



# Co-occurrence of Fatigue and Depression in People With Multiple Sclerosis: A Mini-Review

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Fatigue and depression are common conditions diagnosed in people with multiple sclerosis (MS). Fatigue defined as subjective lack of physical and/or mental energy is present in 35–97% of people with MS, who classify it as one of the most serious symptoms interfering with daily activities and influencing the quality of life. Depression is diagnosed in about 50% of people with MS. Since fatigue and depression frequently coexists, it may be quite hard to differentiate them. Primary fatigue and primary depression in MS are caused by inflammatory, oxidative/nitrosative, and neurodegenerative processes leading to demyelination, axonal damage, and brain atrophy. In people with MS and comorbid fatigue and/or depression there is reported increased serum and cerebrospinal fluid concentration of inflammatory mediators such as tumor necrosis factor, interleukins (IL-1a, IL-1b, IL-6), interferon  $\gamma$  and neopterin. Moreover, the brain atrophy of prefrontal, frontal, parietotemporal regions, thalamus, and basal ganglia was observed in people with MS with fatigue and/or depression. The secondary fatigue and secondary depression in people with MS may be caused by emotional factors, sleep disorders, pain, the coexistence of other diseases, and the use of medications. In some studies, the use of disease-modifying therapies positively influenced fatigue, probably by reducing the inflammatory response, which proves that fatigue and depression are closely related to immunological factors. In this mini-review, the pathogenesis, methods of evaluation and differentiation, and possible therapies for fatigue and depression in MS are discussed.

**Keywords:** multiple sclerosis, fatigue, depression, anhedonia, fatigue scales

## INTRODUCTION

Fatigue and depression are very common conditions diagnosed in people with multiple sclerosis (MS). Fatigue is present in 35–97% of people with MS (1, 2). It is classified as one of the most serious symptoms interfering with daily activities and influencing the quality of life (QoL) (1–3). Fatigue is defined as a subjective lack of physical and/or mental energy. MS-related fatigue is divided into physical and cognitive (4). Physical fatigue, defined as a decline in motor performance during sustained muscle activity, is caused by physical exhaustion and results from muscle weakness. Cognitive fatigue is defined as a decline in performance during cognitive activity, which results from difficulty with concentration, memory loss, and emotional instability (4–8). Cognitive fatigue starts independently from the physical disability in the early stages of MS and may be present

already in the prediagnostic phase of the disease (9, 10). Cognitive fatigue is one of the key factors resulting in a decreased QoL in all people with MS (8, 11–13). Depression is diagnosed in about 50% of people with MS (14). Depression itself can manifest with fatigue and symptoms of depression may be mistaken for fatigue making these conditions difficult to differentiate. Recent studies have identified a strong correlation between fatigue and depression. These conditions jointly affect more than half of people with MS (15).

The leading and common symptom of cognitive fatigue and depression is anhedonia defined as decreased motivation, a lack of positive affect, and the reduced ability to experience pleasure (14, 16–18). Anhedonia is caused by deficiency of neurotransmitters such as dopamine and serotonin, which leads to impairment in the functioning of mesocorticolimbic pathways projecting from the midbrain to the basal ganglia, the limbic system, and the prefrontal cortex. It results in disrupting the brain's reward and valence system (16, 18). The structural and functional alterations of mesocorticolimbic pathways have been confirmed in neuroimaging studies in people with MS suffering from fatigue and/or depression (18).

The frequent coexistence of fatigue and depression in people with MS suggests a common etiology of both conditions (19–21). Primary fatigue and primary depression in MS are most probably caused by inflammatory, oxidative/nitrosative, and neurodegenerative processes leading to demyelination, axonal damage, and brain atrophy (1). In people with MS and comorbid fatigue and/or depression there is reported increased serum and cerebrospinal fluid (CSF) concentration of proinflammatory cytokines, interleukins, interferon  $\gamma$  (IFN $\gamma$ ), and neopterin (1). Many studies have been also reported the brain atrophy of the prefrontal, frontal, parietotemporal region, thalamus, and basal ganglia (16, 22). The secondary causes of fatigue and depression are emotional stress, sleep disorders, pain, the coexistence of other diseases, and the use of some disease-modifying therapies (DMTs), e.g., interferon- $\beta$  (22). The treatment of MS-related fatigue and depression is still challenging. In some studies, the use of natalizumab, fingolimod, and glatiramer acetate positively influenced fatigue, probably by reducing the inflammatory response, which proves that fatigue and depression are related to immunological factors (16).

In the present mini-review, we provide and discuss the latest information on the pathogenesis, methods of evaluation and differentiation, and possible therapies for fatigue and depression in MS.

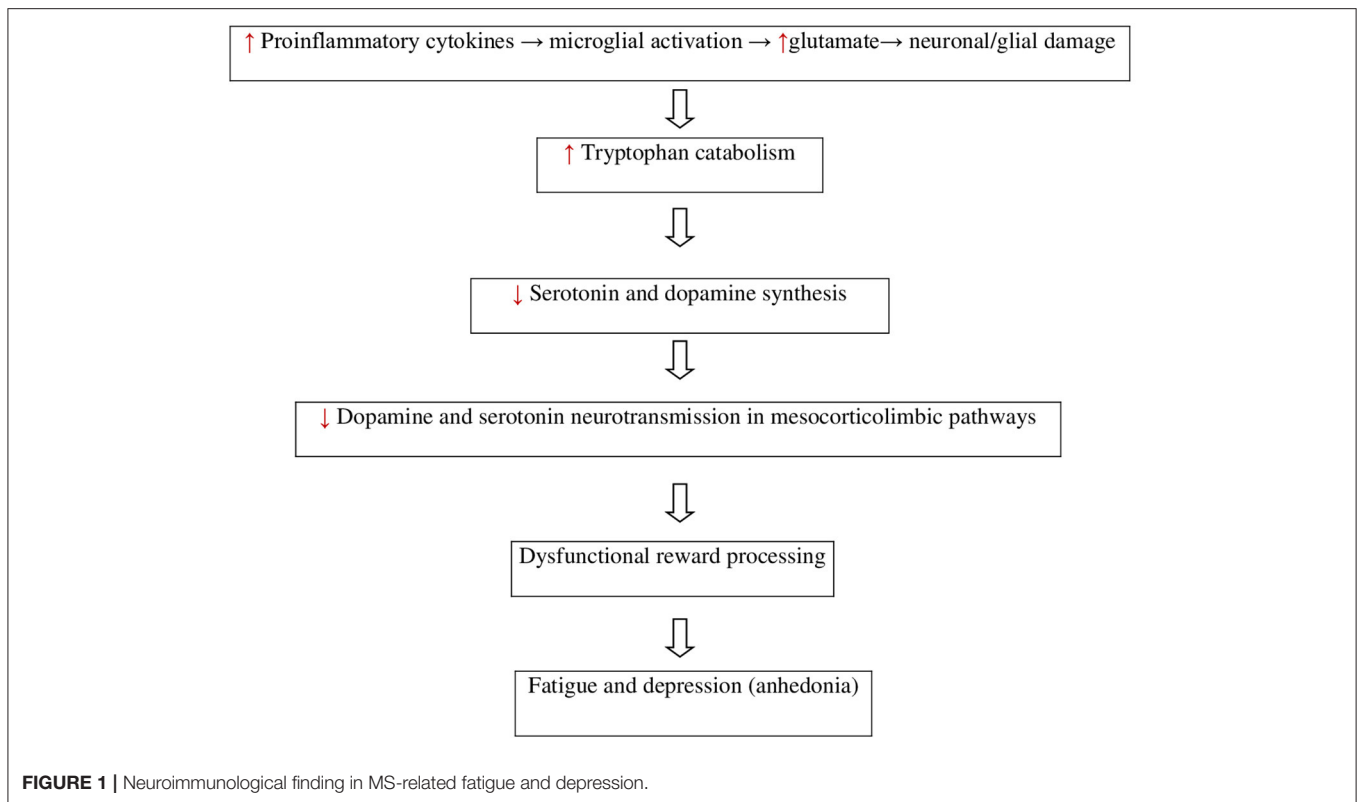
## ETIOPATHOGENESIS OF FATIGUE AND DEPRESSION IN MS

The neuroinflammatory process undergoing the pathogenesis of MS disturbs neural function and may result in fatigue and depression (**Figure 1**) (1–3, 15, 16). In the pathomechanisms of fatigue and depression in MS the crucial role play proinflammatory cytokines including tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukins (IL-1a, IL-1b, IL-2, IL-6), IFN- $\gamma$  released

by mitogen-stimulated peripheral blood lymphocytes, and neopterin produced by macrophages upon IFN- $\gamma$  stimulation (23). The proinflammatory mediators lead to the induction of tryptophan catabolism. Tryptophan is a biochemical precursor for serotonin and kynurenine. The low level of these monoamines may lead to fatigue and depression (23). In people with MS with comorbid fatigue and/or depression, there are reported increased serum and CSF concentrations of the pro-inflammatory cytokines, such as interleukins (IL-1a, IL-1b, IL-2, IL-6), TNF- $\alpha$  and IFN- $\gamma$ . The high concentrations of those pro-inflammatory mediators correlate directly with the level of fatigue and depression (1, 23–25). The proinflammatory cytokines in people with MS induce sickness behavior by disruption of dopamine and serotonin neurotransmission in mesocorticolimbic pathways connecting the midbrain with the basal ganglia, the limbic system, and the prefrontal cortex leading to dysfunctional reward processing and anhedonia (16, 18, 19, 26, 27). Pro-inflammatory cytokines disturb the synthesis of dopamine and serotonin by reducing the synaptic availability of amino acids precursor, disturbing their release, and increasing the reuptake of monoamines (27). The cytokines increase the metabolism of the serotonin precursor tryptophan *via* the alternative kynurenine pathway by inducing indoleamine 2,3 dioxygenase (IDO) (28). In addition, the cytokines decrease the availability of the co-factor tetrahydrobiopterin (BH4) limiting the turnover of the precursor phenylalanine and tyrosine and interfering with the formation of dopamine (29). The synaptic availability of serotonin and dopamine is reduced by decreased presynaptic release and increased activity of pro-inflammatory cytokines acting as reuptake transporters (30).

Recently, it has been shown that the microglia contribute to neurodegeneration by the production of neurotoxic metabolites such as quinolinic acid that maintains inflammation and neurodegeneration through excitotoxicity (16, 28). Increased glutamate levels in the CNS lead to overstimulation of glutamate receptors and neuronal and glial damage (31). Quinolinic acid stimulates release and inhibits the reuptake of glutamate from astrocytes as well as it is direct agonist binding to glutamate N-methyl-D aspartate (NMDA) receptors (32). Stimulation of extrasynaptic NMDA receptors by glutamate was reported to be associated with decreased expression of brain-derived neurotrophic factor (BDNF) and the induction of cell death. The pro-inflammatory cytokines contribute to excitotoxicity in the gray and white matter by hampering glutamate reuptake through astrocytes and oligodendrocytes (16, 31).

The neurodegeneration and decreased neurogenesis are also caused by oxidative and nitrosative stress (O&NS) ongoing in course of MS (1, 23, 33, 34). O&NS induces damage to membrane fatty acids and proteins, which results in the formation of anchorage neo-epitopes, exposed to an autoimmune response. The level of immunoglobulins M (IgM) against these epitopes (ex. palmitic, myristic, S-farnesyl-cysteine) was found to be increased in people with depression and fatigue. O&NS also leads to dysfunction of mitochondria, affects DNA expression, lowers antioxidant and omega-3 polyunsaturated fatty acid levels, and



increases translocation of gram-negative bacteria. Evidence of the O&NS pathways shared by depression and fatigue may explain the common co-occurrence of these conditions in the course of MS (35).

In people with MS and comorbid fatigue and/or depression, there was also reported impairment of the hypothalamic-pituitary-adrenal (HPA) axis. The low cortisol and low dehydroepiandrosterone levels have been implicated in chronic fatigue and depression (22, 36, 37). It suggests a possible endocrine contribution to fatigue and depression. People with MS report increased energy after taking corticosteroids as treatment for MS relapse, which supports a possible positive hormonal influence of steroids on fatigue (22).

The etiopathogenesis of MS-related fatigue and depression is also involved serotonergic regulation *via* the brain serotonin transporters (SERT) (38). In people with MS the SERT regulation may be disturbed (38, 39). The SERT inhibitors, such as fluoxetine and sertraline have been reported to have neuroprotective effects in MS (38, 40). Hesse et al. have reported that serotonergic neurotransmission in people with MS is altered in limbic and paralimbic regions, the frontal cortex, which contributes to cognitive fatigue and depression in MS (38). People with MS and comorbid fatigue and/or depression have been reported to have low SERT availability in cortical and subcortical brain areas, limbic and paralimbic regions such as the cingulate cortex, hippocampal/parahippocampal, and insular (38).

## ANATOMICAL ABNORMALITIES IN FATIGUE AND DEPRESSION IN MS

Fatigue and depression in people with MS are associated with gray matter atrophy in the prefrontal cortex, the basal ganglia, the striatum, and the limbic system (16, 41–44). Many studies have shown decreased monoaminergic neurotransmission in frontostriatal and frontolimbic pathways in people with MS suffering from fatigue and depression (44–47). Roelcke et al. have shown in positron emission tomography study the decreased glucose metabolism in the basal ganglia and the prefrontal cortex. In turn, Finke et al. and Jaeger et al. have reported in the functional magnetic resonance imaging study the decreased functional connectivity between the ventral striatum, the amygdala, and the prefrontal cortex (48).

## SECONDARY CAUSES OF FATIGUE AND/OR DEPRESSION IN MS

Fatigue and/or depression can be a psychological and emotional reaction to the lifestyle changes that occur when people are diagnosed with a chronic disease such as MS (49, 50). Fatigue and depression may be also caused by sleep disorders, pain, and the coexistence of other diseases. Sleep disorders are quite common in people with MS compared to the general population and may result from muscle spasticity and pain, emotional

disturbances, nocturia, taking medications, and restless legs syndrome (RLS) (51). RLS is present in 30–50% of people with MS and deteriorates the sleep quality (52). The frequency of RLS increases with disability progression assessed by the Expanded Disability Status Score (EDSS) (52). In the course of MS dopaminergic diencephalospinal, and reticulospinal pathways projecting to the spinal cord may be damaged, which leads to RLS (53). People with MS presenting medullary lesions affecting respiratory centers may develop sleep breathing disorders such as central sleep apnea (54). The severity of disability assessed with EDSS also proportionally increases the risk of fatigue and depression (15, 55).

The use of some DMTs may also increase the risk of fatigue and depression (56). Fatigue and depression are reported more frequently in people treated with interferon- $\beta$ , which causes side effects like flu-like symptoms resembling sickness behavior (57, 58). In some articles, depression is listed as a possible side effect of interferon- $\beta$  (59, 60). On the contrary, there are several studies that have not found any relationship between DMT type and depression (61). There are still no conclusive data regarding DMTs influence on fatigue symptoms. Some publications raise the positive impact of natalizumab, fingolimod, and glatiramer acetate on fatigue and depression (60, 62–67). One of the theories is that antifatigue and antidepressive effectiveness of some DMTs may be related to the suppression of inflammatory pathways leading to depression (68, 69). However, a causal relationship between DMTs, especially T and B-cell depleting therapies, and the risk of depression remains to be shown. It is also important to consider the mode of administration of DMTs. Additional studies evaluating treatment satisfaction and quality of life of people with MS may shed light on the relation between treatment tolerability, mode of DMTs administration, and risk of fatigue and depression (70). There is a higher risk of DMTs discontinuation in people with MS and depression (60).

## EVALUATION AND DIFFERENTIAL DIAGNOSIS OF FATIGUE AND DEPRESSION IN PEOPLE WITH MS

Fatigue and depression interfere with patients' daily activity and may lead to DMTs discontinuation. Therefore, there is a need for an early diagnosis and treatment. The assessment of fatigue is difficult and still challenging, as it requires objective measurement tools (5). Fatigue and depression may manifest with the same symptoms, like loss of motivation and anhedonia making these conditions difficult to differentiate. The fatigue in people with MS is classified on the basis of symptoms as physical, cognitive, and emotional. The fatigue symptoms are reduction in physical activity, problems with performing cognitive tasks, decreased concentration, memory disorders, executive difficulties, and a feeling of internal tension, anxiety, sadness (71).

The measurement of fatigue in the dimension of its perception is only subjective, while the objective measurement of fatigue may be assessed by analyzing the way cognitive and motor tasks are performed over time (27). In the subjective assessment of fatigue

are used one- or multi-dimensional self-report scales in the form of questionnaires describing fatigue in terms of its occurrence (or not), severity, duration, and dimension (cognitive/physical). The one-dimensional tool is the Visual Analog Scale for Fatigue (VAS-F). The most commonly used multivariate scales are the short seven-point Fatigue Severity Scale (FSS) and the broader 21-point Modified Fatigue Impact Scale (MFIS). MFIS assesses the impact of fatigue on functioning in three dimensions: social, cognitive, and physical (72, 73). Another multidimensional self-report tool is the Fatigue Scale for Motor and Cognitive Function (FSMC), which assesses the occurrence and intensity of physical and cognitive fatigue on two 10-point scales (5). The objective measurement of fatigue in MS is based on quantitative and qualitative data obtained during the performance of the motor and cognitive tasks by patients. Physical fatigue is described in terms of a decrease in strength, energy, accuracy, or speed of performing the activity over time. In the case of cognitive tasks, the indicators of fatigue include the reduction of reaction time and accuracy during task performance (73).

The frequently comorbid depression in MS patients affects the occurrence of cognitive fatigue. The factor connecting both fatigue and depression is attention deficit (74, 75). Brenner and Piehl showed in their studies that depressive patients presented more severe symptoms of fatigue, which suggests that the onset of depression may be a predictor of fatigue and anxiety, and the onset of fatigue and anxiety may be a predictor of depression (76).

According to Penner et al. and Griffith and Zarrouf for depression is a typical depressed mood, hopelessness, loss of self-confidence and self-esteem, causeless self-reproaches or appropriate feelings of guilt, best functionality in the evening, patients usually attribute their illness to psychological factors (35), there is need for excessive sleep (hypersomnia) or early awakening (77). On the other hand for fatigue is typical hopeful and strong wish to recover, best functioning in the morning with a decrease during the day, patients take initiative while searching for treatment (35) and attribute reasons of fatigue for external factors, they may have difficulties to fall asleep and to maintain sleep resulting in decreased sleep quality (77).

In the differential diagnosis of fatigue and depression also should be performed laboratory testing for hematologic and metabolic conditions, such as thyroid studies, iron, 25-hydroxy vitamin D and vitamin B12 deficiency, ferritin, and folate levels (22).

## THERAPEUTIC APPROACH TO FATIGUE AND DEPRESSION IN PEOPLE WITH MS

Up to date, there is not enough evidence supporting the use of any medications for the treatment of MS-related fatigue (78). In clinical practice for fatigue treatment in people with MS are used amantadine, modafinil, and amphetamine-like stimulants (methylphenidate) (78). Amantadine is approved by the Food and Drug Administration (FDA) for treatment of influenza and Parkinson's disease and causes an increase in cholinergic and dopaminergic transmission. Modafinil is approved by the FDA for narcolepsy, shift-work sleep disorder, and obstructive



sleep apnea with residual excessive sleepiness. Amantadine and modafinil have been tested in clinical trials for fatigue in people with MS, but their results have been conflicting (79, 80). Recently, Nourbakhsh et al. in a randomized, double-blind trial compared the efficacy, safety, and tolerability of amantadine, modafinil, methylphenidate, and placebo in people with MS-related fatigue. The results of its study have shown no the superiority of these drugs according to placebo in improving MS-related fatigue, which might have been influenced by comorbid depression and other diseases, MS subtype, the severity of the physical disability, or use of DMTs. However, in *post-hoc* analysis modafinil and methylphenidate might have a marginal, but clinically significant effect on fatigue in patients with excessive daytime sleepiness, which suggests that excessive daytime sleepiness may lead to fatigue in some people with MS (78).

In the treatment of fatigue and depression in people with MS are also used drugs enhancing monoamine neurotransmissions, such as selective serotonin and noradrenaline reuptake inhibitors and psychostimulants with dopaminergic effects (2, 19). Tricyclic antidepressants are effective in reducing clinical depression and improving sleep patterns and are reported beneficial for patients with chronic fatigue.

Recent studies show that non-pharmacological interventions, such as physical exercises and psychological therapy may reduce MS-related fatigue or depression more effectively than pharmacological medications (81, 82). Non-pharmacologic treatment of fatigue or depression includes cognitive-behavioral therapy (CBT), relaxation therapy, physical exercises and rehabilitation, resistance training, mindfulness, yoga, and tai chi, optimal diet, and appropriate sleep hygiene (81, 83, 84). CBT changes the dysfunctional and emphasizes more realistic cognitions, behaviors, and emotions that are responsible for fatigue or depression (82). Recent reports show that CBT has a positive effect on MS-related fatigue, however, this effect decreases with cessation of treatment (85).

The very important strategy in MS-related fatigue and/or depression management is self-management education (SME) (8, 86). This is a complex intervention combining the provision of information and behavior change techniques, to influence the way patients experience the disease (8). SME teaches patients how to cope with a disease's symptoms and enables helpful behaviors, habits, and routines. SME in people with MS reduces fatigue and improves QoL (8). According to Lorig and Holman, SME solves medical, emotional, and role management problems, helps make decisions, and taking action, resources utilization, forms a patient/health care provider partnership (86). The medical management of fatigue is based on symptoms reduction and treatment. Emotional management influences thoughts, beliefs, and behaviors related to cognitive fatigue and is approached by CBT and relaxation exercises. The coping with daily tasks and

duties is provided by occupational therapy (OT), which teaches conservation and management strategies, e.g., daily activity schedules, occupational balance or workload, and environment adaptation (8).

## CONCLUSIONS

The prevalence of fatigue and depression in people with MS is very high. Fatigue and depression in people with MS have multifactorial etiology, such as inflammatory and neurodegenerative processes, oxidative/nitrosative stress, leading to axonal damage, and demyelination, as well as brain atrophy of prefrontal, frontal, parietotemporal regions, thalamus, and basal ganglia. The inflammatory etiology of fatigue and depression in MS was supported by evidence of increased serum and CSF concentration of inflammatory mediators such as TNF, interleukins (IL-1a, IL-1b, IL-6), IFN $\gamma$ , and neopterin. The secondary fatigue and secondary depression in people with MS may be caused by emotional factors, sleep disorders, pain, the coexistence of other diseases and, the use of some medication. There is not enough evidence supporting the use of any medications for the treatment of MS-related fatigue. In the treatment of depression and fatigue in people with MS are frequently used drugs enhancing monoamine neurotransmission and non-pharmacologic methods, such as CBT, relaxation therapy, OT, and physical rehabilitation. Recently, progress has been made in evaluating CBT or OT, but evaluation of the patient's education, which teaches self-management skills, helps to cope with disease-related fatigue, and leads to improvement of QoL, is lacking. The interventions, such as self-management education are difficult to evaluate, because of many possible outcome dimensions, instruments, and measurement time-points.

Therefore, there is needed for further researches on neuroimmune interactions, inflammatory biomarkers, the HPA-axis, and neurotransmitters in the pathogenesis of fatigue and depression in people with MS. There is also a high need for the development of new assessment tools for fatigue diagnostics and its differentiation with depression, the assessment of pharmacological and non-pharmacological treatment effectiveness, and the influence of DMTs on the development and course of MS-related fatigue and depression.

## AUTHOR CONTRIBUTIONS

JT and AK contributed to conception and design of the manuscript and wrote the first draft of the manuscript. JT, AK, KK-T, AC, MC, and JK wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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