

# 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- $\alpha$  (IFN- $\alpha$ ) 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<sup>1</sup>. With an annual prevalence of approximately 7% and lifetime prevalence of 16%, depression carries a significant burden to patients and society<sup>2,3</sup>. Depression is also associated with an increased risk of premature mortality<sup>4,5</sup>. While many depressed patients (up to 1% of women and 7% of men) eventually commit suicide<sup>6</sup>, the condition is also highly comorbid with medical disorders that are associated with increased mortality, such as cancer and some cardiovascular and autoimmune diseases<sup>7,8,9</sup>.

Although current antidepressants lead to some response in many cases, most patients are partially or completely unresponsive to treatment<sup>10</sup>. 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<sup>11</sup>. This includes elevations in relevant proinflammatory cytokines and acute-phase proteins, as well as increased expression of their biomarkers, including chemokines and adhesion molecules<sup>12</sup>. 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<sup>12,13</sup>.

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<sup>13,14,15</sup>. The first pathway is a

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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<sup>27,28</sup>. For example, individuals injected with LPS displayed short-term increases in symptoms of depression and anxiety<sup>27</sup>, and those given a *Salmonella typhi* vaccine exhibited depressed mood, fatigue, mental confusion, and psychomotor slowing<sup>28</sup>. Severity of symptoms, in both cases, correlated with the rise in inflammatory mediators in peripheral blood.

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<sup>29</sup>. 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<sup>11</sup>. Peripheral administration of LPS, for instance, results in cognitive impairment and increased hippocampal concentrations of TNF- $\alpha$  and IL-1<sup>30</sup>. This is linked to a decrease in hippocampal expression of brain-derived neurotrophic fac-

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

**Major depressive disorder during IFN- $\alpha$  therapy.** IFN- $\alpha$ , an important cytokine in the early immune response to viral infection, has both antiproliferative and antiviral properties<sup>29</sup>. IFN plays a significant role in immune-mediated inflammatory diseases (IMID) such as systemic lupus and rheumatoid arthritis (RA)<sup>36</sup>. 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- $\alpha$  is often associated with high rates of neuropsychiatric symptoms, including depressed mood, anhedonia, fatigue, cognitive impairment, and sleep disturbances (Table 1)<sup>37,38,39</sup>.

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

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Suicidal ideation and completed suicides have also been reported<sup>37,40</sup>.

Clinical studies have confirmed that about 15%–45% of patients receiving IFN- $\alpha$  develop major depressive disorder (MDD) during the course of therapy<sup>41,42</sup>. In a double-blind, placebo-controlled study conducted by Musselman, *et al*<sup>42</sup>, 45% of patients (9 of 20) receiving IFN- $\alpha$  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*<sup>43</sup> identified 3 sets of symptoms that were worsened following IFN- $\alpha$  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*<sup>37</sup> noted that neurovegetative and somatic symptoms such as anorexia, fatigue, and pain developed within 2 weeks of IFN- $\alpha$  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- $\alpha$  therapy — and were more responsive to paroxetine treatment.

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

According to Prather, *et al*<sup>46</sup>, patients who developed

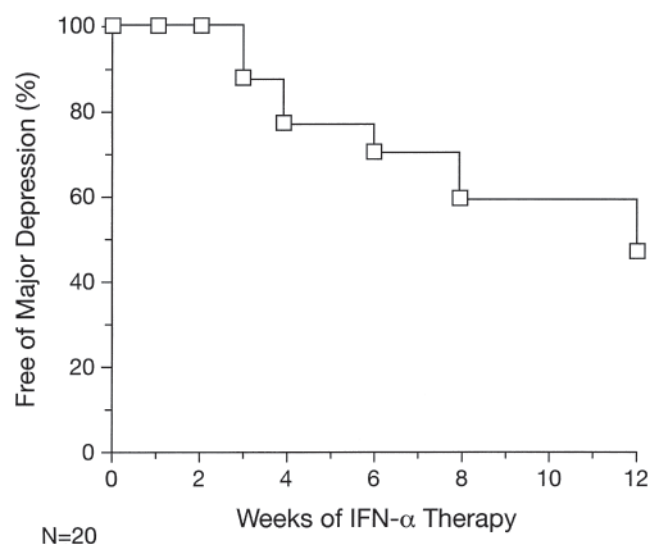


Figure 1. Incidence of major depression during the first 12 weeks of interferon- $\alpha$  (IFN- $\alpha$ ) therapy for malignant melanoma. Kaplan-Meier analysis of the percentage of patients who were free of major depression. Adapted from Musselman, *et al*. N Engl J Med 2001;344:961-6.

MDD during IFN- $\alpha$  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- $\alpha$  therapy ( $p < 0.05$ ; Figure 3). In addition, poor sleep quality was associated with subsequent depression during IFN- $\alpha$  therapy, although the relationship was not bidirectional<sup>47</sup>. 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- $\alpha$  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<sup>48,49,50</sup>. According to a metaanalysis<sup>47</sup> and large association studies<sup>48</sup>, the short/short (S/S) genotype in this region increases risk of MDD. Recently, Lotrich, *et al*<sup>49</sup> examined 5-HTTLPR in 71 nondepressed patients with hepatitis C prior to initiation of IFN- $\alpha$  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- $\alpha$  treatment (Figure 4).

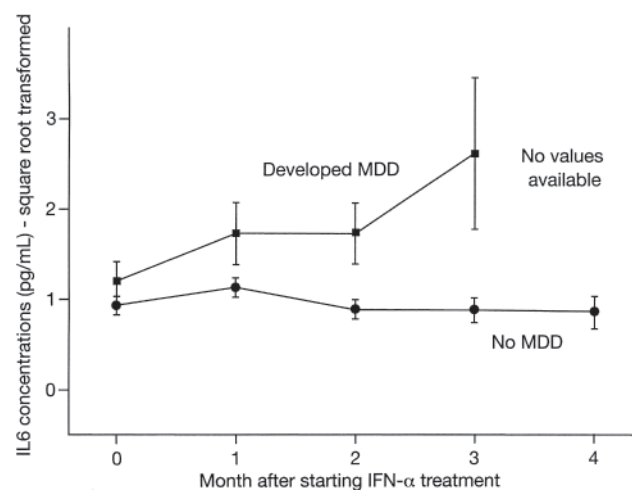


Figure 2. Interleukin 6 (IL-6) concentrations in patients who develop major depressive disorder (MDD) versus those who do not develop MDD during treatment with interferon- $\alpha$  (IFN- $\alpha$ ). Reprinted from Prather, *et al*. Brain Behav Immun 2009;23:1109-16, copyright© 2009, with permission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

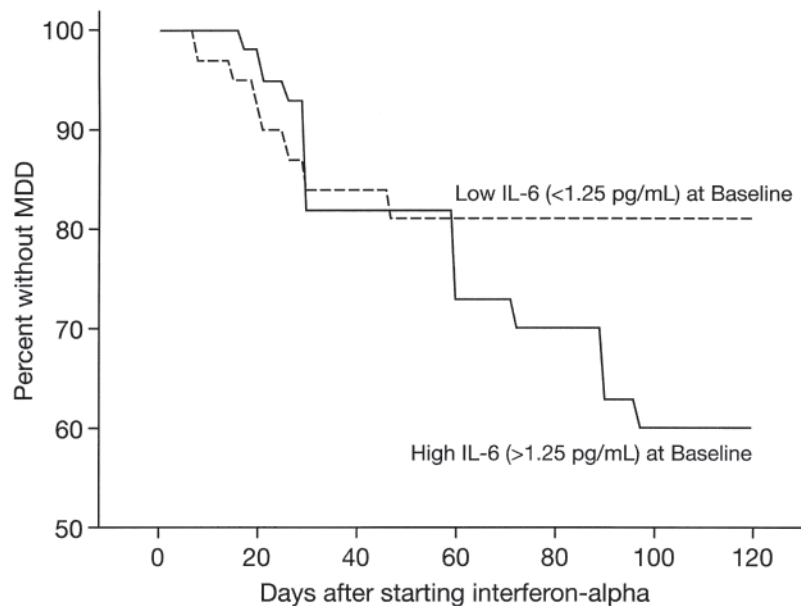


Figure 3. Baseline interleukin 6 (IL-6) levels predict future MDD. Reprinted from Prather, *et al.* Brain Behav Immun 2009;23:1109-16, copyright© 2009, with permission from Elsevier.

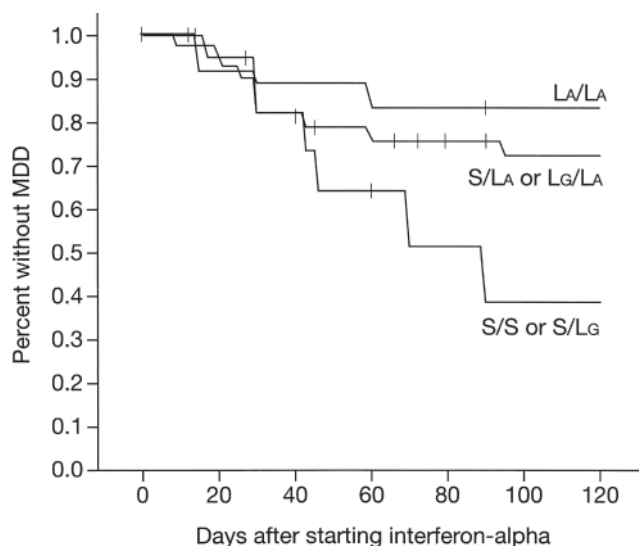


Figure 4. Risk for depression during interferon- $\alpha$  (IFN- $\alpha$ ) treatment is affected by polymorphisms in the promoter region (5-HTTLPR) of the serotonin transporter. Reprinted from Lotrich, *et al.* Biol Psychiatry 2009;65:344-8, copyright© 2009, with permission from Elsevier.

**Efficacy of serotonin reuptake inhibitors in preventing IFN- $\alpha$ -induced MDD.** Prevention studies evaluating the prophylactic use of selective serotonin reuptake inhibitors (SSRI) prior to initiation of IFN- $\alpha$  have produced conflicting results, indicating that SSRI may not be equally effective in this patient population<sup>42,50,51,52,53,54</sup>. In one study, only 11% of patients (2 of 18) treated with paroxetine developed MDD while taking IFN- $\alpha$  treatment compared to 45% of placebo-treated patients<sup>42</sup>. 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- $\alpha$ -related MDD, despite the fact that all patients had a history of affective disorder<sup>50,51,52</sup>. However, these findings were not confirmed by 2 small studies also conducted in patients with hepatitis C<sup>53,54</sup>. 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<sup>54</sup>. This observation is consistent with findings that pretreatment baseline depression-rating scale scores are predictive of subsequent IFN- $\alpha$ -induced MDD<sup>41,43,49</sup>. Therefore, it is reasonable to assume that treating patients with histories of recurrent depressive symptoms might prevent further progression to IFN- $\alpha$ -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<sup>55</sup>.

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



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- $\alpha$ .

*IL-28 polymorphism is linked to efficacy and side effects of IFN- $\alpha$  therapy.* In a recent study, Lotrich, *et al*<sup>59</sup> 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- $\alpha$  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- $\alpha$  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<sup>60,61,62,63</sup>. For example, agents that block production of prostaglandin E<sub>2</sub> [i.e., acetylsalicylic acid and cyclooxygenase (COX)-2 inhibitors], an important mediator of inflammation, also display antidepressant effects<sup>60,61,62</sup>. Further, the COX-2 inhibitor celecoxib was also shown to have positive effects on cognition, which is frequently impaired with depression. Müller, *et al*<sup>60</sup> 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- $\alpha$  and lymphotoxin- $\alpha$  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<sup>64</sup>. 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<sup>65</sup>. In addition, these data are in accord with observations that TNF- $\alpha$  receptor knockout mice exhibit an antidepressant phenotype<sup>66</sup>.

### CONCLUSION

Increasing evidence indicates that cytokine-mediated inflammation may be an underlying mechanism leading to a

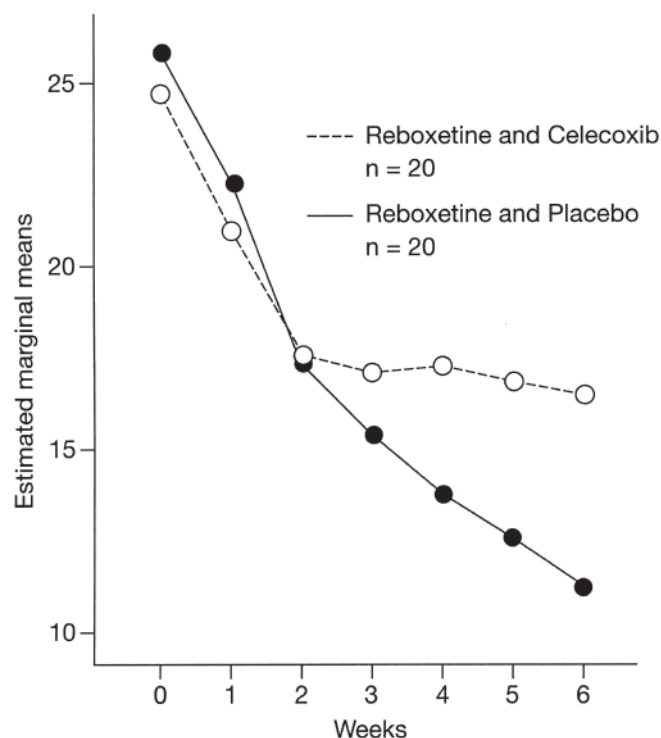


Figure 5. Significantly greater improvement in depression when celecoxib was added to reboxetine. Comparison of Hamilton Depression scores during therapy with celecoxib or placebo (analysis of variance, estimated marginal means; advantage of celecoxib group: Greenhouse-Geisser-corrected  $F = 3.220$ ;  $df\ 2,434$ ;  $p = 0.035$ ) \* $p \leq 0.05$ . Reprinted with permission from Macmillan Publishers Ltd.: Müller, *et al.* Mol Psychiatry 2006;11:680-4, copyright© 2006.

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.

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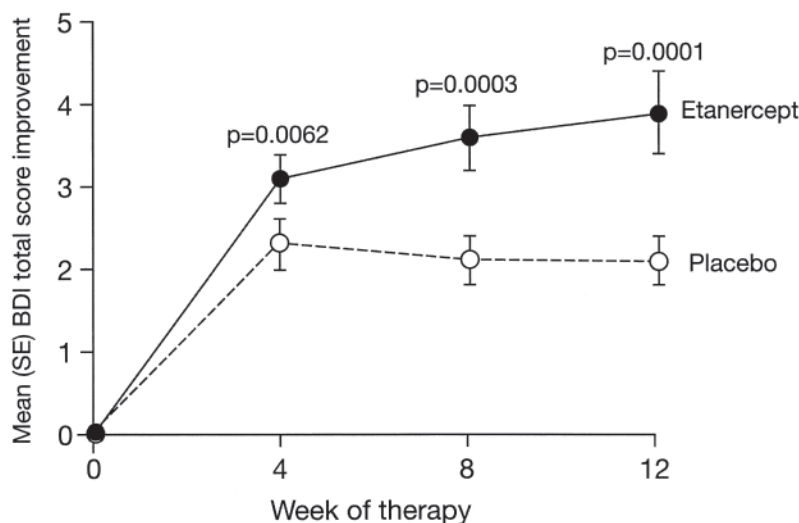


Figure 6. Improvement from baseline in Beck Depression Inventory (BDI) over time. Etanercept significantly improved BDI scores from baseline through Week 12. p values for comparison between etanercept and placebo groups. Reprinted from Tyring, *et al.* Lancet 2006;367:29-35, copyright © 2006, with permission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

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