



BÖLÜM 4

MULTİPL SKLEROZ BESLENME, SEMPTOMATİK VE DESTEK TEDAVİSİ

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GİRİŞ

Multipl Sklerosis veya kısaca MS, öncelikle enflamasyonun hâkim olduğu ar- dından nörodejeneratif süreçlerin baskın hale geldiği santral sinir sisteminin (SSS) progresif, kronik demiyelinizan bir hastalığıdır. Hastalık süreci ön plan- da enflamatuar etkinin baskın olduğu erken süreç ve ardından nörodejeneratif süreçlerin baskın olduğu geç dönem olarak aslında ikiye ayrılabilir; erken dö- nemde enflamasyon tablosuna remiyelinizasyon ile kısmi iyileşmeninde eşlik ettiği görülür (1). MS etiopatogenezinde genetik veimmünolojik altyapı dışında çevresel faktörlerinde belirgin rolü olduğu bilinmektedir (2). MS hastalığının her döneminde çevresel faktörlerin etkisi önemli yer tutar; bunların başında ba-ğırsak flora veya mikrobiyomu ve oluşturdukları metabolitlerin etkisi bulun-maktadır. Henüz bu konuda çalışmalar çok yeni olup, diyet, mikrobiyom ve me- tabolitlerinin MS etiopatogenezinde rolü tam olarak açıklanamamıştır. Bunun yanında mikrobiomda gelişen dengesizliklerin yanı disbiyozisin çoğu hastalığın etiopatogenezinde rol oynadığı gösterilmiş olmak ile birlikte tipik batı diyeti ile disbiyozisin artması ile nöroenflamasyonun tetiklendiği gösterilmiştir (59). MS' te diyetin hastalık başlangıç ve progresyonu üzerine etkisi ile ilgili çalışmalar uzun yillardır devam etmekte olsa da immunomodülatör etkinin Treg hücreler ve IL10-17 sentezi üzerine ve nörodejeneratif prosesin ilerleyişi üstüne etkisi ile ilgili kesin sonuçlara ulaşlamamıştır. D vitamini ve güneşe az maruz kalmak ile MS ilişkisi uzun süredir bilinmektedir .Yine enflamatuar süreçlerin artış göster-diği obezite de özellikle genç erişkinlerde MS gelişimi açısından önemli bir risk

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- Ağrı kontrolü açısından, nöralterapi ve akupunktur
- Yorgunluk yönünden, Sulbutiamine ve CoQ10 desteği
- Bitkisel özler, vitamin/mineraller, Ginseng, selenyum ve vitaminD başta olmak üzere
- Diyetler ve koruyucu/belli besin gruplarından uzak durmak
- Meditasyon, Yoga, Masaj ve gevşeme teknikleri alternatif ve tamamlayıcı tip uygulamaları arasında sayılabilir (98,99).

KAYNAKLAR

1. Ilana Katz , Classification, diagnosis, and differential diagnosis of multiple sclerosis Sand Curr Opin Neurol. 2015 Jun;28(3):193-205. PMID: 25887774
2. A K Hedström 1, Lars Alfredsson, Tomas Olsson, Environmental factors and their interactions with risk genotypes in MS susceptibility Curr Opin Neurol. 2016 Jun;29(3):293-8. PMID: 27035899
3. Cassandra L Munger 1, Lynn I Levin, Bruce W Hollis, Noel S Howard, Alberto Ascherio , Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis JAMA . 2006 Dec 20;296(23):2832-8. PMID: 17179460
4. Anna Karin Hedström 1, Izaura Lima Bomfim, Lisa Barcellos, , Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis Neurology . 2014 Mar 11;82(10):865-72. Epub 2014 Feb 5. PMID: 24500647 PMCID: PMC3959752
5. R L SWANK, O LERSTAD, A STRØM, J BACKER , Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition N Engl J Med. 1952 May 8;246(19):722-8. PMID: 14929306
6. Manuel A Friese 1, Benjamin Schattling 1, Lars Fugger 2, Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis Nat Rev Neurol . 2014 Apr;10(4):225-38. Epub 2014 Mar 18. PMID: 24638138
7. Peizhong Maoa and P. Hemachandra Reddy,a,b, Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta Mol Basis Dis. 2010 Jan; 1802(1): 66–79. Published online 2009 Jul 14. PMCID: PMC2790545
8. Annette Langer-Gould 1, Sonu M Brara, Brandon E Beaber, Corinna Koebnick, Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome Neurology . 2013 Feb 5;80(6):548-52. Epub 2013 Jan 30. PMID: 23365063
9. Bianca Weinstock-Guttman 1, Robert Zivadinov, Naeem Mahfooz, Ellen Carl, Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis J Neuroinflammation . 2011 Oct 4;8:127. PMID: 21970791 PMCID: PMC3228782
10. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and “western-lifestyle” inflammatory diseases. Immunity. 2014 Jun 19;40(6):833-42. doi: 10.1016/j.immu.2014.05.014. PMID: 24950203.

11. Cristina Gutiérrez-Vázquez 1, Francisco J Quintana 2 , Regulation of the Immune Response by the Aryl Hydrocarbon Receptor Immunity . 2018 Jan 16;48(1):19-33. PMID: 29343438
12. Veit Rothhammer 1, Francisco J Quintana 2 Environmental control of autoimmune inflammation in the central nervous system Curr Opin Immunol . 2016 Dec;43:46-53. Epub 2016 Oct 4. PMID: 27710839
13. Kerstin Berer, Lisa Ann Gerdes, Egle Cekanaviciute, et all, Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice Edited by Lawrence Steinman, Stanford University School of Medicine, Stanford, CA, and approved August 7, 2017 (received for review June 30, 2017) September 11, 2017 114 (40) 10719-10724 <https://doi.org/10.1073/pnas.1711233114>
14. Jun Chen 1, Nicholas Chia 2 3, Krishna R Kalari 1, Janet Z Yao 2, Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls Sci Rep . 2016 Jun 27;6:28484. PMID: 27346372 27
15. Stephanie K. Lathrop,^{1,2} Seth M. Bloom,³ Peripheral education of the immune system by colonic commensal microbiota Nature. Nature. 2011 Oct 13; 478(7368): 250–254. Published online 2011 Sep 21. doi: 10.1038/nature10434 PMCID: PMC3192908
16. Shizuo Akira 1, Satoshi Uematsu, Osamu Takeuchi, Pathogen recognition and innate immunity Cell . 2006 Feb 24;124(4):783-801. PMID: 16497588 DOI: 10.1016/j.cell.2006.02.015
17. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011 Feb;11(2):85-97. doi: 10.1038/nri2921. Epub 2011 Jan 21. PMID: 21252989
18. Shawn Winer 1, Geoff Paltser, Yin Chan, Hubert Tsui, Edgar Engleman, Daniel Winer, H-Michael Dosch, Obesity predisposes to Th17 bias Eur J Immunol . 2009 Sep;39(9):2629-35. PMID: 19662632
19. Daniela Cipolletta 1, Dmitriy Kolodkin, Christophe Benoist, Diane Mathis, Tissular T(regs): a unique population of adipose-tissue-resident Foxp3+CD4+ T cells that impacts organismal metabolism Semin Immunol . 2011 Dec;23(6):431-7. Epub 2011 Jul 2. PMID: 21724410
20. Aiden Haghikia 1 et al. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine Immunity. 2015 Oct 20;43(4):817-29. PMID: 26488817
21. Markus Kleinewietfeld 1, Arndt Manzel, Jens Titze, Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells Nature . 2013 Apr 25;496(7446):518-22. PMID: 23467095
22. Liliana Håversen 1, Kristina Norén Danielsson, Linda Fogelstrand, Olov Wiklund, Induction of proinflammatory cytokines by long-chain saturated fatty acids in human macrophages Atherosclerosis. 2009 Feb;202(2):382-93. Epub 2008 May 28. DOI: 10.1016/j.atherosclerosis.2008.05.033
23. Yukihiro Furusawa 1, Yuuki Obata 2, Shinji Fukuda 3, Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells Nature . 2013

▲ Demyelinizan Hastalıklar

- Dec 19;504(7480):446-50. Epub 2013 Nov 13. PMID: 24226770 DOI: 10.1038/nature12721
- 24. Aurélien Trompette, Eva S Gollwitzer, Koshika Yadava, Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis Nature Medicine volume 20, pages159–166 (2014) <https://doi.org/10.1038/nm.3444>
 - 25. Swank RL. Multiple sclerosis: a correlation of its incidence with dietary fat Dept. Neurol.Neurosurg. McGill Univ, Montreal American Journal of Medical Sciences 1950 vol.220 ppt 421-430
 - 26. Swank RL. , James Goodwin Review of MS patient survival on a Swank low saturated fat diet March 2003Nutrition 19(2):161-2 DOI:10.1016/S0899-9007(02)00851-1
 - 27. Kjetil Bjørnevik, M.D., Polyunsaturated fatty acids and the risk of multiple sclerosis Mult Scler. 2017 Dec; 23(14): 1830–1838. Published online 2017 Feb 3. doi: 10.1177/1352458517691150
 - 28. Bianca Weinstock-Guttman 1, Monika Baier, Youngmin Park, Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients, Prostaglandins Leukot Essent Fatty Acids. 2005 Nov;73(5):397-404. PMID: 16099630
 - 29. Yian Gu¹ and Nikolaos Scarmeas^{1,2,3,*} Dietary Patterns in Alzheimer's Disease and Cognitive Aging, Curr Alzheimer Res. Author manuscript; available in PMC 2012 Feb 21. Curr Alzheimer Res. 2011 Aug; 8(5): 510–519. doi: 10.2174/156720511796391836
 - 30. David Goltzman, Michael Mannstadt, Claudio Marcocci, Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis Front Horm Res . 2018;50:1-13. Epub 2018 Mar 29. PMID: 29597231
 - 31. Francesca Sassi 1, Cristina Tamone 2, Patrizia D'Amelio 3 Vitamin D: Nutrient, Hormone, and Immunomodulator , Nutrients. 2018 Nov 3;10(11):1656. PMID: 30400332
 - 32. Matin Khosravi-Largani 1, A review on potential roles of vitamins in incidence, progression, and improvement of multiple sclerosis eNeurologicalSci . 2018 Jan 28;10:37-44. PMID: 29736427
 - 33. Linda Rolf, Illuminating vitamin D effects on B cells – the multiple sclerosis perspective Immunology. 2016 Mar; 147(3): 275–284. Published online 2016 Feb 2. PMCID: PMC4754614
 - 34. Joost Smolders, 1 , 2 , 3 , * Evelyn Peelen, 1 , 2 , 3 Mariëlle Thewissen, 2 Safety and T Cell Modulating Effects of High Dose Vitamin D3 Supplementation in Multiple Sclerosis PLoS One. 2010; 5(12): e15235. Published online 2010 Dec 13. PMCID: PMID: 21179201
 - 35. Munger, K. L., Chitnis, T., Frazier, (2011). Dietary intake of vitamin D during adolescence and risk of multiple sclerosis. Journal of neurology, 258(3), 479–485. <https://doi.org/10.1007/s00415-010-5783-1>
 - 36. Kocer, B., Engur, S., Ak, F., Yilmaz, M. (2009). Serum vitamin B12, folate, and homocysteine levels and their association with clinical and electrophysiological parameters in multiple sclerosis. Journal of clinical neuroscience : official journal of

- the Neurosurgical Society of Australasia, 16(3), 399–403. <https://doi.org/10.1016/j.jocn.2008.05.015>
37. Moghaddasi, M., Mamarabadi, M., Mirzadeh,(2010). Homocysteine, vitamin B12 and folate levels in Iranian patients with ischemic stroke. *Neurological research*, 32(9), 953–956. PMID: 20433777
 38. Najafi, M. R., (2012). Vitamin B(12) Deficiency and Multiple Sclerosis; Is there Any Association? *International journal of preventive medicine*, 3(4), 286–289. PMID: 22624086
 39. Bitarafan, S., Saboor-Yaraghi, A., Sahraian. Impact of Vitamin A Supplementation on Disease Progression in Patients with Multiple Sclerosis. *Arch Iran Med*.2015 Jul;18(7):435-40. PMID: 26161708
 40. Saboor-Yaraghi, A. A., Harirchian, M. H., (2015). The Effect of Vitamin A Supplementation on FoxP3 and TGF- β Gene Expression in Avonex-Treated Multiple Sclerosis Patients. *Journal of molecular neuroscience : MN*, 56(3), 608–612. <https://doi.org/10.1007/s12031-015-0549-y>
 41. Fitzgerald, K. C., Tyry, T., Salter, A., Cofield, S. S., Cutter, G., Fox, R., Marrie, R. A. (2018). Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology*, 90(1), e1–e11. <https://doi.org/10.1212/WNL.0000000000004768>
 42. Xue, Z., Li, D., Yu, W., Zhang, Q., Hou, X., He, Y., Kou, X. (2017). Mechanisms and therapeutic prospects of polyphenols as modulators of the aryl hydrocarbon receptor. *Food function*, 8(4), 1414–1437. <https://doi.org/10.1039/c6fo01810f>
 43. Hashimoto, M., Yamamoto, S., Iwasa, K., Yamashina, K., Ishikawa, M., Maruyama, K., Bosetti,F., Yoshikawa, K. (2017). The flavonoid Baicalein attenuates cuprizone-induced demyelination via suppression of neuroinflammation. *Brain research bulletin*, 135, 47–52. <https://doi.org/10.1016/j.brainresbull.2017.09.007>
 44. Stephen D Skaper 1, Massimo Barbierato 2, Laura Facci 2, Mila Borri 2, Gabriella Contarini 2, Morena Zusso 2, Pietro Giusti 2 Co-Ultramircronized Palmitoylethanolamide/Luteolin Facilitates the Development of Differentiating and Undifferentiated Rat Oligodendrocyte Progenitor Cells Mol Neurobiol . 2018 Jan;55(1):103-114. doi: 10.1007/s12035-017-0722-0. PMID: 28822061 DOI: 10.1007/s12035-017-0722-0
 45. Wu, C., Yosef, N., Thalhamer, T., Zhu, C., Xiao, S., Kishi, Y., Regev, A., Kuchroo, V. K. (2013). Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature*, 496(7446), 513–517. <https://doi.org/10.1038/nature11984>
 46. Kleinewietfeld, M., Manzel, A., Titze, J., Kvakan, H., (2013). Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*, 496(7446), 518-522.
 47. Farez, M. F., Fiol, M. P., Gaitán, M. I., Quintana, F. J., & Correale, J. (2015). Sodium intake is associated with increased disease activity in multiple sclerosis. *Journal of Neurology, Neurosurgery; Psychiatry*, 86(1), 26-31.
 48. Nourbakhsh, B., Graves, J., Casper, T. C., Lulu, S., Waldman, A., Belman, A., Wabant, E. (2016). Dietary salt intake and time to relapse in paediatric multiple sclerosis. *Journal of Neurology, Neurosurgery; Psychiatry*, 87(12), 1350-1353.

49. Anderson, R. M., Le Couteur, D. G., de Cabo, R. (2018). Caloric restriction research: new perspectives on the biology of aging. *The Journals of Gerontology: Series A*, 73(1), 1-3.
50. Piccio, L., Stark, J. L., Cross, A. H. (2008). Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. *Journal of leukocyte biology*, 84(4), 940-948.
51. Choi, I. Y., Piccio, L., Childress, P., Bollman, B., (2016). A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. *Cell reports*, 15(10), 2136-2146.
52. Blinckenberg, M., Rune, K., Jensen, C. V., Ravnborg, M. H., Kyllingsbaek, S., Holm, S., Sørensen, P. S. (2001). Reduced metabolism in cerebral cortex correlates with MRI changes and cognitive dysfunction in patients with disseminated sclerosis. *Ugeskrift for Laeger*, 163(27), 3788-3792.
53. Tenney, J. R., Rozhkov, L., Horn, P., Miles, L., Miles, M. V. (2014). Cerebral glucose hypometabolism is associated with mitochondrial dysfunction in patients with intractable epilepsy and cortical dysplasia. *Epilepsia*, 55(9), 1415-1422.
54. Storoni M, Plant GT. The Therapeutic Potential of the Ketogenic Diet in Treating Progressive Multiple Sclerosis. *Mult Scler Int*. 2015;2015:681289. Epub 2015 Dec 29. PMID: 26839705
55. Amorini, A. M., Nociti, V., Petzold, A., Gasperini,(2014). Serum lactate as a novel potential biomarker in multiple sclerosis. *Biochimica et Biophysica Acta-Molecular Basis of Disease*, 1842(7),1137-1143.
56. Gasior, M., Rogawski, M. A., Hartman, A. L. (2006). Neuroprotective and disease-modifying effects of the ketogenic diet. *Behavioural pharmacology*, 17(5-6), 431.
57. Martinez-Lopez, N., Tarabra, E., Toledo, M., Garcia-Macia, (2017). System-wide benefits of intermeal fasting by autophagy. *Cell metabolism*, 26(6),856-871.
58. Choi, I. Y., Piccio, L., Childress, P., Bollman, B., Ghosh, A.,(2016). A diet mimicking fasting promotes regeneration and reduces autoimmunity andmultiple sclerosis symptoms. *Cell reports*, 15(10), 2136-2146.
59. Riccio P, Rossano R. Diet, Gut Microbiota, and Vitamins D + A in Multiple Sclerosis. *Neurotherapeutics*. 2018 Jan;15(1):75-91. PMID: 29067566; PMCID: PMC5794694.
60. Cignarella, F., Cantoni, C., Ghezzi, L., Salter, A., Dorsett, Y., Chen, L., Piccio, L. (2018). Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. *Cell metabolism*, 27(6), 1222-1235.
61. Yadav, V., Marraccini, G., Kim, E., Spain, R., Cameron, M., Overs, S., Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. *Multiplesclerosis and related disorders*, *Mult Scler Relat Disord*. 2016 Sep;9:80-90. Epub 2016 Jul 6. PMID: 27645350.
62. Rodrigo, L., Hernández-Lahoz, C., Fuentes, D., Alvarez, N., López-Vázquez, A., González, S. (2011). Prevalence of celiac disease in multiple sclerosis. *BMC neurology*, 11(1), 1-7.
63. Stefferl, A., Schubart, A., Storch, M., Amini, A., Mather, I., Lassmann, H., Linington, C. (2000). Butyrophilin, a milk protein, modulates the encephalitogenic T cell

- response to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis. *The journal of Immunology*, 165(5), 2859-2865.
64. Kidd, P. M. (2005). Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. *Alternative Medicine Review*, 10(4), 268.
 65. Schwarz, S., Leweling, H. (2005). Multiple sclerosis and nutrition. *Multiple Sclerosis Journal*, 11(1), 24-32.
 66. Jianrong Li 1, Hong Wang, Paul A Rosenberg, Vitamin K prevents oxidative cell death by inhibiting activation of 12-lipoxygenase in developing oligodendrocytes *J Neurosci Res*. 2009 Jul;87(9):1997-2005. PMID: 19235890, DOI: 10.1002/jnr.22029
 67. G S M Ramsaransing 1, M R Fokkema, A Teelken, A V Arutjunyan, M Koch, J De Keyser, Plasma homocysteine levels in multiple sclerosis *J Neurol Neurosurg Psychiatry*. 2006 Feb;77(2):189-92. PMID: 16421120 PMCID: PMC2077571 DOI: 10.1136/jnnp.2005.072199
 68. Cather M. Cala, BS, Carson E. Moseley, BS, Chad Steele, PhD, Sarah M. Dowdy, T cell cytokine signatures: biomarkers in pediatric multiple sclerosis *J Neuroimmunol*. Author manuscript; available in PMC 2017 Aug 15. *J Neuroimmunol*. 2016 Aug 15; 297: 1–8. Published online 2016 Apr 30.
 69. AncelKeys1AlessandroMenotti2ChristAravanis3, The seven countries study: 2,289 deaths in 15 years *Preventive Medicine* Volume 13, Issue 2, March 1984, Pages 141-154
 70. Michel de Lorgeril, Patricia Salen, Jean-Louis Martin, Isabelle Monjaud, Jacques Delaye and Nicole Mamelle, Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction Final Report of the Lyon Diet Heart Study Originally published 16 Feb 1999 <https://doi.org/10.1161/01.CIR.99.6.779> *Circulation*. 1999;99:779–785
 71. Hasan Oğuz, Haşim Çakırbay, Burcu Yanık. Multipl Skleroz. *Tıbbi Rehabilitasyon* 2015; 479-496.
 72. Orhan Özcan, Oktay Arpacıoğlu, Betül Turan. MS'te Rehabilitasyon Nörorehabilitasyon 2000; 183-205.
 73. Fary Khan, Bhasker Amatya, And Lynne Turner-Stokes. Symptomatic Therapy And Rehabilitation İn Primary Progressive Multiple Sclerosis. *Neurol Res Int* 2011; 2011:740505.
 74. Dalgas U. Rehabilitation and multiple sclerosis: hot topics in the preservation of physical functioning. *J Neurol Sci* 2011; 311(Suppl 1): 43-47.
 75. Vaney, C., Gattlen, B., Lugon-Moulin, V., Meichtry, A., Hausammann, R., Foinant, D., Anchisi-Bellwald, A. M., Palaci, C., & Hilfiker, R. (2012). Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. *Neurorehabilitation and neural repair*, 26(3), 212–221.
 76. DeLuca, J.,& Nocentini, U. (2011). Neuropsychological, medical and rehabilitative management of persons with multiple sclerosis. *NeuroRehabilitation*, 29(3), 197-219.

▲ Demyelinizan Hastalıklar

77. Schwartz, I., Sajin, A., Moreh, E., Fisher, I., Neeb, M., Forest, A., ... & Meiner, Z. (2012). Robot-assisted gait training in multiple sclerosis patients: a randomized trial. *Multiple Sclerosis Journal*, 18(6), 881-890.
78. Frohman, T. C., Castro, W., Shah, A., Courtney, A., Ortstadt, J., Davis, S. L., ... & Frohman, E. M. (2011). Symptomatic therapy in multiple sclerosis. *Therapeutic advances in neurological disorders*, 4(2), 83-98.
79. Crabtree-Hartman, E. (2018). Advanced symptom management in multiple sclerosis. *Neurologic clinics*, 36(1), 197-218.
80. Phé, V., Pakzad, M., Curtis, C., Porter, B., Haslam, C., Chataway, J., & Panicker, J. N. (2016). Urinary tract infections in multiple sclerosis. *Multiple Sclerosis Journal*, 22(7), 855-861.
81. Kragt, J. J., Hoogervorst, E. L., Uitdehaag, B. M., & Polman, C. H. (2004). Relation between objective and subjective measures of bladder dysfunction in multiple sclerosis. *Neurology*, 63(9), 1716-1718.
82. Yang, C. C. (2013). Bladder management in multiple sclerosis. *Physical Medicine and Rehabilitation Clinics*, 24(4), 673-686.
83. Goessaert, A. S. O.,& Everaert, K. C. (2012). Onabotulinum toxin A for the treatment of neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis. *Expert Review of Neurotherapeutics*, 12(7), 763-775.
84. Chancellor, M. B., Patel, V., Leng, W. W., Shenot, P. J., Lam, W., Globe, D. R., ... & Chapple, C. R. (2013). OnabotulinumtoxinA improves quality of life in patients with neurogenic detrusor overactivity. *Neurology*, 81(9), 841-848.
85. Soljanik, I. (2013). Efficacy and safety of botulinum toxin A intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. *Drugs*, 73(10), 1055-1066.
86. DasGupta, R.,& Fowler, C. J. (2003). Bladder, bowel and sexual dysfunction in multiple sclerosis. *Drugs*, 63(2), 153-166.
87. Frohman, T. C., Castro, W., Shah, A., Courtney, A., Ortstadt, J., Davis, S. L., ... & Frohman, E. M. (2011). Symptomatic therapy in multiple sclerosis. *Therapeutic advances in neurological disorders*, 4(2), 83-98.
88. Patti, F. (2012). Treatment of cognitive impairment in patients with multiple sclerosis. *Expert opinion on investigational drugs*, 21(11), 1679-1699.
89. Koch, M. W., Glazeborg, A., Uyttenboogaart, M., Mostert, J., & De Keyser, J. (2011). Pharmacologic treatment of depression in multiple sclerosis. *Cochrane database of systematic reviews*, (2).
90. Hind, D., Cotter, J., Thake, A., Bradburn, M., Cooper, C., Isaac, C., & House, A. (2014). Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis. *BMC psychiatry*, 14(1), 1-13.
91. Feinstein, A., Rector, N., & Motl, R. (2013). Exercising away the blues: can it help multiple sclerosis-related depression?. *Multiple Sclerosis Journal*, 19(14), 1815-1819.

92. Brenner, P.,& Piehl, F. (2016). Fatigue and depression in multiple sclerosis: pharmacological and nonpharmacological interventions. *Acta Neurologica Scandinavica*, 134, 47-54.
93. Rammohan, K. W., Rosenberg, J. H., Lynn, D. J., Blumenfeld, A. M., Pollak, C. P., & Nagaraja, H. N. (2002). Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *Journal of Neurology, Neurosurgery & Psychiatry*, 72(2), 179-183.
94. Lange, R., Volkmer, M., Heesen, C., & Liepert, J. (2009). Modafinil effects in multiple sclerosis patients with fatigue. *Journal of neurology*, 256(4), 645-650.
95. Bethoux, F. (2013). Gait disorders in multiple sclerosis. *CONTINUUM: Lifelong Learning in Neurology*, 19(4), 1007-1022.
96. Goodman, A. D., Brown, T. R., Krupp, L. B., Schapiro, R. T., Schwid, S. R., Cohen, R., ... & Fampridine MS-F203 Investigators. (2009). Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *The Lancet*, 373(9665), 732-738.
97. Rinker, J. R., Salter, A. R., Walker, H., Amara, A., Meador, W., & Cutter, G. R. (2015). Prevalence and characteristics of tremor in the NARCOMS multiple sclerosis registry: a cross-sectional survey. *BMJ open*, 5(1), e006714.
98. Yadav, V., Shinto, L., & Bourdette, D. (2010). Complementary and alternative medicine for the treatment of multiple sclerosis. *Expert review of clinical immunology*, 6(3), 381-395.
99. Apel, A., Greim, B., König, N., & Zettl, U. K. (2006). Frequency of current utilisation of complementary and alternative medicine by patients with multiple sclerosis. *Journal of neurology*, 253(10), 1331-1336.
100. Goodman, A. D., Brown, T. R., Edwards, K. R., Krupp, L. B., Schapiro, R. T., Cohen, R., ... & MSF204 Investigators. (2010). A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Annals of neurology*, 68(4), 494-502.
101. Thompson, A.,& Polman, C. (2009). Improving function: a new treatment era for multiple sclerosis?. *Lancet (London, England)*, 373(9665), 697-698.
102. Birnbaum, G.,& Iverson, J. (2014). Dalfampridine may activate latent trigeminal neuralgia in patients with multiple sclerosis. *Neurology*, 83(18), 1610-1612.
103. Davis, S. L., Wilson, T. E., White, A. T., & Frohman, E. M. (2010). Thermoregulation in multiple sclerosis. *Journal of Applied Physiology*, 109(5), 1531-1537.
104. Van Diemen, H. A. M., Van Dongen, M. M. M. M., Dammers, J. W. H. H., & Polman, C. H. (1992). Increased visual impairment after exercise (Uhthoff's phenomenon) in multiple sclerosis: therapeutic possibilities. *European neurology*, 32(4), 231-234.
105. Nyquist, P. A., Cascino, G. D., & Rodriguez, M. (2001, October). Seizures in patients with multiple sclerosis seen at Mayo Clinic, Rochester, Minn, 1990-1998. In *Mayo Clinic Proceedings* (Vol. 76, No. 10, pp. 983-986). Elsevier.
106. Sokić, D. V., Stojasavljević, N., Drulović, J., Dujimović, I., Mesaroš, Š., Ercegovac, M., ... & Lević, Z. (2001). Seizures in multiple sclerosis. *Epilepsia*, 42(1), 72-79.

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107. Fowler, C. J., Miller, J. R., Sharief, M. K., Hussain, I. F., Stecher, V. J., & Sweeney, M. (2005). A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, 76(5), 700-705.
108. Safarinejad, M. R. (2009). Evaluation of the safety and efficacy of sildenafil citrate for erectile dysfunction in men with multiple sclerosis: a double-blind, placebo controlled, randomized study. *The Journal of urology*, 181(1), 252-258.
109. Jain, V., Arunkumar, A., Kingdon, C., Lacerda, E., & Nacul, L. (2017). Prevalence of and risk factors for severe cognitive and sleep symptoms in ME/CFS and MS. *BMC neurology*, 17(1), 1-10.
110. Lanza, G., Ferri, R., Bella, R., & Ferini-Strambi, L. (2017). The impact of drugs for multiple sclerosis on sleep. *Multiple Sclerosis Journal*, 23(1), 5-13.
111. Chou, R., Peterson, K., & Helfand, M. (2004). Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *Journal of pain and symptom management*, 28(2), 140-175.
- 112) Levinthal DJ, Rahman A, Nusrat S, O'Leary M, Heyman R, Bielefeldt K. Adding to the burden: gastrointestinal symptoms and syndromes in multiple sclerosis. Mult Scler Int. 2013;2013:319201. doi: 10.1155/2013/319201. Epub 2013 Sep 17. PMID: 24163768; PMCID: PMC3791579.