The Role of Inflammation in the Pathophysiology of Depression: Different Treatments and Their Effects

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ABSTRACT. Compelling evidence suggests that inflammation contributes to the development of depression. Many depressed individuals have higher levels of proinflammatory mediators, which appear to interact with many of the pathophysiological domains of depression, including neuroendocrine function, neurotransmitter metabolism, and synaptic plasticity. This is further supported by observation that therapeutic administration of interferon-α (IFN-α) leads to depression in a significant proportion of patients. These findings suggest that targeting proinflammatory cytokines and their signaling pathways may represent a unique therapeutic opportunity to treat depression and related conditions, such as labile anger, irritability, and fatigue. (J Rheumatol 2011;38 Suppl 88:48–54; doi:10.3899/jrheum.110903)

Key Indexing Terms:
INFLAMMATION DEPRESSION INTERFERON

Major depression, according to the World Health Organization, is a leading cause of disability worldwide[1]. With an annual prevalence of approximately 7% and lifetime prevalence of 16%, depression carries a significant burden to patients and society[2,3]. Depression is also associated with an increased risk of premature mortality[4,5]. While many depressed patients (up to 1% of women and 7% of men) eventually commit suicide[6], the condition is also highly comorbid with medical disorders that are associated with increased mortality, such as cancer and some cardiovascular and autoimmune diseases[7,8,9].

Although current antidepressants lead to some response in many cases, most patients are partially or completely unresponsive to treatment[10]. This is partly because the pathophysiology of depression has not been elucidated and currently available treatments do not effectively target all the pathological processes that are responsible for the major symptoms of depression. Thus, there is an urgent need to identify novel pathological pathways relevant to depression upon which new conceptual frameworks and targets to improve treatment outcomes can be built.

In recent years, significant attention has been directed at the relationship between the brain and peripheral organs. One promising development in this area is the emergence of inflammation and an activated immune system as common underlying mechanisms in the development of many neuropsychiatric diseases, including major depression. The aim of this article is to provide an overview of recent evidence in support of this hypothesis.

EVIDENCE FOR INCREASED INFLAMMATION IN DEPRESSION: THE ROLE OF PROINFLAMMATORY CYTOKINES

Patients with major depression, with or without other medical illness, have been found to have activated inflammatory pathways[11]. This includes elevations in relevant proinflammatory cytokines and acute-phase proteins, as well as increased expression of their biomarkers, including chemokines and adhesion molecules[12]. It is important to note that inflammatory markers have been found in the peripheral blood circulation and in the cerebrospinal fluid (CSF), suggesting that the brain is directly influenced by peripherally derived mediators[12,13].

The effect of cytokines from the periphery on the brain is somewhat surprising due to the lack of specific transporters for larger peptides and proteins, such as cytokines at the blood-brain barrier. However, recent experimental evidence suggests at least 3 possible pathways by which such molecules could access the brain[13,14,15]. The first pathway is a

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leaky blood-brain barrier that occurs in major depression. The second pathway involves activation of the endothelial cells that line the cerebral vasculature and produce cytokines inside the blood-brain barrier. Finally, inflammatory mediators can bind to receptors associated with the vagus nerve and thereby signal inflammatory changes in the brain. Once in the brain, proinflammatory cytokines activate both neuronal and non-neuronal cells, similar to their activity in the peripheral inflammatory response[16].

According to a recent metaanalysis by Howren, *et al*[17], increased serum and/or plasma concentrations of interleukin 6 (IL-6) and C-reactive protein (CRP) are the most frequently observed inflammatory markers in depressed patients. Other cytokines implicated in depression include IL-1ß and tumor necrosis factor-α (TNF-α)[18,19,20,21]. Recent literature suggests that functional variants of the IL-1ß and TNF-α genes may increase risk for depression and reduce response to antidepressant therapy[22,23]. Further, according to a prospective study by van den Biggelaar, *et al*[24], elevated levels of CRP and an increased capacity of leukocytes to produce IL-1 predicted later onset of depression in elderly individuals without a history of depression. This suggests that inflammation precedes and potentially leads to depression. Several studies have also reported positive correlations between severity of depressive symptoms and plasma concentrations of various inflammatory mediators[21,25,26].

In addition to data that link inflammatory mediators with depressive symptoms, it has also been shown that both acute and chronic administration of cytokines or cytokine inducers [i.e., lipopolysaccharide (LPS) or vaccination] can cause behavioral symptoms that are similar to those found in people who suffer from major depression[27,28]. For example, individuals injected with LPS displayed short-term increases in symptoms of depression and anxiety[27], and those given a *Salmonella typhi* vaccine exhibited depressed mood, fatigue, mental confusion, and psychomotor slowing[28]. Severity of symptoms, in both cases, correlated with the rise in inflammatory mediators in peripheral blood.

MECHANISMS OF CYTOKINE-INDUCED DEPRESSION

It has been repeatedly demonstrated that cytokines access the brain and interact with virtually every pathophysiological domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, neural circuitry, and synaptic plasticity[29]. A wealth of data indicate that, during prolonged periods of activation, cytokine networks in the central nervous system can induce abnormalities relevant to the pathophysiology of depression, including dysregulation of glial/neuronal interactions and cognitive function[11]. Peripheral administration of LPS, for instance, results in cognitive impairment and increased hippocampal concentrations of TNF-α and IL-1[30]. This is linked to a decrease in hippocampal expression of brain-derived neurotrophic factor (BDNF). BDNF and its signaling pathways are involved in neuronal survival, synaptic plasticity, and hippocampus-dependent learning and memory[31].

Once cytokine signals reach the brain, they can also influence the synthesis, release, and reuptake of mood-relevant neurotransmitters, including serotonin, norepinephrine, and dopamine[16,32,33]. It has also been observed that proinflammatory cytokines influence the hypothalamic-pituitary-adrenal axis[34]. Acute administration of cytokines has been shown to stimulate the expression and release of corticotropin-releasing hormone and adrenocorticotropic hormone, as well as cortisol, which have been found to be elevated in depressed patients[34,35].

IFN-α AS A MODEL SYSTEM TO STUDY CYTOKINE-INDUCED DEPRESSION

Major depressive disorder during IFN-α therapy. IFN-α, an important cytokine in the early immune response to viral infection, has both antiproliferative and antiviral properties[29]. IFN plays a significant role in immune-mediated inflammatory diseases (IMID) such as systemic lupus and rheumatoid arthritis (RA)[36]. It has been used to treat a variety of malignancies and chronic viral infections, including malignant melanoma and hepatitis C. Despite its therapeutic benefits in these serious conditions, administration of IFN-α is often associated with high rates of neuropsychiatric symptoms, including depressed mood, anhedonia, fatigue, cognitive impairment, and sleep disturbances (Table 1)[37,38,39].

Table 1. IFN-α-induced behavioral symptoms in patients with malignant melanoma. Reproduced from Capuron L, *et al*. Neuropsychopharmacology 2002;26:643-52, with permission from Nature Publishing Group. Copyright© 2002 American College of Neuropsychopharmacology.

Symptoms	Percentage of Patients
Depressive	
Depressed mood	60
Anhedonia	30
Suicidal thoughts	10
Feelings of guilt	5
Anxious	
Tension/irritability	50
Anxious mood	45
Fear	15
Cognitive	
Loss of concentration	30
Memory disturbances	15
Word-finding problems	15
Episodes of confusion	10
Indecisiveness	10
Neurovegetative	
Fatigue/loss of energy	80
Abnormal sleep	45
Psychomotor retardation	40
Abnormal appetite	35
Somatic	
Pain	55
Gastrointestinal	50

IFN: interferon.

Suicidal ideation and completed suicides have also been reported[37,40].

Clinical studies have confirmed that about 15%–45% of patients receiving IFN-α develop major depressive disorder (MDD) during the course of therapy[41,42]. In a double-blind, placebo-controlled study conducted by Musselman, *et al*[42], 45% of patients (9 of 20) receiving IFN-α for malignant melanoma developed depression within 12 weeks of therapy (Figure 1). Severe depressive symptoms that required treatment discontinuation were noted in 7 (35%) patients.

Based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders and self-report questionnaire, Lotrich, *et al*[43] identified 3 sets of symptoms that were worsened following IFN-α therapy. These include: (1) symptoms specific to depression, (2) hostility and labile anger, and (3) neurovegetative symptoms including fatigue and loss of appetite. In another study, Capuron, *et al*[37] noted that neurovegetative and somatic symptoms such as anorexia, fatigue, and pain developed within 2 weeks of IFN-α therapy, and did not respond to antidepressant treatment. On the other hand, symptoms of depressed mood, anxiety, and cognitive impairment appeared later — i.e., between week 8 and 12 of IFN-α therapy — and were more responsive to paroxetine treatment.

Relationship between IFN-α, MDD, and circulating IL-6. Several studies have described increases in peripheral levels of IL-6 among patients undergoing IFN-α therapy[44,45]. There is also evidence that levels of IL-6 observed in the CSF of patients receiving IFN-α may negatively correlate with serotonin metabolism, which in turn negatively correlates with depression symptoms[14].

According to Prather, *et al*[46], patients who developed MDD during IFN-α treatment had higher Beck Depression Inventory (BDI) scores at baseline and were more likely to have a history of a mood disorder compared to those not affected with MDD. Further, patients who developed MDD displayed higher levels of IL-6 throughout treatment compared to those without MDD ($p < 0.01$; Figure 2). In patients who did not develop MDD, IL-6 concentrations stayed stable and low during the treatment. As in previous studies, MDD symptoms were apparent within 3 months. The study also found that higher levels of pretreatment IL-6 (> 1.25 pg/ml) predicted the development of MDD during IFN-α therapy ($p < 0.05$; Figure 3). In addition, poor sleep quality was associated with subsequent depression during IFN-α therapy, although the relationship was not bidirectional[47]. Similarly, increased levels of IL-6 were associated with subsequent poor sleep. Yet poor sleep did not lead to an increase in IL-6.

Risk of depression during IFN-α is affected by serotonin transporter polymorphism. Several publications indicate that polymorphisms in the promoter region (5-HTTLPR) of the serotonin transporter may interact with the inflammatory system and influence risk of depression[48,49,50]. According to a metaanalysis[47] and large association studies[48], the short/short (S/S) genotype in this region increases risk of MDD. Recently, Lotrich, *et al*[49] examined 5-HTTLPR in 71 nondepressed patients with hepatitis C prior to initiation of IFN-α therapy. Patients were genotyped for the 5-HTTLPR (L_G, L_A, and S) and the variable number of tandem repeats polymorphism in the second intron. According to the study results, the L_A allele was associated with lower rates of MDD and the S/S genotype appeared the most susceptible to depression while on IFN-α treatment (Figure 4).

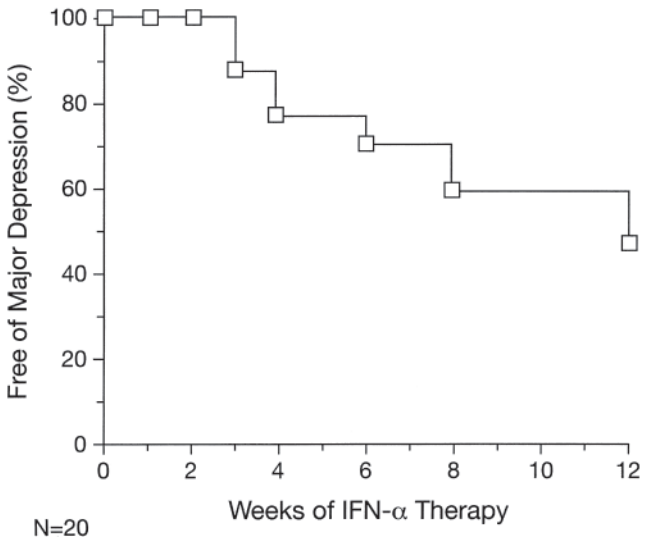

Figure 1. Incidence of major depression during the first 12 weeks of interferon-α (IFN-α) therapy for malignant melanoma. Kaplan–Meier analysis of the percentage of patients who were free of major depression. Adapted from Musselman, *et al*. N Engl J Med 2001;344:961-6.

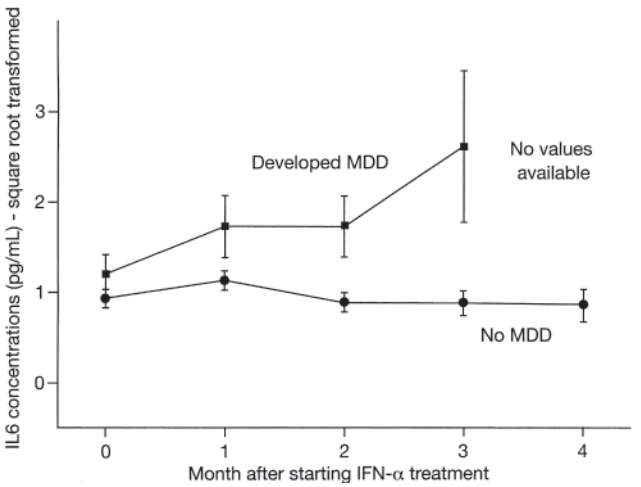

Figure 2. Interleukin 6 (IL-6) concentrations in patients who develop major depressive disorder (MDD) versus those who do not develop MDD during treatment with interferon-α (IFN-α). Reprinted from Prather, *et al*. Brain Behav Immun 2009;23:1109-16, copyright© 2009, with permission from Elsevier.

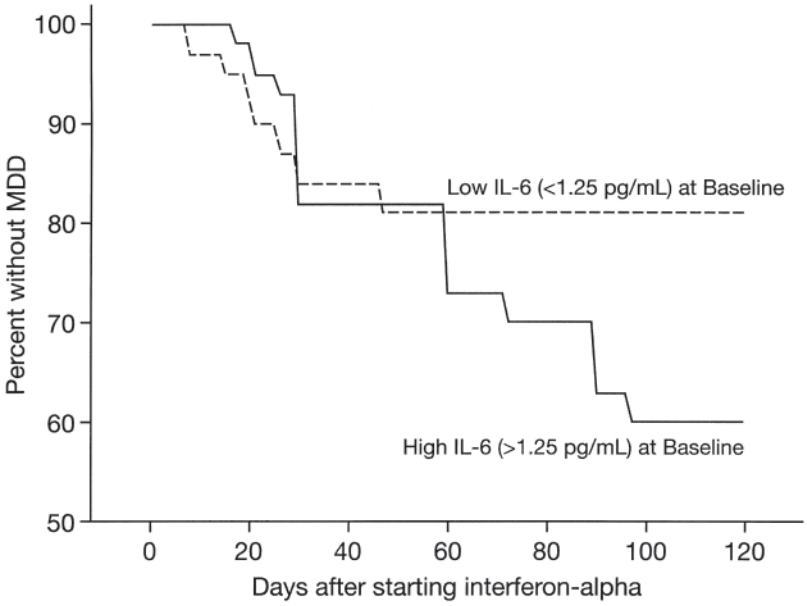

Figure 3. Baseline interleukin 6 (IL-6) levels predict future MDD. Reprinted from Prather, *et al*. Brain Behav Immun 2009;23:1109-16, copyright© 2009, with permission from Elsevier.

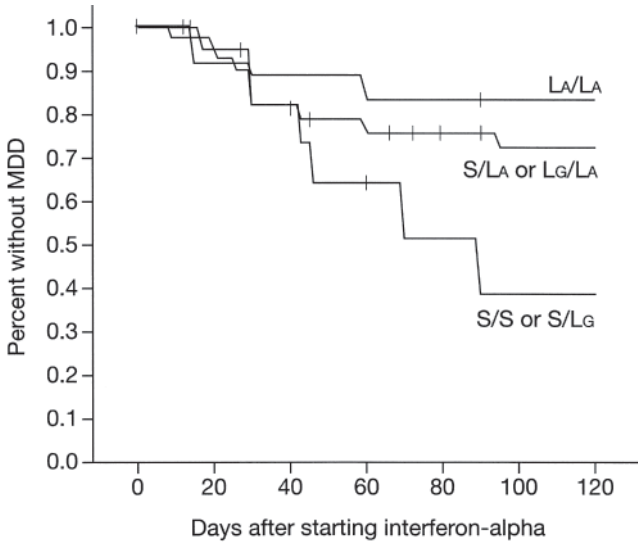

Figure 4. Risk for depression during interferon-α (IFN-α) treatment is affected by polymorphisms in the promoter region (5-HTTLPR) of the serotonin transporter. Reprinted from Lotrich, *et al*. Biol Psychiatry 2009;65:344-8, copyright© 2009, with permission from Elsevier.

Efficacy of serotonin reuptake inhibitors in preventing IFN-α-induced MDD. Prevention studies evaluating the prophylactic use of selective serotonin reuptake inhibitors (SSRI) prior to initiation of IFN-α have produced conflicting results, indicating that SSRI may not be equally effective in this patient population[42,50,51,52,53,54]. In one study, only 11% of patients (2 of 18) treated with paroxetine developed MDD while taking IFN-α treatment compared to 45% of placebo-treated patients[42]. Similar results were obtained in 3 open-label trials of prophylactic SSRI in nondepressed patients with hepatitis C virus: only 9% (3 of 32) developed IFN-α-related MDD, despite the fact that all patients had a history of affective disorder[50,51,52]. However, these findings were not confirmed by 2 small studies also conducted in patients with hepatitis C[53,54]. The exploratory analysis of one of these studies indicated that subjects who already had high pretreatment baseline levels of depressive symptoms may benefit the most from the prophylactic use of SSRI[54]. This observation is consistent with findings that pretreatment baseline depression-rating scale scores are predictive of subsequent IFN-α-induced MDD[41,43,49]. Therefore, it is reasonable to assume that treating patients with histories of recurrent depressive symptoms might prevent further progression to IFN-α-related MDD, a possibility that requires further examination.

In an animal model of depression, colitis emerged; when the animal was treated with antidepressants, not only did the depression improve but so did the colitis, raising the possibility that antidepressants can reduce depression-triggered inflammation. Their influence on IMID is not fully known[55].

IFN-α and labile anger. In addition to MDD, about 25% of patients receiving IFN-α develop labile anger, irritability, and/or hostility[56,57]. This mood disorder, distinct from depression, appears to be associated with TNF-α polymorphism[58]. In a study that involved 105 patients with hepatitis C treated with IFN-α, labile anger was significantly increased in those with the A allele compared to those with G/G genotype. The TNF-α A allele was also associated with fatigue during the IFN-α treatment but not with MDD[58].

Further, labile anger was not predicted by the serotonin transporter polymorphism. Thus, pretreatment with SSRI does not appear to be effective in preventing the occurrence of labile anger in individuals treated with IFN-α.

IL-28 polymorphism is linked to efficacy and side effects of IFN-α therapy. In a recent study, Lotrich, *et al*[59] confirmed that IL-28B polymorphism was associated with differences in sustained viral response as well as with loss of appetite, energy, and sleep complaints during IFN-α treatment. However, the IL-28B genotype did not predict development of depression.

The finding that polymorphisms in different genes are responsible for different psychosocial symptoms carries significant implications for the management of patients treated with IFN-α and subsequently other individuals affected by psychosocial disorders.

ANTIINFLAMMATORY AGENTS AND THEIR ANTIDEPRESSANT EFFECTS

If depression is associated with excess inflammation, it is to be expected that inhibition or reduction in inflammation would diminish depressive symptoms. Several studies in humans support this hypothesis and suggest that immune-targeted therapies may have clinical benefits in depressed patients[60,61,62,63]. For example, agents that block production of prostaglandin E_2 [i.e., acetylsalicylic acid and cyclooxygenase (COX)-2 inhibitors], an important mediator of inflammation, also display antidepressant effects[60,61,62]. Further, the COX-2 inhibitor celecoxib was also shown to have positive effects on cognition, which is frequently impaired with depression. Müller, *et al*[60] demonstrated significantly greater improvements in symptoms of depression in healthy depressed patients treated with the norepinephrine reuptake inhibitor reboxetine in combination with celecoxib than in those who received reboxetine alone (Figure 5).

Antidepressant activity of antiinflammatory agents has also been observed in patients with IMID. For example, a large double-blind, placebo-controlled trial demonstrated that patients with psoriasis who received the TNF-α and lymphotoxin-α antagonist etanercept exhibited significant improvement in depressive symptoms compared with placebo-treated subjects (Figure 6). The effect of etanercept on depressive symptoms was independent of improvement in disease activity[64]. These results are in line with an immense body of evidence in laboratory animals indicating that anti-inflammatory agents or cytokine antagonists can block the development of behavioral changes following immune activation[65]. In addition, these data are in accord with observations that TNF-α receptor knockout mice exhibit an antidepressant phenotype[66].

CONCLUSION

Increasing evidence indicates that cytokine-mediated inflammation may be an underlying mechanism leading to a variety of IMID, but also to symptoms of depression, anxiety, and fatigue often observed in these patient populations. This hypothesis may explain significant improvements in depression-related symptoms after anti-TNF exposure. However, additional research is needed to further determine which underlying factors are responsible for the cascade of events that lead to psychosocial comorbidities in patients with IMID. Further, a broader conceptualization of depression in the context of IMID will permit consideration of the usefulness of different pharmacological approaches in the management of these complex conditions.

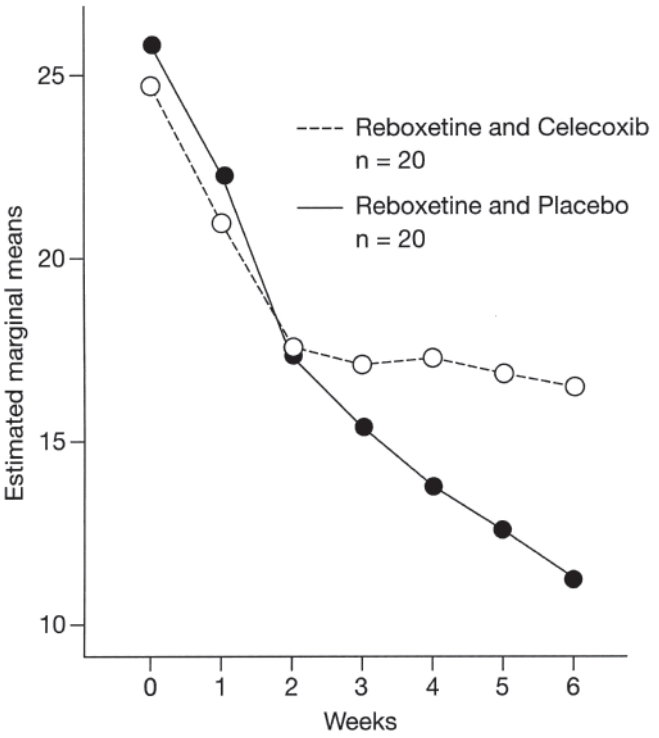

Figure 5. Significantly greater improvement in depression when celecoxib was added to reboxetine. Comparison of Hamilton Depression scores during therapy with celecoxib or placebo (analysis of variance, estimated marginal means; advantage of celecoxib group: Greenhouse–Geisser-corrected F = 3.220; df 2.434; p = 0.035) *p ≤ 0.05. Reprinted with permission from Macmillan Publishers Ltd.: Müller, *et al*. Mol Psychiatry 2006;11:680-4, copyright© 2006.

REFERENCES

1. Moussavi S, Chatterji E, Verdes A, Tandon A, Patel V, Ustun B. Depression, chronic disease and decrements in health: results from WHO surveys. Lancet 2007;370:851-8.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-27.
3. Kessler RC, Berglund P, Delmer O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:590-2.
4. Zheng D, Macera CA, Croft JB, Giles WH, Davis D, Scott WK. Major depression and all-cause mortality among white adults in the

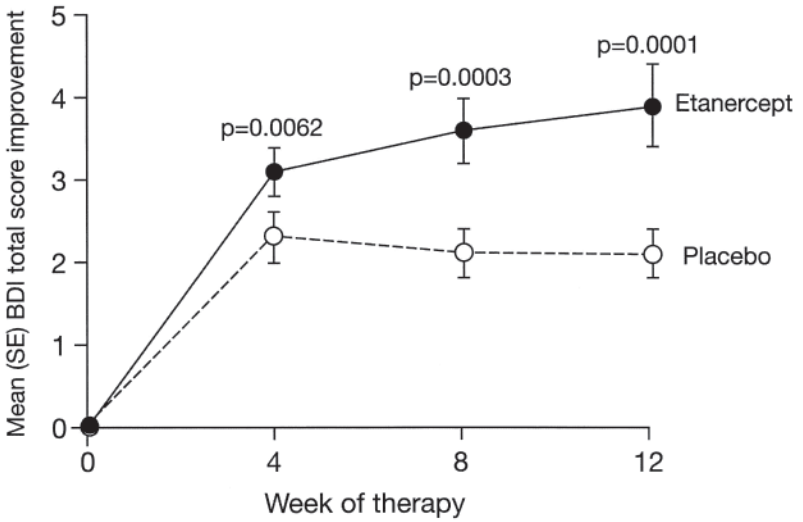

Figure 6. Improvement from baseline in Beck Depression Inventory (BDI) over time. Etanercept significantly improved BDI scores from baseline through Week 12. p values for comparison between etanercept and placebo groups. Reprinted from Tyring, *et al*. Lancet 2006;367:29-35, copyright© 2006, with permission from Elsevier.

United States. Ann Epidemiol 1997;7:213-8.

5. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord 2002;72:227-36.
6. Blair-West GW, Cantor CH, Mellsop GW, Eyeson-Annan ML. Lifetime suicide risk in major depression: sex and age determinants. J Affect Disord 1999;55:171-8.
7. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. Biol Psychiatry 2003;54:283-94.
8. Rivelli S, Jiang W. Depression and ischemic heart disease: What have we learned from clinical trials? Curr Opin Cardiol 2007;22:286-91.
9. Benton T, Staab J, Evans DL. Medical co-morbidity in depressive disorders. Ann Clin Psychiatry 2007;19:289-303.
10. Rush AJ. STAR*D: What have we learned? Am J Psychiatry 2007;164:201-4.
11. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;65:732-41.
12. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24-31.
13. Leonard BE. The concept of depression as a dysfunction of the immune system. Curr Immunol Rev 2010;6:205-12.
14. Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, Woolwine BJ, et al. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. Biol Psychiatry 2009;65:296-303.
15. Si Q, Cosenza M, Kim MO, Zhao ML, Brownlee M, Goldstein H, et al. A novel action of minocycline: inhibition of human immunodeficiency virus type 1 infection in microglia. J Neurovirol 2004;10:284-92.
16. Anisman H, Merali Z, Hayley S. Neurotransmitters, peptides and cytokines process in relation to depressive disorder: comorbidity between depression and neurodegenerative disorder. Prog Neurobiol Biol Psychiat 2008;85:1-74.
17. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171-86.
18. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. Psychopharmacology (Berl) 2003;170:429-33.
19. Hestad KA, Tønseth S, Støen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. J ECT 2003;19:183-8.
20. Owen BM, Eccleston D, Ferrier IN, Young AH. Raised levels of plasma interleukin-1-beta in major and postviral depression. Acta Psychiatr Scand 2001;103:226-8.
21. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1-beta in late-life depression. Am J Psychiatry 2005;162:175-7.
22. Yu YW, Chen TJ, Hong CJ, Chen HM, Tsai SJ. Association study of the interleukin-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response. Neuropsychopharmacology 2003;28:1182-5.
23. Jun TY, Pae CU, Hoon-Han, Chae JH, Bahk WM, Kim KS, et al. Possible association between -G308A tumour necrosis factor-alpha gene polymorphism and major depressive disorder in the Korean population. Psychiatr Genet 2003;13:179-81.
24. van den Biggelaar AH, Gussekloo J, de Craen AJ, Frölich M, Stek ML, van der Mast RC, et al. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. Exp Gerontol 2007;42:693-701.
25. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. J Clin Endocrinol Metab 2005;90:2522-30.
26. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279-83.
27. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001;58:445-52.
28. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 2008;63:1022-9.

29. Borden EC, Parkinson D. A perspective on the clinical effectiveness and tolerance of interferon-alpha. Semin Oncol 1998;25:3-8.
30. Wu CW, Chen YC, Yu L, Chen HI, Jen CJ, Huang AM, et al. Treadmill exercise counteracts the suppressive effects of peripheral lipopolysaccharide on hippocampal neurogenesis and learning and memory. J Neurochem 2007;103:2471-81.
31. Sairanen M, Lucas G, Ernfors P, Castrén M, Castrén E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. J Neurosci 2005;25:1089-94.
32. Miller AH. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. Brain Behav Immun 2009;23:149-58.
33. Felger JC, Alagbe O, Hu F, Mook D, Freeman AA, Sanchez MM, et al. Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. Biol Psychiatry 2007;62:1324-33.
34. Besedovsky HO, del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev 1996;17:64-102.
35. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol Psychiatry 2001;49:391-404.
36. Crow MK. Type 1 interferon in systemic lupus erythematosus. Curr Top Microbiol Immunol 2007;316:359-86.
37. Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643-52.
38. Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P. Mood and cognitive side effects of interferon-alpha therapy. Semin Oncol 1998;25:39-47.
39. Kent S, Bluthé RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. Trends Pharmacol Sci 1992;13:24-8.
40. Janssen HL, Brouwer JT, van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 1994;21:241-3.
41. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. CNS Drugs 2005;19:105-23.
42. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001;344:961-6.
43. Lotrich FE, Rabinovitz M, Gironda P, Pollock BG. Depression following pegylated interferon-alpha: characteristics and vulnerability. J Psychosom Res 2007;63:131-5.
44. Bonaccorso S, Puzella A, Marino V, Pasquini M, Biondi M, Artini M, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. Psychiatry Res 2001;105:45-55.
45. Wichers MC, Kenis G, Koek GH, Robaeys G, Nicolson NA, Maes M. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol. J Psychosom Res 2007;62:207-14.
46. Prather AA, Rabinovitz M, Pollock BG, Lotrich FE. Cytokine-induced depression during IFN-alpha treatment: the role of IL-6 and sleep quality. Brain Behav Immun 2009;23:1109-16.
47. Lotrich FE, Pollock BG. Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Genet 2004;14:121-9.
48. Hoefgen B, Schulze TG, Ohlraun S, von Widdern O, Höfels S, Gross M, et al. The power of sample size and homogenous sampling: association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder. Biol Psychiatry 2005;57:247-51.
49. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. Biol Psychiatry 2009;65:344-8.
50. Gleason OC, Fucci JC, Yates WR, Philipsen MA. Preventing relapse of major depression during interferon-alpha therapy for hepatitis C — a pilot study. Dig Dis Sci 2007;52:2557-63.
51. Kraus MR, Shafer A, Al-Taie O, Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. J Viral Hepatitis 2005;12:96-100.
52. Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol 2005;42:793-8.
53. Morasco BJ, Rifai MA, Loftis JM, Indest DW, Moles JK, Hauser P. A randomized trial of paroxetine to prevent interferon-a-induced depression in patients with hepatitis C. J Affect Dis 2007;103:83-90.
54. Raison CL, Woolwine BJ, Demetrashvili ZM, Borisov AS, Weinreib R, Staab JP, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. Aliment Pharmacol Ther 2007;25:1163-74.
55. Ghia JE, Blennerhassett P, Deng Y, Verdu EF, Khan WI, Collins SM. Reactivation of inflammatory bowel disease in a mouse model of depression. Gastroenterology 2009;136:2280-8.
56. Dan AA, Crone C, Wise TN, Martin LM, Ramsey L, Magee S, et al. Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. Psychosomatics 2007;48:223-9.
57. Préau M, Marcellin F, Spire B, Ravaux I, Dellamonica P, Blanc D, et al. Impaired anger control as an underappreciated side effect of treatments for chronic HCV infection in HIV-HCV coinfected patients. J Clin Gastroenterol 2008;42:92-6.
58. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Labile anger during interferon alfa treatment is associated with a polymorphism in tumor necrosis factor alpha. Clin Neuropharmacol 2010;33:191-7.
59. Lotrich FE, Loftis JM, Ferrell RE, Rabinovitz M, Hauser P. IL28B polymorphism is associated with both side effects and clearance of hepatitis C during interferon-alpha therapy. J Interferon Cytokine Res 2010 Dec 6 [Epub ahead of print].
60. Müller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Müller B, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol Psychiatry 2006;11:680-4.
61. Collantes-Esteves E, Fernandez-Perrez C. Improved self-control of osteoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in Spain. Curr Med Res Opin 2003;19:402-10.
62. 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;21:227-31.
63. Müller N, Riedel M, Schwarz MJ, Engel RR. Clinical effects of COX-2 inhibitors on cognition in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2005;255:149-51.
64. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006;367:29-35.
65. 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;9:46-56.
66. Simen BB, Duman CH, Simen AA, Duman RS. TNF-alpha signaling in depression and anxiety: behavioral consequences of individual receptor targeting. Biol Psychiatry 2006;59:775-85.