

REVIEW

Emotional disorders associated to multiple sclerosis and psychological interventions: a literature review

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Multiple sclerosis is an unpredictable neurologic disease affecting 2.8 million people worldwide. Individuals with MS experience multiple physical and psychological symptoms such as depression, anxiety, fatigue, and pain that impact their general functioning and quality of life. The aim of this review is to highlight the importance of psychological interventions in reducing depression and anxiety symptoms associated with the diagnosis of multiple sclerosis. Cognitive and behavioral techniques are also useful in relieving the specific symptoms of multiple sclerosis. However, few studies have captured the psychological processes involved in reducing the symptoms of depression and anxiety, which is why greater concern is recommended in future studies in order to develop better psychological interventions tailored for patients with multiple sclerosis.

Keywords: multiple sclerosis, depression, anxiety, cognitive behavioral therapy

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Background

Multiple sclerosis (MS) is a neurological disorder consisting in the inflammation and demyelination of the central nervous system (CNS) that affects the young adult population being also one cause of disability at this age [1], and requiring long-term adherence to disease-modifying therapies (DMT) and other medical procedures. A total of 2.8 million people is estimated to live with MS worldwide [2]. The clinical manifestations of MS include motor deficits, ataxia, blurred vision, sensitive and sphincter disorders, pain [3], gait changes, spasticity, and cognitive dysfunction [4] that have a major impact on quality of life even in the early stages. Although the causes of MS are not clearly known, it is considered that genetic and certain environmental factors have an impact on CNS demyelination. [5,6]. There are multiple types of MS: Clinically isolated syndrome (CIS), Relapsing-remitting multiple sclerosis (RRMS), Secondary progressive multiple sclerosis (SPMS) and Primary progressive multiple sclerosis (PPMS). CIS is an episode of neurological symptoms which lasts for at least than 24 hours, without meeting the criteria for MS. RRMS is manifested by the appearance of attacks accompanied by existing and or new neurological symptoms followed by a period of remission. Worldwide, 85% of people with MS are initially diagnosed with RRMS [7]. Most of the RRMS patients will develop the SPMS type which is characterised by symptoms worsening and a slowly increase in disability. PPMS is the progressive form of the disease that occurs since the illness onset and only 10% of patients manifest this type of MS [7].

At this time, the treatment of choice in MS is one that slows down the evolution of the disease and alleviates its

symptoms. It is addressed in the first phase of acute attack management, corticosteroid therapy being the main treatment. The efficiency of high-dosage of corticosteroid (CS), like oral or intravenous methylprednisolone, in treating relapses has been attested by several studies [8,9]. Another treatment category targets the underlying disease. In this case three types of treatment have been approved. The first is represented by injectable DMT, immunomodulatory therapies among which Beta-interferons and glatiramer acetate, which have been shown to be safe and effective in treating relapses at various stages of MS [10]. Oral disease-modifying therapies, the second type of treatment, are an alternative to injectable DMT that appears to be more tolerable and to have higher efficacy: dimethylfumarate, diroximelfumarate, monomethylfumarate, teriflunomide, fingolimod, siponimod, ozanimod, and cladribine [11]. Natalizumab, ocrelizumab, ofatumumab and alemtuzumab are monoclonal antibodies also used in the treatment of MS. Their therapeutic efficacy has been demonstrated in multiple randomized clinical trials [12, 13, 14, 15]. The third line of treatment, which includes: mitoxantrone and autologous haematopoietic stem cell transplantation (AHST) are recommended in aggressive cases of MS [16, 17]. Unfortunately, these treatments involve a wide range of long-term side effects leading to a decrease in adherence to the therapeutic process: infections, headache, diarrhoea, nausea, bradycardia, upper respiratory tract infections, lymphocytopenia, gastrointestinal tract disorders, hepatotoxicity, leukopenia, autoimmunity, menstrual change, mouth sores, flu-like syndrome [10].

Given the multitude and the diversity of symptoms associated with this condition, and all the side effects of an intrusive treatment, it is expected that patients have a much lower quality of life, psychosocial impairments,

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especially since MS is unpredictable in evolution and has no curative treatment.

The purpose of the review is to highlight the increased prevalence of emotional disorders associated with the diagnosis of MS, disorders that could accelerate the disease progression and to present the importance of psychological interventions as a treatment in patient with MS.

Material and Method

This review included studies investigating the comorbidity between MS and emotional disorders (depression, anxiety) in adult population. In this regard research on the prevalence of depression and anxiety as well as the effectiveness of Cognitive Behavioral Therapy (CBT) on treating MS patients with affective disorders were selected. Articles published in PubMed, Scopus, Web of Science, ScienceDirect, were identified using following terms: “depression in multiple sclerosis”, “anxiety in multiple sclerosis”, “CBT and multiple sclerosis”.

Literature review section

Emotional disorders associated to multiple sclerosis

Emotional disorders, which include depression and anxiety disorders, are characterized by the experience of frequent and intense negative emotions to which individuals manifest an aversive reaction and a low perception of control engaging in efforts to escape or avoid the emotional experience that is negatively appraised. Emotional disorders are always associated with chronic and significant distress and functional impairment [18].

Emotional disorders occur at much higher rates in patient with MS than in the general population [19,20,21]. Depression is the most present and impactful mental health condition among the psychiatric comorbidities that can occur throughout the course of MS, although there is a reported higher risk of depression in the first years after the diagnosis [22]. According to Boeschoten and colleagues, the lifetime prevalence of clinically significant symptoms of depression in patients with MS is 31% while 21% of patients may suffer from Major Depressive Episode (MDE). In the same systematic review and meta-analysis, the authors identified that the prevalence of a current MDE is much higher (17%) in MS compared with the general population (6%) [21].

The incidence of depression is caused by both neurobiological and psychological factors. There are studies indicating that atrophy of the cortical areas of the brain due to the destruction of white matter may be related to depression symptoms [23, 24, 25]. Also, the progressive decrease of the grey matter could be responsible for the aggravation of depressive symptoms [26]. Although early studies have shown that there is a correlation between treatment with INFβ-1a, INFβ-1b, and occurrence of depression [27,28] early studies, like the SPECTRIMS and COGIMUS trials, suggest no evidence that the DMT increases the risk for

depressive disorders [29, 30, 31]. The biological implications of MDE are supported by monoaminergic and glutamatergic theories. Low levels in serotonin, norepinephrine and dopamine are linked to MDE [32], and interruptions of glutamate absorption from the synapse, related to low sensitivity as a reward, may increase the risk of MDE [33].

Psychosocial factors for depression include younger age, lower education, marital status, employment status [34] disease duration [35], and perceived limited social support [36], poor quality of relationships, high stress, cognitive distortions involving negative automatic thoughts as a maladaptive cognitive component [37] and elevated levels of fatigue when compared to healthy individuals [38]. Also, the discrepancy between the ideal Self (life before MS) and real Self (life after the onset of the disease) can contribute to the apparition of MDE. The discrepancy could be explained by the patient's belief that all his needs, goals, aspirations and the expectations that others have from him won't be accomplished because of his disability caused by the MS diagnosis.

The consequences associated with depression in MS include worsening of MS symptoms. Depressive symptoms are related to higher fatigue, disability, and cognition lower employment and speed of processing [39], have an influence on one's management and perceived self-efficacy over their disease [40], alcohol and other substance use [41], reduced adherence to treatment, increased suicidal ideations and attempts [35], and decreased quality of life. Studies found a strong association between depression and the severity of MS as indicated by Expanded Disability Status Scale (EDSS) [34,35].

Fatigue is one of the most common symptoms of MS which could affect up to 75–90% of MS patients [42, 43, 44] and one of the main contributors to activity limitations and participation restrictions. The relationship between depression and fatigue has been captured by several recent studies. One of these is the study conducted by Greeke et al. [45] that emphasizes the correlation between depression and fatigue in people with MS. Specifically, they noticed that people without depression but with high fatigue scores are prone to elevated depression scores in the future and vice versa [45].

Anxiety symptoms were less studied, one of the reasons why anxiety remains underdiagnosed in patients with MS is due to the overlapping somatic symptoms [46]. However, anxiety has a prevalence of 22% in patients with MS [21]. According to Korostil and Feinstein, the most frequent anxiety disorders encountered in patients with MS are Generalized Anxiety Disorder (18.6%) and Panic Disorder (10%) [47]. During the illness, anxiety has been linked to lower educational levels [46] and relapsing-remitting (RR) disease course [20]. Anxiety is more strongly related to the patients' attitudes towards the unpredictability of MS, and to the assessment of their personal resources to face the uncertain future, and less with the evolution of disability. Nevertheless, anxiety has often been linked to depressive

symptoms and cognitive and social factors [20,48]. Higher anxiety symptoms were related to lower physical disability and remaining employed, lower acceptance and adaptation to their disability status, as well as worrying about the negative impact of MS [39]. Therefore an anxiety can reduce the quality of life, negatively influence treatment compliance and exacerbate MS symptoms.

Suicidal ideation in MS patients is 2.3 to 14 times higher than in the general population and estimated rates of suicide vary from 1.8% to 15.1% of all the deaths and the relative suicide risk is higher in the first 5 years after diagnosis, with 50% of all suicides occurring in that interval [49]. The strongest predictors of suicide attempts in patients with MS are depression, illness severity, a high number of recurrences, a longer duration of illness, a low level of education [50], social isolation and alcohol abuse [51], being unmarried [49]. Also, depressive symptoms were found to mediate the relationship between perceived disability and suicide ideation [52]. Conforming to Shen and colleagues, in a meta-analysis, the risk of suicide was higher at MS diagnosis (SRR 2.12) than at symptom onset (SRR 1.69), and that suicide risk is higher in women with MS than men (SRR 1.74 vs. 1.54) [53].

Emotional disorders in MS can influence the patient response to DMT and therapies, the increased relapses and suicide attempts, the intensification of the secondary symptoms of the disease and also the social and functional impairment. Consequently, the quality of life of the patients decreases. Recognizing and treating these emotional disorders with individualised and combined pharmacological and psychotherapeutic interventions is important for the conditions of people with MS [54].

Psychological interventions

In addition to the drug therapy recommended and extremely efficient in the treatment of depression and anxiety disorders in patients with MS [55], the effectiveness of Cognitive-Behavioral Therapies (CBT) is based on a large body of data that qualify it as one of the recommended psychological interventions for these patients. Psychological interventions represent an alternative to psychopharmacological treatment, given that certain antidepressants are not well tolerated by MS patients [56]. Among these drugs, desipramine can exacerbate urinary retention, cognitive changes, and fatigue [57, 58, 59], while paroxetine (an SSRI) can cause nausea, headache, and dry mouth.

CBT is a problem-focused psychological intervention developed to help individuals overcome emotional problems by using cognitive strategies which helped them identify, challenge and manage unhelpful thoughts and behavior techniques like progressive muscle relaxation, controlled breathing exercises, behavior activation, problem solving skills.

The effectiveness of CBT protocols for depression was highlighted in a meta-analysis conducted by Cjiupers et al. which included 115 randomized clinical trials to compare

CBT intervention with different types of control groups, pharmacological therapies and other forms of psychotherapy [60]. CBT turned out to be superior to all control groups and more effective than other psychotherapies. Also, CBT in combination with pharmacological treatment is more efficient than pharmacological therapy alone in patients diagnosed with depression [60].

CBT constitutes the psychological intervention with the strongest empirical/scientific support and the highest number of publications in the field of chronic pathologies. This finding is confirmed by Fiest et al. in their systematic review and meta-analysis of 13 clinical trials which tested the effectiveness of psychological and pharmacological interventions in treating depression and anxiety in patients with MS, eight of these studies utilising cognitive behavioral therapies. Their results proved that psychological interventions may have a moderate effect in reducing depressive symptoms in these patients [56].

In a recent pilot trial conducted on 60 patients newly diagnosed with MS, Kiropoulos and colleagues [61] showed that an adapted CBT intervention, based on Beck's protocol for depression [62], compared with a supportive listening intervention, is more effective in reducing depressive and anxiety symptoms significantly and provides an increase in the quality of life, reducing fatigue, pain and sleep disturbances [61].

Ghielen and colleagues [63] investigated the effectiveness of CBT and Mindfulness-Based Therapies to treat emotional disorders in patients with progressive neurological disorders by conducting two main meta-analyses of 19 randomized controlled trials, and identified that both therapies have positive effect on reducing depression and anxiety symptoms in patients with Parkinson disease and MS [63].

Lately, researchers have begun to address more and more concerns for delivering CBT for MS using a computerized format. Online CBT may represent an alternative for MS patients because it is more accessible and reduces travel expenses [64, 65]. On the other hand, online psychological interventions may reduce the social interactions of patients, failing to meet their need to improve social support [66]. In addition, there could also be some limitations regarding the online interventions accessibility due to some MS symptoms [65].

CBT also helps patients with MS who have anxiety disorders to identify and restructure their worrying thoughts about the disease and its unpredictability, which can lead to the maintenance and worsening of anxiety symptoms. [67]. Also, there is a large number of studies that proved the efficacy of CBT in reducing fatigue, one of the most reported symptoms by MS patients [68, 69] pain [70], sleep quality [71] and increasing the quality of life [72].

Most studies have focused on CBT in depression in patients with MS, and less on CBT treatment of anxiety disorders. In this regard there is one trial that examined an intervention to reduce anxiety for self-injection [73].

Moreover, the vast majority of the studies have shown the effectiveness of CBT in depression associated with MS without investigating the psychological processes that could explain changes in depression and anxiety symptoms. According to Güner et al., MS patient group from their study had significantly higher depression and anxiety scores in contrast to healthy controls, as well as higher scores at the Automatic Thoughts Questionnaire (ATQ) [37]. These results emphasise the importance of exploring these psychological constructs as cognitive mechanisms involved in emotional disorders for the development of more efficient psychological therapies.

Early provision of psychological treatments may increase psychological flexibility, may influence the progression of MS disease by increasing adherence to treatment and at the same time leading to better social and functional outcomes [74].

According to the new paradigm in the CBT the transdiagnostic approaches is focus more on the process than on the content, in the treatment of different psychopathology spectrum. Therefore, the process involved in the therapeutic relations with the patients but also the mediation between different processes like: low frustration tolerance, catastrophizations, cognitive distortions, etc, can represent the core of the CBT intervention, situations in which a lot of comorbidities may occur [75].

For example, a number of studies certified CBT/Rational Emotive Behavioural Therapy (REBT) interventions as effective for improving emotional functioning in individuals by reducing/decreasing irrational beliefs. According to REBT [76, 77], when individuals encounter stressful situations, they can have irrational beliefs about these activating events which trigger the experience of dysfunctional negative emotions and the engagement in maladaptive behaviors. The improvement of emotional functioning has consistent effects and persistent changes in diverse psychological outcomes [78], but was also effective in changing personality traits by increasing emotional stability [79]. This is particularly relevant for MS patients, since this condition may lead to neuropsychiatric symptoms and personality changes [78, 80].

Conclusions

The literature offers a significant body of studies that sows the effectiveness of individual or group, face-to-face or telephone / online CBT interventions in reducing depression associated with multiple sclerosis, but there are few data for the psychological processes involved in reducing depression and anxiety symptoms, which are less studied, in patients with MS. Therefore, an intervention to address these psychological processes in depression and anxiety symptoms, better tailored to the needs of patients with MS is highly recommended. As far as we know, integrative and multimodal cognitive behavioral therapy in patients with chronic diseases can contribute to the alleviation of emotional disorders associated with multiple sclerosis, re-

sulting in an increase in emotional stability and quality of life.

Considering the amplitude of the clinical manifestations of multiple sclerosis as well as the prevalence of depressive and anxiety disorders, early psychological intervention is highly recommended. Untreated, emotional disorders can represent a factor of maintenance and aggravation, will impact the course of the disease in the ways that contribute to higher suicide rates, treatment non-adherence and the relapses.

Authors' contribution

AS: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing

COP: Conceptualization, Supervision, Writing - original draft, Writing - review & editing

CC: Investigation, Resources, Visualization, Writing - original draft, Writing - review & editing

Conflict of interest

None to declare.

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