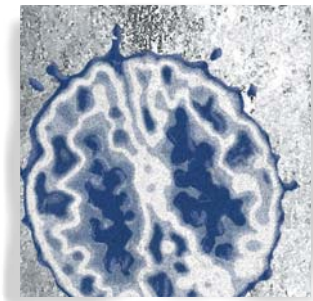# Translational research

# Neuropsychiatric manifestations of depression in multiple sclerosis: neuroinflammatory, neuroendocrine, and neurotrophic mechanisms in the pathogenesis of immune-mediated depression

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## Historical perspective on multiple sclerosis and depression

Multiple sclerosis (MS) is characterized by inflammation, demyelination, axonal injury, and gliosis (scarring), and can involve the brain, spinal cord, and optic nerves. The course of MS can be relapsing-remitting or progressive, but typically involves insults that are multiphasic and multifocal (ie, disseminated in time and

*Evidence suggests that depression in multiple sclerosis (MS) is largely biologically mediated by some of the same processes involved in the immunopathogenesis of this neurologic disease. In particular, the increase in proinflammatory cytokines, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and reduction in neurotrophic factors that occur in MS may each account for the increased rate of depression seen in MS. The possible contributions of these neuroinflammatory, neuroendocrine, and neurotrophic mechanisms suggest a diverse array of novel treatment strategies for depression, both in the context of inflammatory conditions as well as in idiopathic depression. Furthermore, if such processes in MS play a causative role in the pathogenesis of depression, and depression in turn has affects on neurophysiological processes related to immune function, then treatment of depression might have a positive effect on MS disease progression. This makes treating MS depression a neuropsychiatric imperative.*

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# Translational research

location). By conservative estimates, at least 350 000 individuals in the United States have MS.[1] MS is usually diagnosed between the ages of 20 and 40, and is twice as common in women compared with men. In Western societies, MS is second in frequency only to trauma as a cause of neurologic disability in early to middle adulthood. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments. Although attention is typically focused on the neurologic disability associated with MS, the profound impact of neuropsychiatric comorbidities of MS on the presentation and prognosis of this autoimmune disease has recently begun to be appreciated.[2-6]

From its earliest characterization, depression was among the first symptoms recognized as being associated with MS. Jean-Martin Charcot (1825–1893) was the first individual to provide an accurate and comprehensive clinicopathological description of MS.[7] His first case presentation was Mlle V, whom he diagnosed with the classic cerebrospinal pattern of MS. Mlle V was a 31-year-old woman who suffered from severe depression, during which she ceased eating and had to be fed by a stomach pump to be kept alive.[7] Thus, even from its earliest description, depression has been recognizable as a serious and potentially life-threatening component of MS.

## Epidemiology and diagnosis of Major Depressive Disorder in MS

Major Depressive Disorder (MDD) is extremely common in MS, with a point prevalence of major depression among clinic patients of 15% to 30%, and a lifetime prevalence of 40% to 60%.[8] This rate of depression is 3 to 10 times that of the general population. Depression is more common in MS than in other chronic illnesses, including other neurologic disorders.[9] Depression in MS patients causes great personal suffering and dramatically affects function, quality of life, and longevity.

The *DSM-IV* criteria for MDD require the presence of five or more of the following symptoms during the same 2-week period accompanied by functional impairment: (i) insomnia or hypersomnia; (ii) loss of interest or pleasure (anhedonia); (iii) feelings of worthlessness or inappropriate/excessive guilt; (iv) fatigue or loss of energy; (v) depressed mood; (vi) diminished ability to think or concentrate, or indecisiveness; (vii) significant weight loss when not dieting or weight gain, or decrease or increase in appetite; (viii) psychomotor agitation or retardation; and (ix) recurrent thoughts of death or suicide. In order to meet criteria for Major Depression, at least one of the five or more symptoms that are present must either be depressed mood or loss of interest/pleasure. A frequently used mnemonic can be employed to remember these criteria: SIGEMCAPS (Sleep, Interest, Guilt, Energy, Mood, Concentration, Appetite, Psychomotor agitation or retardation, Suicidal ideation).

## Impact of MS on MDD and of MDD on MS

The impact of clinical depression on an MS patient's quality of life, function, and longevity should not be underestimated by patients, their caregivers, or their care providers. Multiple studies have suggested that depression is the primary determining factor in a patient's self-reported quality of life, with a greater impact than other variables investigated, including physical disability, fatigue, and cognitive impairment.[10-12]

Depression has a significant impact on the daily function of MS patients, including their interpersonal relationships, cognition, and fatigue.[6] The level of depression in patients with MS is the primary determining factor in the quality of their primary relationship when rated both by the patients and significant others,[13] which has important long-term implications for the ability of MS patients to maintain their stable social support systems. In MS patients, depression is associated with increased time lost from work, disruption of social support, and decreased adherence to neuromedical treatment regimens for MS.[4] There is a 30% lifetime incidence of suicidal intent in patients with MS, defined as a desire to kill oneself.[3] An astounding 6% to 12% of patients with MS eventually attempt to kill themselves. It is therefore not surprising

that studies have suggested that suicide, the most acutely grave consequence of severe depression, occurs in MS at a rate 7.5 times that of the age-matched general population.[14] In a large study at outpatient MS clinics, suicide was the third leading cause of death (accounting for 15% of all deaths during this 16-year period), close behind malignancy (16%) and pneumonia (23%).[14]

## Evidence for an immune-mediated mechanism for MDD in MS

The high rate of depression in MS begs the question of what accounts for this close association. There is no correlation between the rate and severity of depression in MS and the degree of physical disability. Furthermore, the incidence of depression in devastating but noninflammatory diseases, such as amyotrophic lateral sclerosis (ALS), is not similarly elevated.[15] These observations argue against depression resulting primarily from the psychosocial stress of this chronic neurodegenerative disease.[16-18] In addition, the risk of depression in first-degree relatives of depressed MS patients is no greater than the risk in nondepressed MS patients, suggesting that the genetic contribution to the development of depression in MS is small compared with the effects of MS itself.[19] Several studies have demonstrated an increased rate of depression and suicide at times of exacerbation, thereby providing clinical evidence for an association between immune activation and depression.[20-22] Indeed, additional conditions characterized by chronic inflammation, such as rheumatoid arthritis, allergy, and stroke, also have high rates of comorbid depression.[23] In the case of MS, the immune abnormalities have often been demonstrated to appear prior to the development of depression, consistent with the idea that the depression occurs secondary to inflammation.[24]

## Theories of mechanisms of depression in MS: etiology and pathophysiology

### Neuroimaging studies of brain pathology in MS depression

*Relevance of lesion location to depression*

Neuroimaging studies in patients with MS have revealed associations between brain abnormalities and depression. One of the earliest studies which analyzed data from computed tomography (CT) scans of patients with MS[25] found that patients with lesions in the brain were more depressed than those with lesions only in the spinal cord. Subsequent studies have examined relationships between the location of brain lesions and incidence of depression. A magnetic resonance imaging (MRI) study in 45 outpatients at an MS clinic reported that, although there was no relation between total lesion volume and depression, Beck Depression Inventory (BDI) scores were significantly associated with lesions in the arcuate fasciculus of the left hemisphere.[26] In a more recent MRI study, depressed MS patients had more hyperintense lesions in the left inferior medial frontal regions and greater atrophy of left anterior temporal regions. Together, these two brain regions accounted for ~42% of the variance in a logistic regression model for predicting depression.[27]

*Brain injury and atrophy*

MRI studies are useful in assessing the relationship between depression and not only lesion location, but also brain volume (ie, detection of atrophy). An MRI study of 95 consecutive MS patients, in which 19% of the patients met the criteria for major depression, reported that severity of depression and a diagnosis of major depression were correlated not only with right frontal lesion load but also with right temporal brain volume.[28] Furthermore, black holes as detected on T1-weighted images (which are thought to reflect severe tissue damage) in the superior frontal and superior parietal regions have been found to predict depression in MS patients.[29]

*Abnormalities of normal appearing tissue*

MRI findings often correlate weakly with clinical disability, probably because of the existence of abnormalities in normal appearing white matter (NAWM) and normal appearing gray matter (NAGM), which are not detected by MRI but are revealed by magnetic resonance spectroscopy (MRS). In MS, MRS studies have demonstrated significant axonal pathology in NAWM[30] and neuronal pathology in NAGM,[31,32] consistent with autopsy studies revealing axonal loss in tissue a substantial distance from any MS plaques.[33] Abnormalities in NAWM and NAGM seen using MRS are detectable earlier than lesions seen via MRI in patients with MS, and correlate well with both levels of disability and cog-

nitive function.[34-36] However, though there is extensive research on the MRS abnormalities in patients suffering from idiopathic depression,[37] further research needs to be undertaken in order to assess whether the abnormalities in NAWM and NAGM are associated with depression in patients with MS.

These imaging techniques may provide additional insights into the specific pathology that underlies the development of depression in MS patients. Nonetheless, the association between depression and pathology revealed by existing imaging studies suggest that immune-mediated effects on the brains of MS patients, rather than an environmental stressor triggering a genetically vulnerable individual, play a key role in the pathogenesis of MS depression.

## Neuroendocrine changes in MS depression

### The hypothalamic-pituitary-adrenal axis

A great deal of evidence suggests involvement of the hypothalamic-pituitary-adrenal (HPA) axis in the development of depression. Both excess cortisol and dexamethasone suppression test (DMT) nonsuppression have been reported for many years to be associated with mood disorders,[38] and DMT nonsuppression is related to the number of depressive episodes.[39] Furthermore, DMT nonsuppression normalizes as mood symptoms subside, with persistent non-suppression associated with a higher probability of relapse.[40] Upstream of cortisol production, patients suffering from depression display elevated levels of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid (CSF) and a blunted adrenocotrotropic hormone (ACTH) response to administered CRH, presumably due to chronic high levels of CRH causing downregulation of pituitary CRH receptors as well as negative feedback from high levels of circulating cortisol.[41,42] These changes in both CR and ACTH normalize after the depression is treated.[43,44] Finally, the volume of the hippocampus, an area with high concentrations of glucocorticoid receptors, is reduced in depressed patients, and this change is prevented by administering antidepressants.[45] However, little evidence currently exists as to whether reduction of hippocampal volume is directly due to elevated levels of cortisol, though it has been postulated that elevated cortisol may influence cognitive performance and mood state.[46]

MS patients are known to have a chronically activated HPA axis,[47] and HPA axis activity correlates with progression ratings and cognitive impairment over 3 years.[48] In addition, MRI studies[28] have shown an association between depression in MS and temporal lobe atrophy (though not specifically hippocampal atrophy). Given the association between depression and both HPA activity and hippocampal atrophy, the chronic activation of the HPA axis in MS may be one source of these patients' increased susceptibility to the development of depression.

### Steroid treatment

Consistent with a role for the HPA axis in the mechanism of depression, exogenous corticosteroids have been shown to have powerful mood-altering effects. Corticosteroids are often used in high doses to treat exacerbations in MS. They are associated with a great number of side effects, including effects on mood.[49] Their short-term use often produces an activated state characterized by increased energy, decreased sleep, and variable euphoria, which can be quite destabilizing to a patient's mood state. With initial dosing, long-term use, and discontinuation, steroid administration can result in new depressive symptoms as well as dramatic and even life-threatening worsening of mood in those already suffering from depression.[50] The effects of steroids on mood regulation provides further support for a role of the HPA axis in precipitating depression.

## The role of inflammation in MS depression

The increased incidence of depression in MS may be directly related to the inflammation which is the hallmark of this autoimmune disease. Alterations in the immune function of depressed patients have been observed for many years, although the precise nature of the changes has been variable, with some reflecting suppression and others activation of the immune system.[51-53] Recent work has demonstrated that depression is associated with an activation of inflammatory pathways, as evidenced by increases in C-reactive protein and other changes.[54-57] In MS, depression scores are higher in patients with increased CSF white blood cell counts, in vitro interferon (IFN)-$\gamma$ production, increased messenger ribonucleic acid (mRNA) for tumor necrosis factor (TNF)-$\alpha$ and IFN-$\gamma$, and central nervous system (CNS) inflammation as demonstrated by gadolinium-enhancing lesions on T1-weighted MRI.[5,21,58]

**Cytokines**

Proinflammatory cytokines are chemical messengers that are produced by immunocompetent cells and mediate communication between cells of the immune system, and are elevated in MS.[59-61] Interest in the role of inflammation in depression has focused largely on the contribution of increased levels of these proinflammatory cytokines.[62-64] A variety of evidence supports a role for cytokines in mediating depression[65]: (i) cytokine levels are elevated in depressed patients; (ii) administration of cytokines induces depression; (iii) stress, which can play a critical role in the development of depression, impacts cytokine production; (iv) cytokines interact with brain systems that have been implicated in depression; (v) elevated cortisol levels in depressed patients could reflect effects of elevated cytokine levels; and (vi) chronic antidepressant treatment reverses cytokine and cortisol elevations.

*Depression is associated with increased cytokines*

A number of studies have observed that patients suffering from depression have increased levels of various proinflammatory cytokines, including interleukin (IL)-6, IL-1β, TNF-α, and IFN-γ.[62,63,66-68] In some studies, the degree of cytokine elevation is positively correlated with the severity of symptoms.[5,69] Cytokines are similarly increased in depressed patients suffering from an inflammatory disorder: IFN-γ has been demonstrated to be increased in MS patients with depression, as is IL-6 in those with rheumatoid arthritis.[70]

*Administration of cytokines evokes depression*

The administration of certain cytokines (eg, for treatment of hepatitis C and cancer) frequently results in the development of depressive symptoms. In this context, IFN-α and IL-2 evoke depression, irritability, impaired memory, insomnia, loss of appetite, and asthenia.[62,63,71] Furthermore, the degree to which treatment alters cytokine levels is predictive of whether individual patients develop depression in response to treatment.[72] IFN-β therapy for MS may produce similar effects in some patients, although the evidence in relation to this cytokine is less compelling.[73] The psychiatric symptoms of cytokine administration become apparent several weeks into treatment, well after the appearance of phys-

ical symptoms, and tend to linger after physical symptoms have abated; thus, they are unlikely to be a reaction to physical discomfort.[74] These side effects of cytokine therapy are responsive to treatment with antidepressants (as described below).

In animals, administration of proinflammatory cytokines produces a syndrome of "sickness behavior" including anorexia, increased sleeping, hyperalgesia, decreased motor activity, decreased interest in the environment, and decreased libido, which looks very much like depression and is reversed by chronic administration of antidepressants.[23] Furthermore, the animal model of MS, experimental autoimmune encephalomyelitis (EAE), is associated with similar symptoms which are at least partially dependent on alterations in cytokines[75,76]; indeed, IL-6 knockout mice are resistant to EAE.[77]

*Stress increases cytokines*

Just as stress is thought to play a role in MS exacerbations,[78] it is generally accepted that stress can contribute to the development of depression. Furthermore, stress is associated with increased levels of cytokines.[79-82] Activation of proinflammatory cytokines in MS may be a route through which stress contributes to depression. Furthermore, cytokines and stressors appear to act synergistically in some studies.[83,84] Immune activation may have enhanced effects when there is concomitant stress. Indeed, this possibility may underlie the observation that stress is associated with immune exacerbations and lesion burden in MS.[85]

*Cytokines interact with the HPA axis*

As previously discussed, hyper-reactivity of the HPA axis is a hallmark of depression, and cytokines are potent activators of the HPA axis. Indeed, three cytokines—TNF-α, IL-1, and IL-6—account for most of the activity in plasma that stimulates the HPA axis.[86] Furthermore, clinical research findings suggest that the action of cytokines on the HPA axis contributes to the development of depression. For example, HPA axis reactivity in patients with depression correlates with cytokine levels.[87] Furthermore, both IL-6 and IL-1β production correlate with cortisol elevations after the dexamethasone suppression test.[88] In addition, patients who are treated with INF-α are more likely to develop major depressive symptoms if the initial dose results in a large

increase in ACTH and cortisol.[89] It has been suggested that cytokines may mediate the impairment of negative feedback, which normally acts to prevent excess levels of cortisol, which can occur in depressed subjects.[63,90] Observations from animal models are also consistent with cytokine-mediated alterations of HPA function: administration of endotoxin, which evokes "sickness behavior" and is considered to be an animal model of depression, no longer stimulates the HPA axis when coadministered with antibodies against IL-6.[91] Thus, elevations of proinflammatory cytokines in MS may facilitate depression via actions on the HPA axis and associated stress hormones.

*Cytokines interact with serotonergic systems*

Cytokines can influence serotonin (5-HT) neurotransmission by altering the metabolism of tryptophan (TRP), the metabolic precursor of 5-HT. IFN-γ, in particular, is known to activate the TRP-metabolizing enzyme indoleamine-2,3-dioxygenase (IDO),[92] recruiting TRP away from the 5-HT-synthesizing indolamine pathway to the alternate kynurenine (KYN) pathway. Activation of IDO thus results in increased production of 3-hydroxy-kynurenine (KYN) and quinolinic acid (QUIN).[93] Increased levels of KYN and QUIN have been proposed to contribute to the development of depressive symptoms.[94] Enhanced production of the neurotoxic metabolite QUIN may result in excess stimulation of *N*-methyl-D-aspartate (NMDA) receptors, causing hippocampal damage and the loss of corticosteroid receptors which mediate negative feedback of the HPA axis, thereby accounting for changes in hippocampal volume and HPA axis regulation seen in depression.[94] Activation of IDO causes depletion of TRP,[63,94] which can result in secondary 5-HT depletion and may precipitate relapses in depressed patients.[95] Thus, cytokine-mediated decreases in available TRP, and therefore 5-HT, may play a role in immune-mediated depression. Indeed, immunotherapy with IL-2 or IFN-α has been reported to cause significant depletions of TRP which are correlated to the severity of depressive symptoms,[96] and depressed patients exhibit lower levels of plasma TRP in association with elevations of IL-6.[97] Alternatively, the relevant action of cytokines on monoaminergic systems may be their effect on the 5-HT transporter: IL-1β administration results in increased levels and activity of the 5-HT transporter,[98] while IFN-α or IFN-γ increase mRNA for the transporter.[99] Such effects would be expected to result in decreased synaptic 5-HT. In MS, increases in proinflammatory cytokines may act via any of these mechanisms to decrease serotonergic neurotransmission and facilitate depression.

*Cytokines may alter neurogenesis*

In the past several years, it has become clear that new neurons are generated throughout the mammalian lifespan in specific brain areas, particularly the subventricular zone and the subgranular zone of the dentate gyrus in the hippocampus.[100,101] The functional relevance of this adult neurogenesis remains unclear, but a great deal of interest has focused on the possibility that impairment of hippocampal neurogenesis plays a role in depression.[102] Although the role of the hippocampus in learning and memory is typically emphasized, the hippocampus is classically considered to be part of the limbic system, and is intimately connected with other brain areas, such as the prefrontal cortex and the amygdala, thought to be involved in depression and regulation of mood. Indeed, subjects with long-standing depression have been shown to have decreases in hippocampal volume.[103] Furthermore, both stress and the resulting glucocorticoids, which are implicated in depression, reduce hippocampal neurogenesis.[104]

The precise mechanism by which hippocampal neurogenesis might be impaired in depression is not known, but a variety of evidence suggests that cytokines are involved. Chronic overexpression of IL-6 in transgenic mice results in decreased hippocampal neurogenesis,[105] and proinflammatory cytokines released by microglia have recently been shown to block hippocampal neurogenesis, with IL-6 being the key regulator of this inhibition.[106] Furthermore, IL-6 has been demonstrated to affect the differentiation of newly born cells, biasing cells to develop into glia rather than neurons,[106] and IFN-α may act via IL-1 to reduce neurogenesis in the hippocampus.[107] Alterations in hippocampal neurogenesis may be particularly relevant in MS, as EAE has been reported to reduce neurogenesis.[108]

**Neurotrophic factors in MS depression**

It has been suggested that BDNF plays a role in depression[109,110]: stress reduces BDNF in the hippocampus,[111] BDNF is decreased in the serum of depressed

patients,[112,113] and a polymorphism in the *BDNF* coding region may be associated with an increased incidence of depression.[114,115] Furthermore, overexpression of TrkB, the receptor for BDNF, has antidepressant effects in transgenic mice.[116] The possibility that decreased BDNF is involved in depression may be particularly relevant in MS, which is associated with reductions in this neurotrophic factor.[117] Although the precise mechanisms by which BDNF may affect mood are unknown, it seems likely that its known actions on neuronal plasticity and survival are relevant. In this context, reductions in neurotrophic factors such as BDNF may be relevant for the decreases in hippocampal volume which have been associated with depression.[118]

## Mechanisms of treatment response

The existing evidence suggests a role for cytokines in the pathogenesis of depression in MS, with the same mediators of inflammatory damage to the CNS causing perturbations in mood regulation. Likewise, neurotrophic factors may be relevant for the psychiatric symptoms of depression as well as for neurologic symptoms. We propose that MS depression presents an ideal opportunity to study a lesion model of mood disorders, where the neuroinflammatory insults that characterize this autoimmune CNS disease often results in immune-mediated depression.

### Anti-inflammatory mechanisms of treatment response

Depression in this context can therefore be viewed as both a pathophysiological complication as well as a clinical symptom of MS. It would be logical to hypothesize that treating the CNS inflammation that results in the characteristic insults seen in MS would ameliorate depression in affected patients. Although preliminary, there is support for this hypothesis from diverse avenues of investigation.

Ironically, concern about an association of IFN treatment for MS and the onset of symptoms of depression was raised early on in the first clinical trial of IFNβ-1b (see below, **IFN treatment, depression, and treatment response**). However, a recent review of the literature by Goeb et al[73] revealed that most studies (14 out of 16) discard an association between IFN-β and depression or suicide. In fact, two prospective studies have demonstrated that IFN-β-1 treatment of patients with relaps-ing-remitting multiple sclerosis (RRMS) decreases the prevalence of depression, independent of changes in disability.[16,119] Based on nonstandardized or anecdotal evidence, however, there may be a few patients, especially those with a history of depression, who might be at higher risk for depression when treated with IFNβ. Nonetheless, for those patients with RRMS whose MS responds to IFNβ, there may be a beneficial secondary effect of this treatment on mood.

Although there is as yet no clinical or experimental support for glatiramer acetate (GA) functioning as an antidepressant for patients with MS through its anti-inflammatory effects, theoretically the mechanisms of action of this treatment suggests it could have a role in managing MS depression.[120] GA could have antidepressant effects by increasing central BDNF, stimulating neurogenesis or through its anti-inflammatory effect. Clinical tests of this hypothesis are needed to assess its validity.

If the immune activation that accompanies MS supports a potential role for inflammation in the pathogenesis of mood disorders, then anti-inflammatory medications might be expected to ameliorate depression. Statins, a family of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are used primarily to reduce atherogenesis and cardiovascular morbidity. Recently they have also been shown to have immunomodulatory properties that might be of benefit for the treatment of autoimmune disorders, and are currently being investigated in clinical trials for their potential use in treating MS.[121] Previous studies have also found that statins may be of benefit in the treatment of depression. Young-Xu and colleagues studied patients from an outpatient cardiology clinic, and found that long-term use of statins appeared to be associated with a reduced incidence of anxiety, depression, and hostility.[122] Analysis from the United Kingdom General Practice Research Database found that individuals currently on statins have a lower risk of developing depression.[123] In a double-blind pilot study, subjects who took statins for 1 year were found to improve in ratings of depressive symptoms.[124]

A potential role of inflammation mediated by prostaglandin E2 (PGE2) in depression has recently been explored. As cyclo-oxygenase-2 (COX-2) inhibitors inhibit PGE2 production and the production of proinflammatory cytokines, there are a growing number of investigations into a potential role for these medications for treating depression. Aspirin has been shown to dramatically accelerate the onset of action of a selective serotonin reuptake

inhibitor (SSRI) in an animal model of depression.[125] More persuasively, a double-blind placebo controlled trial in 40 patients with MDD demonstrated that addition of celecoxib had significant therapeutic effects on the action of the antidepressant reboxetine compared with treatment with reboxetine and a placebo.[126]

The potential interrelatedness of treatments for depression and their impact on inflammation is suggested by vagus nerve stimulation (VNS). VNS therapy is an effective adjunctive treatment for chronic or recurrent treatment-resistant depression in adults. The mechanism of action of VNS and how it ameliorates depression is not known. A series of elegant studies by Tracey and colleagues have identified the cholinergic anti-inflammatory pathway as a neural, efferent vagus nerve-based mechanism that controls inflammation.[127] Vagus nerve cholinergic signaling interacts with α-7nAchR on immune cells and inhibits the production of TNF and other proinflammatory cytokines and excessive inflammatory responses. Thus, it is interesting to speculate that part of the antidepressant effects of VNS could relate to the control of innate immunity and inflammation by vagal nerve activity, consistent with an immune-mediated pathogenesis of some types of depression.

There is some evidence that antidepressant drugs have direct immunomodulatory effects, particularly when administered chronically.[128] Many studies have reported that the depression induced by the therapeutic administration of cytokines is responsive to antidepressants,[63,74] and remission of symptoms following antidepressant treatment may be associated with normalization of cytokine levels.[66] Furthermore, alterations in cytokine levels are predictive of treatment response: increased levels of TNF-α are lowered by antidepressant administration in patients who respond to the treatment, but not in nonresponders.[67] In MS, successful antidepressant treatment of depressive symptoms is associated with normalized levels of IFN-γ.[5] Increased IFN-γ levels precede exacerbations and correlate with more aggressive disease course, suggesting that the immunomodulatory actions of antidepressants may be generally relevant in the treatment of MS, in addition to their efficacy for depressive symptoms.[5]

Further suggesting an intimate relationship between depression and inflammation, some antidepressants have been shown to have direct anti-inflammatory effects in autoimmune or infectious diseases.[129] Bupropion in particular has been shown to have several interesting potential immunomodulatory effects: (i) bupropion has been

associated with the induction of remission in Crohn's disease in patients even in absence of depression; (ii) bupropion led to the lowering of circulating TNF in a patient with hepatitis B infection; and (iii) bupropion profoundly lowers levels of TNF, IFN-γ, and IL-1β in vivo, in a mouse inflammation model of sepsis. Whether the immunomodulatory effects of some antidepressants play a supplementary role in their mechanism of treatment response for depression remains to be elucidated.

**Neurogenesis and treatment response**

The possibility that impaired neurogenesis contributes to depression suggests a novel mechanism for the action of antidepressants: a restoration of normal hippocampal neurogenesis. Consistent with this possibility, antidepressants enhance hippocampal neurogenesis both in vitro and in vivo,[130-133] and this effect requires chronic treatment, consistent with the time course of the therapeutic action of these drugs.[102] Furthermore, blockade of hippocampal neurogenesis has been reported to prevent the actions of antidepressants in behavioral models of depression.[134] In addition to antidepressant drugs, electroconvulsive therapy (ECT) and exercise—treatments known to be effective in decreasing depressive symptoms—also facilitate hippocampal neurogenesis.[135,136] These effects could occur via alterations in cytokines, as antidepressants are reported to decrease levels of proinflammatory cytokines[137] and, in fact, such effects may be necessary for antidepressant action.[138] Thus, the effectiveness of antidepressants in treating MS depression may be due in part to their effects on neurogenesis, particularly as EAE is known to impair neurogenesis.

**HPA axis and treatment response**

Given the evidence that patients with MS suffer from chronic activation of the HPA axis, and the link between HPA overactivity and depression, it appears to be a logical postulation that control of the HPA axis should assist in the control of the symptoms of depression in such patients. Indeed, antidepressants can enhance both the expression of and functioning of glucocorticoid receptors (GR) in vivo and in vitro, which may increase negative feedback and hence reduce levels of circulating cortisol.[139] Similarly, COX-2 inhibitors, which augment the effects of the antidepressant reboxetine in treating patients with major depression,[126] have shown

the capacity to enhance GR expression and function.[140] In addition, more novel treatments of depression based on restoring normal HPA tone have been explored. For example, the adrenal steroid dehydroepiandrosterone (DHEA) has been used with some success in the treatment of depression,[141] and this may be related to its antiglucocorticoid properties.[142] Low levels of DHEA have been linked to fatigue in MS[143]; since fatigue is often a consequence of depression, DHEA administration may be a useful treatment for fatigue and possible associated depression in MS. A second possible intervention is inhibition of steroid synthesis; administration of daily ketoconazole reduced cortisol levels and depressive symptoms within 72 hours in a case of treatment-resistant depression,[144] and metyrapone can be an effective adjunct in the treatment of major depression.[145] However, not all studies have shown consistent results regarding efficacy of this method,[146] and there is as yet no data regarding this treatment for depression in MS patients. Finally, mifepristone, which is a competitive inhibitor of the GR but is relatively inactive at the mineralocorticoid receptor (MR), has shown some efficacy in the treatment of psychotic major depression. This drug may reduce the GRs' transmission in response to cortisol, which may in itself cause an improvement in symptoms. It may also cause an increase in circulating cortisol due to reduced GR negative feedback, resulting in downregulation of the MR and a resetting of the HPA axis.[147] These treatments represent possible means of restoring normal HPA axis tone and therefore ameliorating depressive symptoms in MS.

One method to reduce the activation of the HPA axis in major depression that is currently under investigation is the use of CRH receptor antagonists.[148] Hypothalamic CRH acts by simulating the pituitary to secrete ACTH, which in turn stimulates adrenal cortisol production. Hence CRH receptor antagonists reduce the secretion of ACTH and hence cortisol. Studies are currently being carried out, but as yet there is no data as to their efficacy in the treatment of depression. There is no data available for the use of CRH receptor antagonists in depression in MS patients.

**Neurotrophic factors and treatment response**

It has recently become appreciated that antidepressants have a stimulatory effect on BDNF, and that this action may be relevant in their therapeutic value. Essentially all treatments for depression, including antidepressants and

ECT, increase BDNF mRNA in the hippocampus and the cortex.[110] Reduced brain and blood levels of BDNF are normalized by antidepressants,[112,113,149] as is stress-induced reduction of BDNF.[111] Furthermore, antidepressants increase the activation of the TrkB receptor.[150] The benefit of stimulating BDNF may be related to this neurotrophic factor's role in plasticity and neuronal support. In addition, BDNF is known to play a key role in neurogenesis by promoting the long-term survival of newly born neurons,[151] and this action may contribute to facilitation of neurogenesis by antidepressants. Finally, animal models of depression demonstrate that BDNF may be necessary for the behavioral effects of antidepressants, as such are reduced in animals with inhibition of TrkB signaling or reduced brain BDNF levels,[150,152] and because ECT-induced increases in dendritic sprouting seen in the hippocampus are decreased in BDNF heterozygote knockout mice.[153]

In the treatment of MS, GA not only decreases proinflammatory cytokines, but also increases BDNF.[154] Likewise, in an animal model of MS (EAE), mice exhibit reductions in BDNF that normalize upon administration of GA.[155] BDNF is produced by T-helper cells that respond to GA[156] and BDNF is expressed in cells in MS brain lesions.[156] Thus, the therapeutic value of GA may be related to its effect on BDNF. Indeed, in one study of relapsing-remitting MS, only those people who ultimately entered remission had had increased BDNF during their relapse.[157,158] Actions on BDNF may provide a mechanism by which GA administration restores neurogenesis in EAE,[108] suggesting that this treatment may have specific effects on depression in MS.

Chronic administration of lithium, as well as another mood stabilizer, valproate, has been reported to increase BDNF in the frontal cortex.[159] These drugs also increase hippocampal neurogenesis.[160] It has been suggested, therefore, that lithium and valproate may be efficacious not only for bipolar disorder, but for neurodegenerative disorder.[161]

**Interferon treatment, depression, and treatment response**

A link between depression and IFN-β treatment of MS patients was suggested based on data from the pivotal IFN-β-1b (Betaseron) study in 372 subjects over 5 years, during which five patients (2%), all on active treatment, attempted suicide.[162] While these differences were not statistically significant, they created initial concern about a potential causal link between IFN-β treatment of MS

and depression.[163] Subsequently, there have been anecdotal reports of depression occurring after the initiation of IFN-β treatment, and some studies have shown an increase in physician perception of depression in IFN-β relative to placebo-treated patients. However, whenever validated psychiatric instruments have been used, no increase in the rates of depression was found in IFN-β treated patient relative to placebo-treated controls.

A recent analysis of all data from Serono sponsored trials of IFNβ-1a (including Rebif, Avonex, and placebo) sheds some interesting light on these confusing findings,[162] demonstrating that (i) when using validated psychiatric instruments there is no increase in the rate of depression in IFN-β vs placebo-treated patients; (ii) treating physicians' perceptions of depression were higher in IFN-β vs placebo-treated patients, but the false-positive rate for these perceptions were better than chance (57%), perhaps due to side effects of the IFN-β such as flu-like symptoms and fatigue confounding the physicians' assessments of depression; (iii) the odds ratio (OR) of suicide attempts for patients receiving IFN-β compared with placebo was 0.77 overall (CI 0.30-1.93); (iv) the rate of suicide attempts among SPMS patients treated with IFN-β were greater than placebo (OR 1.45, CI 0.44-4.73), in contrast to RRMS patients treated with IFN-β, whose rates of suicide attempts were less than placebo (OR 0.42, CI 0.09-1.88); and (v) suicide attempts and completed suicides were statistically more common in secondary progressive multiple sclerosis (SPMS) than RRMS (OR 3.5, CI 2.19-5.58).

A plausible biological model to fit these results would be the following: (i) theoretically, IFN-β can moderately increase the risk of depression in patients with MS (perhaps with a rate of 23% if comparable to IFN-α in HCV patients); (ii) MS can dramatically increase the rate of depression (50%); (iii) by ameliorating the effects of MS on increasing the rates of depression, IFN-β treatment, when effective, actually results in no increase or a net reduction in the rate of depression compared with placebo; and (iv) in those patients relatively refractory to the benefit of IFN-β treatment, such as SPMS patients, the risk of IFN-β induced depression is manifest because it is no longer offset by the gains in reducing the severity of MS.

**Treatment of depression may improve MS outcome**

Evidence presented here supports the model that the inflammation that is related to CNS insults in MS can result in depression in affected patients. Depression can

therefore be viewed as both a pathophysiological complication as well as a clinical symptom of MS. This would suggest that the management of depression is an integral part of the general management of MS, analogous to the treatment of other disease-related disabilities involving motor, sensory, and autonomic dysfunction, with potential prognostic implications for the overall course of the disease progression. If CNS inflammation in MS plays a causative role in the pathogenesis of depression, and depression in turn has affects on neurophysiological processes related to immune function (such as the HPA axis), then it is plausible that amelioration of depression might affect MS disease progression.

Mohr and colleagues[5] showed a positive correlation between depression and in vitro IFN-γ production. IFN-γ is the main proinflammatory cytokine produced by activated TH1 cells, and is regarded as a major effector mechanism in the pathogenesis of MS. In this study, amelioration of depression after psychotherapy or antidepressant medication treatment was paralleled by decreases in the capacity to produce IFN-γ. These findings suggest that the production of the proinflammatory cytokine IFN-γ by autoaggressive T cells in RRMS is related to depression, and that treatment of depression may decrease IFN-γ production. In another study supportive of a bidirectional relationship between the impact of MS on depression, treatment of MS depression with lofepramine, a derivative of the antidepressant medication imipramine, was associated with decreases of gadolinium-enhancing lesion load on T1-weighted scans.[164] Thus, treatment of depression may provide a novel disease-modifying therapeutic strategy as well as a symptomatic treatment for patients with MS.

Depression may also predispose to inflammatory conditions. A recent study reported that mild depressive symptoms are associated with enhanced systemic inflammatory responses to immune challenge.[165] Furthermore, in an animal model of stress-induced depression, early life depression led to enhanced vulnerability to colitis in adulthood[166]; this susceptibility was reversed by antidepressant therapy. The observation that depression increased vulnerability to intestinal inflammation led the authors to speculate that pre-existing depression may facilitate the expression of inflammatory bowel diseases in humans.

Thus, it is conceivable that depression can predispose vulnerable individuals to autoimmune diseases such as MS, which further cause and amplify the severity of the

depression. This in turn worsens the severity of the state of MS immune activation, generating a positive feedback loop that could become self-sustaining.

## Conclusions

We have surveyed the research supporting a biological basis of depression in MS, which we suggest is an ideal model to study immune-mediated mood disorders. We discuss the possible contributions of neuroendocrine, neuroinflammatory, and neurotrophic mechanisms in the pathogenesis of immune-mediated depression in MS. These mechanisms suggest a novel and diverse array of potential treatment strategies that may lead to new treatments for depression, which are currently much needed since it has been almost two decades since the introduction of a treatment for major depressive disorder that was not based on the traditional monoamine hypothesis of depression. Whether these treatments will lend themselves specifically to the management of

depression in the context of inflammatory conditions, or whether they will also have utility in idiopathic depression, will await future clinical evaluation.

From the available evidence we conclude that depression in MS is largely biologically mediated by some of the same mechanisms that give rise to the underlying immunopathogenesis of the neurologic disease. Depression has devastating consequences that require it to be carefully assessed and managed clinically, including the possibility that the depression worsens the severity of the MS. Finally, it is important to note that current treatments for MS depression, while nonspecific, can be dramatically effective and lead to complete resolution of the depressive syndrome. Further work in the area of MS depression should lead us to a new understanding of the pathophysiological mechanisms of mood disorders, with the promise of producing a host of novel treatments in the near future, perhaps some that are already being employed in the management of inflammatory conditions. ❑

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### *Manifestaciones neuropsiquiátricas de la depresión en la esclerosis múltiple: mecanismos neuroinflamatorios, neuroendocrinos y neurotróficos en la patogénesis de la depresión mediada por la inmunidad*

*La evidencia sugiere que la depresión en la esclerosis múltiple (EM) está mediada en gran medida biológicamente por algunos de los mismos procesos involucrados en la inmunopatogénesis de esta enfermedad neurológica. En especial, el aumento de citoquinas proinflamatorias, la activación del eje HHA y la reducción de los factores neurotróficos que ocurre en la EM pueden dar cuenta del aumento de la frecuencia de depresión observada en la EM. La posible contribución de estos mecanismos neuroinflamatorio, neuroendocrino y neurotrófico sugieren una serie diferente de nuevas estrategias de tratamiento para la depresión, tanto en el contexto de condiciones inflamatorias como en la depresión idiopática. Además, si tales procesos en la EM tienen un rol causal en la patogénesis de la depresión, y la depresión a su vez tiene efectos en los procesos neurofisiológicos relacionados con la función inmune, entonces el tratamiento de la depresión es posible que tenga un efecto positivo en la progresión de la EM. De esto se deduce que el tratamiento de la depresión en la EM es un imperativo neuropsiquiátrico.*

### *Manifestations neuropsychiatriques de la dépression dans la sclérose en plaques : mécanismes neuro-inflammatoires, neuroendocriniens et neurotrophiques dans la pathogénie de la dépression à médiation immunitaire*

*Certains processus impliqués dans l'immunopathogénèse de la sclérose en plaques (SEP) semblent intervenir en grande partie biologiquement dans la dépression qui lui est associée. En particulier, l'augmentation des cytokines pro-inflammatoires, l'activation de l'axe HPA et la réduction des facteurs neurotrophiques au cours de la SEP entrent en jeu dans l'augmentation des taux de dépression observés dans cette pathologie. Les implications éventuelles de ces mécanismes neuro-inflammatoires, neuroendocriniens et neurotrophiques laissent entrevoir la possibilité d'un large éventail de nouvelles stratégies thérapeutiques pour la dépression, aussi bien dans le contexte des pathologies inflammatoires que dans celui de la dépression idiopathique. Si de plus ces processus liés à la SEP sont responsables de la pathogenèse de la dépression, et que celle-ci influe à son tour sur les processus neuropsychologiques liés à la fonction immunitaire, le traitement de la dépression pourrait alors avoir un effet positif sur la progression de la SEP. Le traitement de la dépression liée à la SEP devient donc un impératif neuropsychiatrique.*

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