint AM, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Cytokine changes and tryptophan metabolites in medication-naive and medication-free schizophrenic patients. Neuropsychobiology 2009;59 (2):123-9.
27. Logan RW, Sarkar DK. Circadian nature of immune function. Mol Cell Endocrinol 2012 Feb 5;349 (1):82-90.
28. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature 2006 Apr 20;440 (7087):1054-9.
29. Turrigiano GG. More than a sidekick: glia and homeostatic synaptic plasticity. Trends Mol Med 2006 Oct;12 (10):458-60.
30. Santello M, Volterra A. TNFalpha in synaptic function: switching gears. Trends Neurosci 2012 Oct;35 (10):638-47.
31. Chakrabarti S. Thyroid functions and bipolar affective disorder. J Thyroid Res 2011;2011:306367.
32. Khan S, Haddad P, Montague L, Summerton C. Systemic lupus erythematosus presenting as mania. Acta Psychiatr Scand 2000 May;101 (5):406-8.
33. Iacovides A, Andreoulakis E. Bipolar disorder and resembling special psychopathological manifestations in multiple sclerosis: a review. Curr Opin Psychiatry 2011 Jul;24 (4):336-40.
34. Avari JN, Young RC. A patient with bipolar disorder and antiphospholipid syndrome. J Geriatr Psychiatry Neurol 2012 Mar;25 (1):26-8.
35. Alevizos B, Anagnostara C, Christodoulou GN. Resistant bipolar disorder precipitated by Behcet's syndrome. Bipolar Disord 2004 Jun;6 (3):260-3.
36. Osby U, Brandt L, Correia N, Ekbom A, Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001 Sep;58 (9):844-50.
37. Tsuang MT, Woolson RF, Fleming JA. Causes of death in schizophrenia and manic-depression. Br J Psychiatry 1980 Mar;136:239-42.
38. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, III, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A

statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003 Jan 28;107 (3):499-511.
39. Simon GE, Von KM, Saunders K, Miglioretti DL, Crane PK, van BG, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry 2006 Jul;63 (7):824-30.
40. Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord 2002 Jun;70 (1):19-26.
41. McIntyre RS, Konarski JZ, Wilkins K, Bouffard B, Soczynska JK, Kennedy SH. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. Headache 2006 Jun;46 (6):973-82.
42. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. Neurology 2005 May 24;64 (10 Suppl 2):S9-15.
43. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest 2005 Feb;127 (2):558-64.
44. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. Lancet 2001 Mar 10;357 (9258):763-7.
45. Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 2000 Dec;23 (12):1835-9.
46. 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 2006 Sep 18;166 (16):1756-62.
47. Wagner-Jauregg J. Über die Einwirkung fieberhafter Erkrankungen auf Psychosen. Allgemeine Zeitschrift für Psychiatrie , 93-131. 1887. Ref Type: Generic
48. Vee ML, Lecureur V, Stieger B, Fardel O. Regulation of drug transporter expression in human hepatocytes exposed to the proinflammatory cytokines tumor necrosis factor-alpha or interleukin-6. Drug Metab Dispos 2009 Mar;37 (3):685-93.
49. Spennati A, Pariante CM. Withdrawing interferon-alpha from psychiatric patients: clinical care or unjustifiable stigma? Psychol Med 2012 Sep 14;1-6.
50. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc 2006 Oct;81 (10):1361-7.
51. Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety 2009;26 (7):607-11.
52. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res 2007 Feb;90 (1-3):179-85.
53. Muller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, et al. Celecoxib treatment in an early stage of schizophrenia: results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res 2010 Aug;121 (1-3):118-24.
54. Muller N, Riedel M, Scheppach C, Brandstatter B, Sokullu S, Krampe K, et al. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 2002 Jun;159 (6):1029-34.
55. Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psychopharmacol 2008 Mar;23 (2):87-94.
56. Muller N, Riedel M, Schwarz MJ, Engel RR. Clinical effects of COX-2 inhibitors on cognition in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2005 Apr;255 (2):149-51.
57. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. Int Clin Psychopharmacol 2006 Jul;21 (4):227-31.
58. Stolk P, Souverein PC, Wilting I, Leufkens HG, Klein DF, Rapoport SI, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. Prostaglandins Leukot Essent Fatty Acids 2010 Jan;82 (1):9-14.
59. Galecki P, Szemraj J, Bienkiewicz M, Zboralski K, Galecka E. Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. Hum

Psychopharmacol 2009 Jun;24 (4):277-86.
60. Giuliani F, Hader W, Yong VW. Minocycline attenuates T cell and microglia activity to impair cytokine production in T cell-microglia interaction. J Leukoc Biol 2005 Jul;78 (1):135-43.
61. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010 Feb;71 (2):138-49.
62. Brietzke E, Scheinberg M, Lafer B. Therapeutic potential of interleukin-6 antagonism in bipolar disorder. Med Hypotheses 2011 Jan;76 (1):21-3.
63. Tyring S, Bagel J, Lynde C, Klekotka P, Thompson EH, Gandra SR, et al. Patient-reported outcomes in moderate-to-severe plaque psoriasis with scalp involvement: results from a randomized, double-blind, placebo-controlled study of etanercept. J Eur Acad Dermatol Venereol 2011 Dec 21.