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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 chronical 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, Kiropoulus 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 it's unpredictability, which can lead to the maintenance and worsening of anxiety symptoms. [67]. Also, there is a large number of studies that proved the efficacity 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, resulting 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.

References

1. Reich DS, Lucchinetti CF Calabresi PA,2018. Multiple Sclerosis. N. Engl. J. Med 2018; 378: 169–180.
2. Walton C, King R, Rechtman L et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler 2020;26(14):1816-1821.
3. Maier S, Bălaşa R, Buruian M, Maier A, Bajko Z. Depression in multiple sclerosis – Review. Romanian Journal of Neurology/ Revista Romana de Neurologie 2015; XIV: 22-29.
4. Cerqueira AC, Andrade PS, Godoy-Barreiros JM, Silva ACO, Nardi AE. Risk factors for suicide in multiple sclerosis: a case-control study. J Bras Psiquiatr 2015;64(4):303-6.
5. Abreu P, Mendonça MT, Guimaraes J, Sa MJ. Esclerose múltipla: epidemiologia, fisiopatologia e diagnostico diferencial. Sinapse 2012;12(2):5e14.
6. Hatch MN, Schaumburg CS, Lane TE, Keirstead HS. Endogenous remyelination is induced by transplant rejection in a viral model of multiple sclerosis. J Neuroimmunol 2009;212(1):74e81.
7. Atlas of MS, 3rd Edition. The Multiple Sclerosis International Federation (MSIF), London, September 2020. Available at https://www.msif.org/wp-content/uploads/2020/10/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf Accessed October 2, 2021.
8. Smets I, Van Deun L, Bohyn C et al. Belgian Study Group for Multiple Sclerosis. Corticosteroids in the management of acute multiple sclerosis exacerbations. Acta Neurol Belg 2017;117(3):623-633.
9. Horta-Hernández AM, Esaclera-Izquierdo B, Yusta-Izquierdo A et al. High-dose oral methylprednisolone for the treatment of multiple sclerosis relapses: cost-minimisation analysis and patient's satisfaction. Eur J Hosp Pharm 2019;26(5):280-284.
10. Callegari I, Derfuss T, Galli E. Update on treatment in multiple sclerosis. Presse Med. 2021;50(2):104068. doi: 10.1016/j.lpm.2021.104068.
11. Derfuss T, Mehling M, Papadopoulou A, Bar-Or A, Cohen JA, Kappos L. Advances in oral immunomodulating therapies in relapsing multiple sclerosis. Lancet Neurol 2020;19:336–47.
12. van Pesch V, Sindic CJ, Ferna´ndez O. Effectiveness and safety of natalizumab in real-world clinical practice: review of observational studies. Clin Neurol Neurosurg 2016;149:55–63.
13. Butzkueven H, Kappos L, Wiendl H, et al. Tysabri Observational Program (TOP) Investigators. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J Neurol Neurosurg Psychiatry 2020 ;91(6):660-668.
14. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209–20.
15. Baker D, Herrod SS, Alvarez-Gonzalez C, Giovannoni G, Schmierer K. Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials

of alemtuzumab. JAMA Neurol 2017;74:961–9.
16. Fabis-Pedrini MJ, Carroll WM, Kermode AG. Efficacy and safety of mitoxantrone use in aggressive multiple sclerosis (P3.414). Neurology 2018;90(15):P3.414.
17. Cohen JA, Baldassari LE, Atkins HL, et al. Autologous hematopoietic cell transplantation for treatment-refractory relapsing multiple sclerosis: position statement from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2019;25:845–54.
18. Bullis JR, Boettcher H, Sauer-Zavala S, Farchione TJ, Barlow DH. What is an emotional disorder? A transdiagnostic mechanistic definition with implications for assessment, treatment, and prevention. Clin Psychol Sci Pract. 2019;26:e12278.
19. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol 2014;10(9):507-517.
20. Butler E, Matcham F, Chalder T. A systematic review of anxiety amongst people with multiple sclerosis. Mult. Scler. Relat. Disord 2016;10 :145–168.
21. Boeschoten RE, Braamse AMJ, Beekman ATF, et al. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci 2017;372:331-341.
22. Possa MF, Minacapelli E, Canale S, Comi G, Martinelli V, Falautano M. The first year after diagnosis: psychological impact on people with multiple sclerosis. Psychol Health Med 2017;22:1063-1071.
23. Pujol J, Bello J, Deus J, Martí-Vilalta JL, Capdevila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. Neurology 1997;49:1105-1110.
24. Bakshi R, Czarnecki D, Shaikh ZA, et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. Neuroreport 2000;11:1153-1158.
25. Gobbi C, Rocca MA, Riccitelli G, et al. Influence of the topography of brain damage on depression and fatigue in patients with multiple sclerosis. Mult Scler 2014;20:192- 201.
26. Stuke H, Hanken K, Hirsch J, et al. Cross-sectional and longitudinal relationships between depressive symptoms and brain atrophy in MS patients. Front Hum Neurosci 2016;10:622.
27. Minden SL, Feinstein A, Kalb RC, et al. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82:174-181.
28. Brenner P, Piehl F. Fatigue and depression in multiple sclerosis: pharmacological and non-pharmacological interventions. Acta Neurol Scand 2016;134:47-54.
29. Patten SB, Metz LM. Interferon beta1a and depression in secondary progressive MS: data from the SPECTRIMS Trial. Neurology 2002;59:744-746.
30. Patti F, Amato MP, Trojano M, et al. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study. Mult Scler 2011;17:991-1001.
31. Zephir H, De Seze J, Stojkovic T, et al. Multiple sclerosis and depression: influence of interferon beta therapy. Mult Scler 2003;9(3):284-288.
32. Drago A, Crisafulli C, Sidoti A, Serretti A. The molecular interaction between the glutamatergic, noradrenergic, dopaminergic and serotoninergic systems informs a detailed genetic perspective on depressive phenotypes. Prog Neurobiol. 2011;94:418-60.
33. Bechtholt-Gompf AJ, Walther HV, Adams MA, Carlezon WA, Öngür D, Cohen BM. Blockade of astrocytic glutamate uptake in rats induces signs of anhedonia and impaired spatial memory. Neuropsychopharmacology. 2010;35:2049–2059. doi: 10.1038/npp.2010.74.
34. Maier S, Buruian M, Maier A, et al. The determinants of depression in a Romanian cohort of multiple sclerosis patients. Acta Neurol Belg 2016;116:135–143.
35. Tauil CB, Grippe TC, Dias RM, et al. Suicidal ideation, anxiety, and depression in patients with multiple sclerosis. Arq Neuropsiquiatr 2018;76(5):296-301.
36. McGuigan C, Hutchinson M. Unrecognised symptoms of depression in a community– based population with multiple sclerosis. J. Neurol 2006; 253 (2): 219–223.
37. Güner MC, Yazarb MS, Meterelliyozb KS. Cognitive predictors of depression and anxiety in individuals with newly diagnosed Multiple Sclerosis. Eur. J. Psychiat 2020;34(4):202-210.
38. Coughlin SS, Sher L. Suicidal behavior and neurological illnesses. J Depress Anxiety 2013; 9(1):12443.
39. Gill S, Santo J, Ph.D., Blair M, Morro SA. Depressive Symptoms Are Associated With MoreNegative Functional Outcomes Than Anxiety Symptoms in Persons With Multiple Sclerosis. J Neuropsychiatry Clin Neurosci 2019; 31:37–42.
40. Hanna M, Strober LB. Anxiety and depression in Multiple Sclerosis (MS): Antecedents, consequences, and differential impact on well-being and quality of life. Mult Scler Relat Disord 2020;44:102261.
41. Suh Y, Motl RW and Mohr DC. Physical activity, disability, and mood in the early stage of multiple sclerosis. Disabil Health J 2010; 3(2): 93–98.
42. Ayache SS, Chalah MA. Fatigue in multiple sclerosis – insights into evaluation and management? Neurophysiol Clin 2017;2017 (47):139–71.
43. Ayache SS, Chalah MA, Kümpfel T, Padberg F, Lefaucheur JP, Palm U. Multiple sclerosis fatigue, its neural correlates, and its modulation with tDCS. Fortschr Neurol Psychiatr 2017;85:260–9.
44. Herring TE, Alschuler KN, Knowles LM, et al. Differences in correlates of fatigue between relapsing and progressive forms of multiple sclerosis, Mult Scler Relat Disord 54:103109.
45. Greeke EE, Chua AS, Healy BC, Rintell DJ, Chitnis T, Glanz BI. Depression and fatigue in patients with multiple sclerosis. J Neurol Sci. 2017 Sep 15;380:236-241.
46. Poddaa J, Ponzioa M, Uccellia MM, et al. Predictors of clinically significant anxiety in people with multiple sclerosis: A one-year follow-up study. Mult Scler Relat Disord 2020;45:102417.
47. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler 2007;13:67-72.
48. Wallis O, Bol Y, Köhler S, van Heugten C. Anxiety in multiple sclerosis is related to depressive symptoms and cognitive complaints. Acta Neurol Scand 2020;141(3):212-218.
49. Brenner P, Burkill S, Jokinen J, Hillert J, Bahmanyar S, Montgomery S. Multiple sclerosis and risk of attempted and completed suicide-a cohort study. Eur J Neurol. 2016 Aug;23(8):1329-36. doi: 10.1111/ene.13029.
50. Romaniuc A, Bălaşa R, Ştirbu N, et al. The Main Determinants for Suicidal Ideation in a Romanian Cohort of Multiple Sclerosis Patients. Behav Neurol. 2020;2594702.
51. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology 2002;59:674-678.
52. Lewis VM, Williams K, KoKo C, Woolmore J, Jones C, Powell T. Disability, depression and suicide ideation in people with multiple sclerosis. J Affect Disord 2017;208:662-669.
53. Shen Q, Lu H, Xie D, Wang H, Zhao Q, Xu Y. Association between suicide and multiple sclerosis: An updated meta-analysis. Mult Scler Relat Disord 2019;34:83-90.
54. Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. Psychiatry Investig 2019;16(12):877-888.
55. Stamoula E, Siafis S, Dardalas I, et al. Antidepressants on Multiple Sclerosis: A Review of In Vitro and In Vivo Models. Front Immunol 2021;12:677879.
56. Fiest KM, Walker JR, Bernstein CN, et al. Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis. Mult Scler Relat Disord 2016;18:96–104.
57. Politte LC, Huffman JC, Stern TA. Neuropsychiatric manifestations of multiple sclerosis. Prim Care Companion J Clin Psychiatry 2008;10(4):318-324.
58. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging 2009;4:225-33.
59. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med 2015;175(3):401-7.
60. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry 2013;58(7):376-85.
61. Kiropoulos L, Kilpatrick T, Kalincik T, et al. Comparison of the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression in those newly diagnosed with multiple sclerosis (the ACTION-MS trial): protocol of an assessor-blinded, active comparator, randomised controlled trial. Trials 2020; 21(1):100.
62. Beck AT, Rush AJ, Shaw BE, Emery G. Cognitive therapy of depression. New York: Guilford Press, 1979.
63. Ghielen I, Rutten S, Boeschoten RE, et al. The effects of cognitive behavioral and mindfulness-based therapies on psychological distress in patients with multiple sclerosis, Parkinson's disease and Huntington's disease: Two meta-analyses. J Psychosom Res 2019;122:43-51.
64. Hind D, Cotter J, Thake A, et al. Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis. BMC Psychiatry 2014 ;14:5.
65. Ratajska A, Zurawski J, Healy B, Glanz BI. Computerized Cognitive Behavioral Therapy for Treatment of Depression in Multiple Sclerosis: A

Narrative Review of Current Findings and Future Directions. Int J MS Care 2019;21(3):113-123.
66. Huguet A, Rao S, McGrath PJ, Wozney L, Wheaton M, Conrod J, Rozario S. A Systematic Review of Cognitive Behavioral Therapy and Behavioral Activation Apps for Depression. PLoS One 2016 ;11(5):e0154248.
67. Hayter AL, Salkovskis PM, Silber E, Morris RG. The impact of health anxiety in patients with relapsing remitting multiple sclerosis: Misperception, misattribution and quality of life. Br J Clin Psychol 2016;55(4):371-386.
68. Chalah MA, Ayache SS. Cognitive behavioral therapies and multiple sclerosis fatigue: A review of literature. J Clin Neurosci 2018;52:1-4.
69. van den Akker LE, Beckerman H, Collette EH, et al. TREFAMS-ACE Study Group. Cognitive behavioral therapy positively affects fatigue in patients with multiple sclerosis: Results of a randomized controlled trial. Mult Scler 2017;23(11):1542-1553.
70. Gromisch ES, Kerns RD, Beauvais J. Pain-related illness intrusiveness is associated with lower activity engagement among persons with multiple sclerosis. Mult Scler Relat Disord 2020;38:101882.
71. Abbasi S, Alimohammadi N, Pahlavanzadeh S. Effectiveness of cognitive behavioral therapy on the quality of sleep in women with multiple sclerosis: a randomized controlled trial study. Int J Community Based Nurs Midwifery 2016;4:320–8.
72. Calandri E, Graziano F, Borghi M, Bonino S. Improving the quality of life and psychological well-being of recently diagnosed multiple sclerosis patients: preliminary evaluation of a group-based cognitive behavioral intervention. Disabil Rehabil 2016;1–8.
73. Mohr DC, Cox D, Merluzzi N. Self-Injection Anxiety Training: a treatment for patients unable to self-inject injectable medications. Mult. Scler 2005;11(2):182-185.
74. Topcu G, Griffiths H, Bale C, et al. Psychosocial adjustment to multiple sclerosis diagnosis: A meta-review of systematic reviews. Clin Psychol Rev 2020; 82: 101923,
75. Hofmann SG, Hayes SC. The Future of Intervention Science: Process-Based Therapy. Clin Psychol Sci. 2019;7(1):37-50.
76. David D, Schnur J, Belloiu, A. Another Search for the “Hot” Cognitions: Appraisal, Irrational Beliefs, Attributions, and Their Relation to Emotion. J Ration Emot Cogn Behav Ther 2002; 20(2): 93–131.
77. Ellis A. Changing rational-emotive therapy (RET) to rational emotive behavior therapy (REBT). J Ration Emot Cogn Behav Ther 1995;13(2): 85–89.
78. David D, Cotet C, Matu S, Mogoase C, Stefan S. 50 years of rational emotive and cognitive-behavioral therapy: A systematic review and meta-analysis. J. Clin. Psychol 2018; 74(3): 304–318.
79. Popa CO, Predatu R. The effect of an integrative CBT/REBT intervention in improving emotional functioning and emotional stability in Romanian medical students. J Evid-Base Psychot 2019;19(1):59-72.
80. Maggio MG, Cuzzola MF, Latella D, et al. How personality traits affect functional outcomes in patients with multiple sclerosis: A scoping review on a poorly understood topic. Mult Scler Relat Disord 2020;46.