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Advancements in the diagnosis and treatment of multiple sclerosis in adults over two decades – a literature review

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Abstract

Introduction. Multiple sclerosis is an autoimmune disease of the central nervous system, leading to irreversible disability through inflammatory demyelinating changes due to oxidative stress. Symptoms such as spasticity, muscle weakness, and cognitive impairment typically appear between the ages of 20 and 40, more frequently in women. MS treatment includes corticosteroid therapy for relapses and plasmapheresis in severe cases, as well as disease-modifying therapies and symptomatic treatments. Significant advances in the understanding, diagnosis, and treatment of multiple sclerosis have been made over the past two decades. ***Purpose of the work.*** The aim of this article is to discuss the latest advancements in the diagnosis and treatment of multiple sclerosis, highlighting the benefits of precise diagnostic criteria and modern therapies in improving patients' quality of life. ***Materials and methods.*** This review article was written based on databases: PubMed, Google Scholar, ViaMedica, Embase, and Medline. Research studies and meta-analyses from 2020-2024 were used, applying keywords: multiple sclerosis, treatment, disability, quality of life. ***Results.*** The 2017 McDonald criteria, which utilize magnetic resonance imaging and immunoglobulin G analysis in cerebrospinal fluid, enable faster diagnosis, reducing the risk of disability. Pharmacological treatment includes disease-modifying drugs such as interferon-β-1a, teriflunomide, and dimethyl fumarate, which reduce relapse rates and slow disease progression. Non-pharmacological interventions, including physical rehabilitation and proper diet, also significantly impact the course of the disease and patients' quality of life. These therapies allow for prolonged independence and delay the onset of disability, which translates to an increased average lifespan for patients. ***Discussion.*** Precise diagnostic criteria allow for early disease detection and quicker therapy initiation, preventing axonal demyelination, although treatments can have side effects, such as flu-like symptoms with interferon-β or the risk of leukoencephalopathy with natalizumab. ***Conclusions.*** Accurate diagnostic criteria enable early detection of multiple sclerosis and timely therapy initiation, potentially extending the time to mobility limitations by 20 years and enhancing patients' quality of life.
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Keywords: multiple sclerosis, treatment, disability, quality of life

Introduction

Multiple sclerosis is a multifocal, autoimmune disease of the central nervous system that is characterized by inflammatory demyelinating lesions affecting white and gray matter. The constant accumulation of damage over time leads to irreversible disability that characterizes advanced stages of the disease [1,2]. In experimental models, oxidative stress leads to mitochondrial dysfunction, causing cell membrane damage and ultimately neuronal cell death [3]. Symptoms usually appear between the ages of 20 and 40, with a clear female predominance [4]. Epidemiological estimates indicate that the global population of people affected by multiple sclerosis is approximately 2.8 million (35.9 per 100,000 people) [4]. In the years 2013-2020, an increase in the incidence of multiple sclerosis was observed in all regions of the world (figure 1) [5].

The main complaints of patients include: spasticity, muscle weakness, limb paresis, pain, ataxia, mental disorders, urination disorders and cognitive impairment. Exacerbation of the disease occurs in the form of relapses, which indicate the appearance or worsening of neurological symptoms. The disease flare lasts for at least 24 hours, without concomitant fever or infection [6-8].

There are four main forms of multiple sclerosis [9,10].

Relapsing-remitting form of multiple sclerosis. It affects approximately 85-90% of patients. It is characteri-

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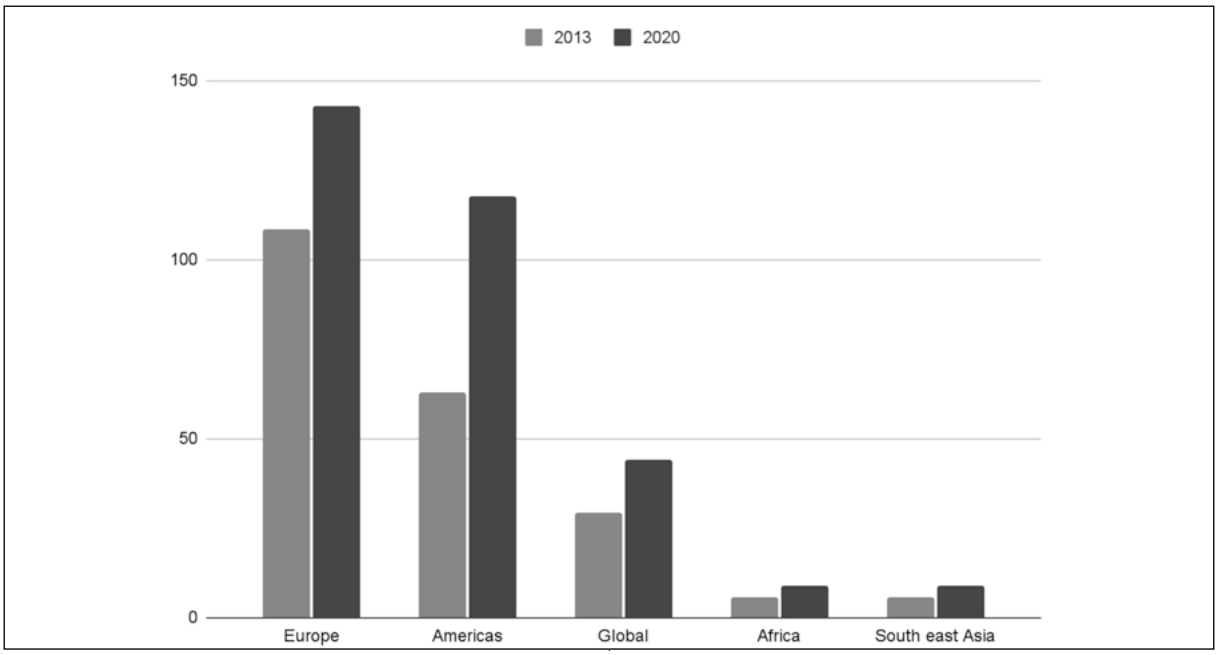

Figure 1. Incidence of multiple sclerosis per 100,000 inhabitants by world regions in 2013 and 2020 [5]

zed by the occurrence of deterioration and improvement, i.e. relapses and remissions, and a state of neurological stability during remission. In this form, variable disease activity occurs [7].

Secondary progressive multiple sclerosis. It is a consequence of the relapsing-remitting form and affects approximately 65% of patients. The main feature is the constant increase in disability [8].

Primary progressive multiple sclerosis. It affects approximately 10% of patients. No remission is observed. From the beginning of the disease, there is a systematic deterioration of the patient's neurological condition [11].

Aggressive form of multiple sclerosis. It occurs in previously untreated patients who have two or more disabling relapses and one or more MRI changes within 12 months [new 1-6].

The treatment of multiple sclerosis is divided into three main categories: relapse treatment, disease-modifying therapies, and symptomatic treatment [12]. In the context of the treatment of acute attacks, glucocorticoids, methylprednisolone and prednisone, are used due to their ability to shorten the duration of relapse [13,14]. If the patient's condition does not improve after treatment with glucocorticosteroids and if the relapses are more severe, plasmapheresis is used, usually five cycles [6,15]. In order to improve the patient's quality of life, disease--modifying therapies are used, which aim to achieve a state in which disease recurrences do not occur, the progression of disability is inhibited, and new pathological changes or atrophy are not visible in images obtained using magnetic resonance imaging [12,16].

Materials and methods

This review article was constructed based on the following databases: Pubmed, Google Scholar, ViaMedica, Embase and Medline. In the process of creating the work, research and meta-analyses conducted in 2020-2024 were used, using the following keywords: multiple sclerosis, treatment, disability, quality of life.

Results

Diagnostics

The current parameters used to diagnose multiple sclerosis are the McDonald criteria, which were formulated in 2001 and updated in 2017. They are mainly based on the analysis of images obtained using magnetic resonance imaging, the occurrence of disease episodes and the detection of immunoglobulin G (IgG) in the cerebrospinal fluid [17,18]. Before these criteria were accepted, diagnosis was based on the 1983 Poser crite-

ria, which required clinical symptoms and analysis of cerebrospinal fluid [19]. In a 2021 study by Tintore et al. on a group of 1,174 patients, it was found that patients diagnosed according to the 2017 McDonald criteria received a faster final diagnosis of multiple sclerosis compared to the Poser criteria. Additionally, patients diagnosed according to the 2017 McDonald criteria had a lower risk of becoming disabled [20].

When the diagnosis of multiple sclerosis is made to a patient who is over 50 years of age, late-onset multiple sclerosis (LOMS) is diagnosed [21,22]. LOMS is diagnosed in 5-10% of all patients diagnosed with multiple sclerosis [21]. In the context of an aging society, the incidence of LOMS is likely to increase [23]. Age may influence the prognosis in multiple sclerosis. Disability usually increases with age, regardless of the duration of the disease [24].

The EDSS scale (Expanded Disability Status Scale) is a tool used to assess the degree of disability in patients suffering from multiple sclerosis, with degrees ranging from 0 to 10 (table I) [25]. The EDSS scale is assessed on the basis of eight functional systems (FS): cerebellum, brain stem, sensation, pyramidal system, bladder and large intestine functions, mental changes, ocular functions and others [25]. The degree of disability is assessed on the basis of this scale [25].

Pharmacological treatment

Interferon-β-1a, which was approved for use in 1993, is the first drug modifying the course and prognosis of multiple sclerosis [26]. In a study conducted in 2010 by Mazdech et al., the effect of interferon β-1a (Avonex) on the progression of multiple sclerosis was analyzed. This study was conducted on a group of 30 patients and lasted 2 years. The initial EDSS result was 4.3 ± 1.61, and after the examination it was 3.01 ± 2.05, which resulted in a 29.76% decrease in EDSS [27]. However, in a study conducted in 2022 by Vermersch et al., which lasted 96 weeks and included a group of 156 patients, it was found that in the case of multiple sclerosis in children, dimethyl fumarate is more effective than Interferon β-1a. For dimethyl fumarate, the relapse-free rate was 66.2%, compared to 52.3% for interferon β-1a [28]. A 2024 study by Nakamura et al. for 2 years showed that the use of natalizumab in people with multiple sclerosis contributes to the alleviation of gray matter atrophy. Compared to the placebo group, a 64.3% reduction in the mean percentage of gray matter volume loss was observed in the 2nd year of treatment [29]. Due to their favorable and known safety profile and long-term effectiveness, interferon-β-1a and teriflunomide are used as first-line treatment for multiple sclerosis [30]. However, natalizumab and fingolimod have been recognized as second-line drugs. They reduce the frequency of relapses by over 50% while increasing the risk of side effects. When deciding to start using a new drug, the potential benefits of its administration for the patient and the possible risk of side effects should be assessed. [6].

Non-pharmacological treatment

Table I. EDSS scale [25]

Degree	Description
0	Normal neurological examination. All grades 0 in FS (Functional System)
1	No disability, minimal symptoms in one FS
2	Minimum disability in one FS
3	Moderate disability in one FS or mild disability in three or four FS
4	Ambulates completely unaided and is self-sufficient for more than 12 hours per day despite severe disability including one grade of FS 4 or a combination of minor grades exceeding the limits of the previous grades. Can walk about 500 meters without assistance or rest
5	Can walk about 200 meters without help or rest. The disability is severe enough to prevent full daily activities involving one FS 5 grade or a combination of minor grades exceeding the limits of the previous grades
6	Intermittent or unilateral permanent assistance (cane, crutch or brace) required to walk 100 meters with or without rest
7	He is unable to walk more than 5 meters even with assistance. He moves mainly in a wheelchair – over 12 hours a day
8	He only uses a wheelchair, but spends most of the day outside it. He can use his upper limbs
9	Helpless patient lying in bed. He can communicate and eat
10	Death from multiple sclerosis

Current research provides evidence that diet and rehabilitation may influence the occurrence, course and quality of life of patients with multiple sclerosis [31,32]. In a 2020 study by Drehmer et al. it was found that patients with multiple sclerosis often follow a low-carbohydrate and high-lipid diet, which is associated with abdominal obesity and a higher BMI. This condition leads to a pro-inflammatory state, increasing the levels of IL-6, TNF-alpha and leptin, i.e. factors associated with the pathogenesis of multiple sclerosis [33]. Physical rehabilitation in multiple sclerosis should be started as soon as possible after the disease is diagnosed or even if its occurrence is suspected. Early involvement in motor rehabilitation may influence the course of the disease in the central nervous system and the development of motor patterns in the future. The physical activity of a patient with MS should be adapted to his or her health condition, taking into account the shorter duration of specific tasks compared to a healthy person [6,34]. Regular physical activity can help maintain fitness and improve patients' quality of life. A meta-analysis by Gooch et al. in 2021 showed that strength training is associated with improved muscle strength and plays a clear role in people with muscle weakness as well as overall fitness [32].

Impact on quality of life

Currently used therapies have a significant impact on the quality of life of patients [35]. Disease-modifying drugs may contribute to prolonging the period until the first clinical event occurs [36]. A reduction in demyelinating processes is observed, which leads to inhibition of the progression of disability [37]. The patient is able to maintain independence. Thanks to the availability of over 25 disease-modifying therapies, the time to the onset of mobility limitations can be delayed by up to 20 years, and the average life expectancy of patients is constantly increasing [38]. Current evidence for the effectiveness of physical activity and strength training focuses on patients with multiple sclerosis who are able to walk [32]. As patients are able to maintain the ability to walk longer, the effectiveness of rehabilitation increases and the number of exercise restrictions decreases [39-41].

Discussion

Current treatments for multiple sclerosis have higher patient success rates than treatments used two decades ago [42]. The increase in the effectiveness of therapy results from more precise diagnostic criteria that allow for early detection of multiple sclerosis, which allows for faster implementation of treatment, which in turn prevents excessive demyelination of axons [43, 44,45]. Elderly patients suffering from MS experience fewer relapses and have a longer life expectancy, which positively affects their quality of life [46]. Unfortunately, multiple sclerosis is associated with an increased risk of developing depression, which in MS patients leads to a reduced quality of life and an increased risk of suicide [47,48].

Despite their benefits, disease-modifying therapies for multiple sclerosis may cause side effects. For example, interferon-β may cause flu-like symptoms, and natalizumab is associated with the risk of developing progressive multifocal leukoencephalopathy [12,49]. Other drugs, such as fingolimod or glatiramer acetate, may increase the risk of exacerbations of liver disease [50]. The final choice of therapy should therefore take into account the potential benefits and risks for the patient, especially in the context of comorbidities and the patient's general health condition [46,49]. Currently, thanks to the wide availability of drugs that modify the course of MS, it is possible to adapt the treatment to the individual needs of the patient so that the therapy is as effective as possible and has minimal side effects [49,51,52]. Additionally, access to subcutaneous and oral therapies facilitates patients' daily functioning [53].

Conclusions

Thanks to clinical trials and pathogenesis analysis, it was possible to formulate the most precise diagnostic criteria for multiple sclerosis. This allows for early detection of the disease and implementation of appropriate therapy aimed at delaying the neurodegeneration process as much as possible. Current research indicates that the time until mobility limitations occur can be extended by 20 years, which increases the rehabilitation possibilities of patients by eliminating restrictions in exercise programs. This has a direct impact on improving the quality of life of patients, especially in older age, where the progression of the disease is more advanced. Nevertheless, further prospective clinical trials are necessary to monitor changes in patients' quality of life and the degree of disease progression over several years.

Conflict of interest
None
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References

1. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015;5(9):e00362. doi: 10.1002/brb3.362.
2. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132(Pt 5):1175-89. doi: 10.1093/brain/awp070.
3. Mao P, Reddy PH. Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta. 2010 Jan;1802(1):66-79. doi: 10.1016/j.bbadis.2009.07.002.
4. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J. 2017;19(1):1-10. doi: 10.22074/cellj.2016.4867.
5. 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. doi: 10.1177/1352458520970841.
6. Losy J, Bartosik-Psujek H, Członkowska Anna, et al. Leczenie stwardnienia rozsianego Zalecenia Polskiego Towarzystwa Neurologicznego. Polski Przegląd Neurologiczny 2016; 12 (2): 80–95.
7. Galea I, Ward-Abel N, Heesen C. Relapse in multiple sclerosis. BMJ. 2015 Apr 14;350:h1765. doi: 10.1136/bmj.h1765.
8. Inojosa H, Proschmann U, Akgün K, et al. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. J Neurol. 2021 Apr;268(4):1210-1221. doi: 10.1007/s00415-019-09489-5.
9. Makhani N, Tremlett H. The multiple sclerosis prodrome. Nat Rev Neurol. 2021 Aug;17(8):515-521. doi: 10.1038/s41582-021-00519-3.
10. Arias M, Dapena D, Arias-Rivas S, et al. Late onset multiple sclerosis. Neurologia. 2011 Jun;26(5):291-6. English, Spanish. doi: 10.1016/j.nrl.2010.09.008.
11. Zimmermann M, Brouwer E, Tice JA, et al. Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. CNS Drugs. 2018 Dec;32(12):1145-1157. doi: 10.1007/s40263-018-0566-9.
12. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clin Med (Lond). 2016;16(Suppl 6):s53-s59. doi: 10.7861/clinmedicine.16-6-s53.
13. Wilf-Yarkoni A, Feldmann K, Rubarth K, et al. Effectiveness of oral prednisone tapering following intravenous methylprednisolone for acute optic neuritis in multiple sclerosis. PLoS One. 2023;18(12):e0288366. doi: 10.1371/journal.pone.0288366.
14. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. Lancet. 2015;386(9997):974-81. doi: 10.1016/S0140-6736(15)61137-0. Jun 28. Erratum in: Lancet. 2016;387(10016):340. doi: 10.1016/S0140-6736(16)00096-9.
15. Blechinger S, Ehler J, Bsteh G, et al. Therapeutic plasma exchange in steroid-refractory multiple sclerosis relapses. A retrospective two-center study. Ther Adv Neurol Disord. 2021;14:1756286420975642. doi: 10.1177/1756286420975642.
16. Amin M, Hersh CM. Updates and advances in multiple sclerosis neurotherapeutics. Neurodegener Dis Manag. 2023;13(1):47-70. doi: 10.2217/nmt-2021-0058.
17. Filippi M, Preziosa P, Arnold DL, et al. Present and future of the diagnostic work-up of multiple sclerosis: the imaging perspective. J Neurol. 2023;270(3):1286-99. doi: 10.1007/s00415-022-11488-y.
18. Jankowska A, Chwojnicki K, Szurowska E. The diagnosis of multiple sclerosis: what has changed in diagnostic criteria? Pol J Radiol. 2023;88:e574-e581. doi: 10.5114/pjr.2023.133677.
19. Fox CM, Bensa S, Bray I, et al. The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. J Neurol Neurosurg Psychiatry. 2004;75(1):56-60.
20. Tintore M, Cobo-Calvo A, Carbonell P, et al. Effect of Changes in MS Diagnostic Criteria Over 25 Years on Time to Treatment and Prognosis in Patients With Clinically Isolated Syndrome. Neurology. 2021;97(17):e1641-e1652. doi: 10.1212/WNL.0000000000012726.
21. Nociti V, Romozzi M, Mirabella M. Challenges in Diagnosis and Therapeutic Strategies in Late-Onset Multiple Sclerosis. J Pers Med. 2024;14(4):400. doi: 10.3390/jpm14040400.
22. Buscarinu MC, Reniè R, Morena E, et al. Late-Onset MS: Disease Course and Safety-Efficacy of DMTS. Front Neurol. 2022;13:829331. doi: 10.3389/fneur.2022.829331.
23. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019;92(10):e1029-e1040. doi: 10.1212/WNL.0000000000007035. Erratum in: Neurology. 2019 Oct 8;93(15):688. doi: 10.1212/WNL.0000000000007915.
24. Scalfari A, Neuhaus A, Daumer M, et al. Age and disability accumulation in multiple sclerosis. Neurology. 2011;77(13):1246-52. doi: 10.1212/WNL.0b013e318230a17d.

25. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. doi: 10.1212/wnl.33.11.1444.
26. Bermel RA, Rudick RA. Interferon-beta treatment for multiple sclerosis. Neurotherapeutics. 2007;4(4):633-46. doi: 10.1016/j.nurt.2007.07.001.
27. Mazdeh M, Afzali S, Jaafari MR. The therapeutic effect of Avonex, Rebif and Betaferon on EDSS and relapse in multiple sclerosis: a comparative study. Acta Med Iran. 2010;48(2):83-8.
28. Vermersch P, Scaramozza M, Levin S, et al. Effect of Dimethyl Fumarate vs Interferon β-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA Netw Open. 2022;5(9):e2230439. doi: 10.1001/jamanetworkopen.2022.30439.
29. Nakamura K, Sun Z, Hara-Cleaver C, et al. Natalizumab reduces loss of gray matter and thalamic volume in patients with relapsing-remitting multiple sclerosis: A post hoc analysis from the randomized, placebo-controlled AFFIRM trial. Mult Scler. 2024;30(6):687-695. doi: 10.1177/13524585241235055.
30. Newsome SD, Mokliatchouk O, Castrillo-Viguera C, et al. Matching-adjusted comparisons demonstrate better clinical outcomes in patients with relapsing multiple sclerosis treated with peginterferon beta-1a than with teriflunomide. Mult Scler Relat Disord. 2020;40:101954. doi: 10.1016/j.msard.2020.101954.
31. Jayasinghe M, Prathiraja O, Kayani AMA, et al. The Role of Diet and Gut Microbiome in Multiple Sclerosis. Cureus. 2022;14(9):e28975. doi: 10.7759/cureus.28975.
32. Gooch H, Hill J, Clegg A. Strength training for people with multiple sclerosis and the current recommendations. Br J Neurosci Nurs. 2021;17(Sup3):S32-S41. doi: 10.12968/bjnn.2021.17.Sup3.S32.
33. Drehmer E, Platero JL, Carrera-Juliá S, et al. The Relation between Eating Habits and Abdominal Fat, Anthropometry, PON1 and IL-6 Levels in Patients with Multiple Sclerosis. Nutrients. 2020;12(3):744. doi: 10.3390/nu12030744.
34. Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. Mult Scler. 2020;26(12):1459-69. doi: 10.1177/1352458520915629.
35. Howard JF Jr, Nowak RJ, Wolfe GI, et al. Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients With Moderate to Severe Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial. JAMA Neurol. 2020;77(5):582-92. doi: 10.1001/jamaneurol.2019.5125.
36. Lebrun-Frénay C, Siva A, Sormani MP, et al. Teriflunomide and Time to Clinical Multiple Sclerosis in Patients With Radiologically Isolated Syndrome: The TERIS Randomized Clinical Trial. JAMA Neurol. 2023;80(10):1080-8. doi: 10.1001/jamaneurol.2023.2815.
37. Hauser SL, Bar-Or A, Weber MS, et al. Association of Higher Ocrelizumab Exposure With Reduced Disability Progression in Multiple Sclerosis. Neurol Neuroimmunol Neuroinflamm. 2023;10(2):e200094. doi: 10.1212/NXI.0000000000200094. Erratum in: Neurol Neuroimmunol Neuroinflamm. 2023 Mar 27;10(3):e200120. doi: 10.1212/NXI.0000000000200120.
38. Bromley LE, Weinstock-Guttman B. Effects of Physical Therapy and Dalfampridine on Function and Quality of Life in Nonambulatory Individuals With Multiple Sclerosis: A Randomized Controlled Trial. Int J MS Care. 2024;26(3):98-103. doi: 10.7224/1537-2073.2023-063.
39. Duan H, Jing Y, Li Y, et al. Rehabilitation treatment of multiple sclerosis. Front Immunol. 2023;14:1168821. doi: 10.3389/fimmu.2023.1168821.
40. Learmonth YC, Motl RW. Exercise Training for Multiple Sclerosis: A Narrative Review of History, Benefits, Safety, Guidelines, and Promotion. Int J Environ Res Public Health. 2021;18(24):13245. doi: 10.3390/ijerph182413245.
41. Corrini C, Gervasoni E, Perini G, et al. Mobility and balance rehabilitation in multiple sclerosis: A systematic review and dose-response meta-analysis. Mult Scler Relat Disord. 2023;69:104424. doi: 10.1016/j.msard.2022.104424.
42. Aykaç S, Eliaçık S. What are the trends in the treatment of multiple sclerosis in recent studies? – A bibliometric analysis with global productivity during 1980-2021. Mult Scler Relat Disord. 2022;68:104185. doi: 10.1016/j.msard.2022.104185.
43. Uher T, Adzima A, Srpova B, et al. Diagnostic delay of multiple sclerosis: prevalence, determinants and consequences. Mult Scler. 2023;29(11-12):1437-51. doi: 10.1177/13524585231197076.
44. Kaisey M, Solomon AJ. Multiple Sclerosis Diagnostic Delay and Misdiagnosis. Neurol Clin. 2024b;42(1):1-13. doi: 10.1016/j.ncl.2023.07.001.
45. Aires A, Barros A, Machado C, et al. Diagnostic Delay of Multiple Sclerosis in a Portuguese Population. Acta Med Port. 2019 Apr 30;32(4):289-294. doi: 10.20344/amp.11187.
46. DiMauro KA, Swetlik C, Cohen JA. Management of multiple sclerosis in older adults: review of current evidence and future perspectives. J Neurol. 2024. doi: 10.1007/s00415-024-12384-3.
47. Kalb R, Feinstein A, Rohrig A, et al. Depression and Suicidality in Multiple Sclerosis: Red Flags, Management Strategies, and Ethical Considerations. Curr Neurol Neurosci Rep. 2019;19(10):77. doi: 10.1007/s11910-019-0992-1.
48. Longinetti E, Frisell T, Englund S, et al. Risk of depression in multiple sclerosis across disease-modifying therapies. Mult Scler. 2022;28(4):632-41. doi: 10.1177/13524585211031128.
49. Langer-Gould A, Moses HH, Murray TJ. Strategies for managing the side effects of treatments for multiple sclerosis. Neurology. 2004;63(11 Suppl 5):S35-41. doi: 10.1212/wnl.63.11_suppl_5.s35.
50. Biolato M, Bianco A, Lucchini M, et al. The Disease-Modifying Therapies of Relapsing-Remitting Multiple Sclerosis and Liver Injury: A Narrative Review. CNS Drugs. 2021;35(8):861-80. doi: 10.1007/s40263-021-00842-9.
51. Rommer PS, Zettl UK. Managing the side effects of multiple sclerosis therapy: pharmacotherapy options for patients. Expert Opin Pharmacother. 2018;19(5):483-98. doi: 10.1080/14656566.2018.1446944.

52. Walther EU, Hohlfeld R. Multiple sclerosis: side effects of interferon beta therapy and their management. Neurology. 1999;53(8):1622-7. doi: 10.1212/wnl.53.8.1622.
53. Gholamzad M, Ebtekar M, Ardestani MS, et al. A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future. Inflamm Res. 2019;68(1):25-38. doi: 10.1007/s00011-018-1185-0.