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European Journal of Behavioral Sciences
ISSN 2538-807X

Investigating the Relationship between Using Natalizumab in Patients with Multiple Sclerosis on Developing Depression

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ARTICLE INFO

Keywords:
Natalizumab,
Multiple Sclerosis,
Depression,
Beck Depression Inventory

ABSTRACT

Aims: This study aimed to investigate the relationship between using Natalizumab in patients with Multiple Sclerosis on developing Depression. **Method:** The Beck Depression Inventory (BDI-II) was used in this quasi-experimental study of 54 Multiple Sclerosis patients receiving Natalizumab. The mean of Depression before using the Natalizumab was 28.94, which is in the range of 16-31; the patients had mild Depression, but after using the Natalizumab, the mean of Depression was 48.38, which showed deep Depression. So, the mean of Depression in the post-test was more than the pre-test. **Results:** The Natalizumab's effect after one month of using Natalizumab was slightly more significant than before using Natalizumab. Obtained data indicated that patients had no significant depressive symptoms before treatment and before using Natalizumab, but after treatment with Natalizumab, depressive symptoms increased. **Conclusion**: Multiple sclerosis patients may experience Depression after receiving Natalizumab.

1. Introduction

Multiple sclerosis (MS) sufferers are more likely to suffer from psychiatric disorders than the general population, and the incidence and prevalence of those disorders are higher in MS patients. (Marrie et al., 2015). There is a link between Depression and anxiety in MS and adverse outcomes. (Mohr et al., 1997). It remains unclear what causes the increased burden of psychiatric comorbidities in MS patients. The effects of chronic stress and inflammation on the body can be influenced by genetics and environment. (Gold and Irwin, 2009, Rossi et al., 2017). In addition to structural changes in the brain, adverse reactions to MS therapies may also contribute to the disease. Mood disturbances are known to be associated with corticosteroids used in the short term to treat relapses. (Ciriaco et al., 2013).

An inflammatory, autoimmune, and neurodegenerative disease of the central nervous system (CNS), multiple sclerosis (MS) is the world's most common neurological condition. In the central nervous system, MS attacks myelinated axons, destroying the myelin and the axons to varying degrees. (Goldenberg, 2012). Having good mental health means being able to cope with life's stresses and being productive. (Niknafs et al., 2022).

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Cite this article as:
Niknafs, A. (2023). Investigating the Relationship between Using Natalizumab in Patients with Multiple Sclerosis on Developing Depression. *European Journal of Behavioral Sciences, 6*(2): 1-9. https://doi.org/10.33422/ejbs.v6i2.1003

Initially, beta-interferons, the first DMTs approved for MS, were reported to cause Depression. Subsequently, this was not confirmed. (Pandya and Patten, 2002) . Therefore, the risk of incident depression might be mediated by intrinsic factors. (Alba Palé et al., 2018).

The use of second-generation DMTs in MS has increased in recent years, despite the approval of multiple second-generation DMTs. (Ogino et al., 2017, Warrender-Sparkes et al., 2015). There has been little research on their potential adverse psychiatric effects (APE). The only thing known about APE is Depression.

Multiple sclerosis (MS) can result in neurological issues as well as significant inflammatory lesions in the central nervous system in addition to severe physical and cognitive disabilities (CNS). The current papers demonstrate that MS is multifaceted, involving genetic predisposition as well as environmental factors such exposure to infectious agents, vitamin deficiencies, and smoking, despite the lack of understanding of the etiology and pathogenesis of the disease. These substances cause the immune system to set off a series of events that lead to neuronal cell death, nerve demyelination, and neuronal dysfunction. Anti-inflammatory and immunomodulatory medications are frequently used to treat MS; however, they do not stop the degeneration of nerve tissue. Knowing the most recent data on the pathogenesis, etiology, diagnostic standards, and therapy of MS is crucial for neurologists. (Ghasemi et al., 2017).

Psychiatric disorders are treated primarily with drugs. (Niknafs, 2022).

Multiple sclerosis is treated in a variety of ways, each carrying its own risks. In order to minimize risks associated with treatment, it is essential to be aware of and monitor these possible side effects. Some of these therapies lack long-term experience, and this needs to be addressed. (Rommer & Zettl, 2018). Demographic factors, relapses, symptom characteristics, MRI activity, and other biomarkers are all predictive of aggressive MS.

Natalizumab, alemtuzumab, fingolimod, and ocrelizumab can be used to select patients for more aggressive therapies. Patients with severe diseases can also receive off-label treatments. Therapeutic decisions must take into account both benefits and side effects. (Bowen, 2019).

According to Penner et al., Multiple sclerosis (MS) is often characterized by fatigue, which is often associated with depression and sleep disorders, making symptomatic treatment decisions challenging. One year after treatment with Natalizumab, patients with relapsing-remitting MS showed a clinically significant improvement in Depression and fatigue in the single-arm, observational phase IV TYNERGY study. (Penner et al., 2015).

Longinetti (2022) indicated that DMT discontinuation and MS relapse were associated with Depression and antidepressants only to a limited extent. Inhibiting leukocyte trafficking into the central nervous system, Natalizumab is a monoclonal antibody. The FDA has approved it for treating relapsing-remitting multiple sclerosis (RRMS).

Natalizumab decreased the risk of sustained disability progression, prevented the accumulation of multiple sclerosis (MS) lesions on magnetic resonance imaging, and decreased the annualized relapse rate during Phase III clinical trials, according to Brandstadter et al. Progressive multifocal leukoencephalopathy (PML), a rare brain infection brought on by the reactivation of the John Cunningham virus (JCV) and seen in severely immunocompromised patients, is a major safety concern related to Natalizumab. Strategies to reduce risk have been developed in order to increase safety when risk factors for PML in MS patients receiving natalizumab treatment, notably the presence of anti-JCV antibodies, were identified. The use of additional biomarkers in risk classification is now under investigation. Natalizumab is frequently used in both first-line and second-line MS treatments because of its strong efficacy and good tolerance profile. (Brandstadter et al., 2017).

About half of MS patients will experience a depressive episode in their lifetime. (Vattakatuchery et al., 2011). The "clinically significant depressive symptom score" shows that nearly a third of MS patients in primary care have a moderate to a severe depressive episode. (Chwastiak et al., 2002).

The center of epidemiologic research depression measure was used by Svenningson et al. to examine Nat's impact on depression as part of the open-label, uncontrolled TYNERGY experiment. (Svenningsson et al., 2013).

A state of good mental health is one that enables people to manage the demands of everyday life and function effectively. (Niknafs et al., 2022).

Based on the Beck depression index, Iaffaldano described an improvement as compared to the baseline in an open-label observational study. However, the differences were small, and the design does not exclude other confounders as well as regression to the mean, so independent trials should confirm these findings. (Iaffaldano et al., 2012).

Johnson (2007) reported that Natalizumab recently joined beta interferon and glatiramer acetate as approved therapies for treating relapsing MS. However, unresolved safety issues restrict its use to patients with poor response to other immunomodulators.

According to the findings of this study, Natalizuman can raise the score of Depression in the Beck Depression Inventory(BDI-II); Moreover, according to these findings, Natalizumab can cause Depression in patients with Multiple Sclerosis (MS).

2. Method & Measure

2.1. Participants and Procedure

This study was a quasi-experimental research. The statistical population was all hospitals in Tehran, and Tandis hospital was selected as an available sampling. The Beck Depression Inventory (BDI-II) was used in this study of 54 Multiple Sclerosis patients before and after receiving Natalizumab. Depressive symptoms were evaluated by the Beck Depression Inventory (BDI-II) before consumption of Natalizumab and one month after consumption of Natalizumab. Oral and written consents were taken from patients who met the eligibility criteria before starting the research.

2.2. Beck Depression Inventory (BDI-II)

The Beck Depression Inventory (BDI-II) is a 21-item, self-rated scale that evaluates key symptoms of Depression, including mood, pessimism, sense of failure, feelings of dissatisfaction, guilt, punishment, feelings of disliking, feeling accused of being depressed, suicidal thoughts, crying, irritation, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. (Beck & Steer, 1993; Beck, Steer & Garbing, 1988).

According to the BDI-II, respondents are asked about their moods over the last two weeks, including today, based on 21 items rated on a 4-point Likert scale. Scores range from 0 to 63, with a higher score indicating more severe symptoms. Beck et al. (1996) determined severity cut-offs for minimal (0–13), mild (14–19), moderate (20–29), and severe (29–63) depression. According to McPherson and Martin (2010), the BDI-II factor structure is consistent with either two or three-factor models, depending on the population. There are common factors across studies, including cognitive, somatic, and affective factors. (Johnson et al., 2006; Manian et al., 2013; Skule et al., 2014; Tobias et al., 2017).

3. Results

3.1. Descriptive Statistics

Table 1.
Central tendency and dispersion of Depression in pre-test and post-test

Variable	Pretest		Post-test	
	Mean	Std.Deviation	Mean	Std.Deviation
Depression	28.94	11.10	48.38	8

As it can be seen in Table 1, the mean of Depression before using the Natalizumab was 28.94, and it is in the range of 16-31 the patients had mild Depression, but after using the Natalizumab, the mean of Depression was 48.38 shows deep Depression. So, the mean of Depression in posttest is more than pretest. However, for checking the significance difference, statistical tests should be done. Therefore, the tests are discussed below.

3.2. Inferential Statistics

Before checking the hypothesis, the normality of data has to check. Kolmogrov-Smirnov test for checking the normality of data was done, and the results are shown in Table 2.

Table 2.
One-Sample Kolmogorov-Smirnov Test

variable		N	Kolmogorov-Smirnov Z	P-value
Depression	Pretest	54	0.068	0.200
	Post-test	54	0.143	0.093

As it is shown in Table 2, the p-values for Depression in the pre-test and post-test are more than 0.05. So the normality of these variables is accepted, and the parametric tests can be used for the hypotheses.

- **Hypothesis. Using Natalizumab plays an influential role in increasing Depression in patients with MS.**

For checking this hypothesis, because of the normality of data, paired sample t-test was used for the comparison of the post-test and pre-test results. The following tables show the results:

Table 3.
Paired Samples Statistics for Depression

Variable	N	Mean(Std.dev)
Pretest	54	28.94(11.10)
Posttest	54	48.38(8)

Table 4.
Paired Samples Test

	Paired Differences		
Pretest-Posttest	Mean(Std.dev)	T(Sig)	Df
	-19.44(6.5)	-21.98(.001)	53

In Table 3, the mean and standard deviation of the pre-test and post-test of Depression are given. As it is seen, the mean of post-test (48.38) is more than the mean of the pre-test (28.94). However, to explore the significant difference between the posttest and pre-test, paired sample t-test is done. In Table 4, the p-value is 0.001, which is lower than 0.05. So this

hypothesis is confirmed in 95% of confidence. Using Natalizumab has significant effects on Depression and it increases Depression. In Figure 1, a comparison between the pre-test and post-test of Depression is shown.

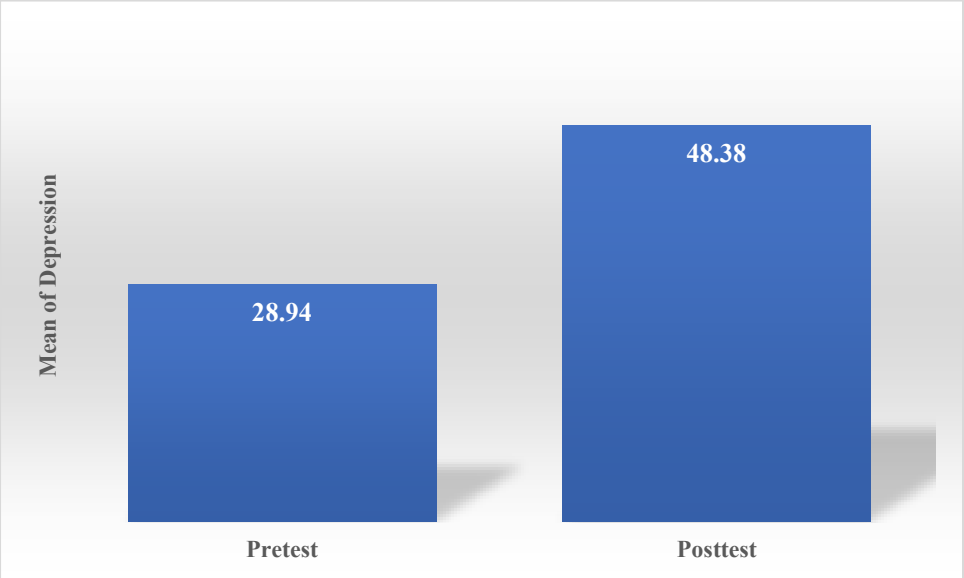

Figure 1. Comparison between pretest and posttest of Depression

4. Discussion

This study aimed to investigate the relationship between using Natalizumab in patients with Multiple Sclerosis on developing Depression. Results indicated that using Natalizumab can cause depressive symptoms in patients with Multiple Sclerosis. Several studies support this hypothesis.

According to Vattakatuchery et al. (2014), approximately half of MS patients will suffer from Depression at some point in their lives. Clinically significant depressive symptom score indicates that nearly a third of MS patients in a primary care setting have a moderate to a severe depressive episode. (Chwastiak et al., 2022). A center of epidemiologic studies depression scale was also used by Svenningson et al. in the open-label, uncontrolled TYNERGY trial. (Svenningsson et al., 2013). Improvements were noted in comparison to the baseline. (Stephenson et al.,2012). According to Iaffaldano's open-label observational study that used the Beck depression index, there were no significant differences, but other confounders and regression to the mean cannot be excluded. (Iaffaldano et al., 2012).

Multiple sclerosis (MS) patients are more likely than the general population to be depressed and to use antidepressants, but it is not clear whether psychiatric comorbidity is associated with different disease-modifying treatments (DMTs). (Longinetti et al., 2022).

According to Solarco et al. (2018), in MS, neuroinflammation interferes with neural function, which may cause fatigue, Depression, and pain.

Patients and society are burdened by fatigue, Depression, and pain associated with multiple sclerosis (MS). The pathophysiology of these symptoms is unclear, and the current treatments are only partially effective. A lack of positive affect and reduced motivation are clinical signs of anhedonia. Reward processing areas in the brain are associated with overlapping structural and functional alterations. Furthermore, neuroinflammation directly impairs reward-related monoaminergic neurotransmission. (Heitmann et al., 2022). Multiple sclerosis (MS) patients are significantly more likely to suffer from Depression; a study found that even after

controlling for age and gender, there was a 2.3-fold increase in depression risk. (Patten et al., 2003). Currently, there is no consensus regarding the pathophysiological link between MS and Depression; however, some researchers suggest that patients with lesions in specific brain areas (e.g., right temporal lobe, superior frontal or parietal regions) are more likely to suffer from Depression; others have found no such link to exist. (Chwastiak et al.,2007). According to some studies, Depression has been associated with poorer quality of life, increased disability levels, poorer adherence to MS treatment, and an increased risk of suicide in patients with MS. (Treadaway et al.,2009). According to Polman et al. (2006), MS treatment agents include 4aminopyridine, glatiramer, fingolimod, mitoxantrone, and Natalizumab. The two medications studied specifically for Depression are Natalizumab and fingolimod. A randomized controlled trial (RCT) of Natalizumab found an increased risk of Depression. (Polman et al., 2006).

5. Conclusion

Test results indicated that the mean difference between the stages of the test was not accidental, and drug treatment increased this mean difference**.** A month after using Natalizumab, the drug's effect was slightly greater than before using it.

According to the data obtained, patients had no significant depressive symptoms before treatment and before using Natalizumab, but after treatment with Natalizumab, depressive symptoms increased. In addition, these findings demonstrate Natalizumab's side effects in patients with MS.

References

Alba Palé, L., León Caballero, J., Samsó Buxareu, B., Salgado Serrano, P., & Pérez Solà, V. (2017). A systematic review of Depression in patients with multiple sclerosis and its relationship to interferonβ treatment. *Multiple sclerosis and related disorders*, *17*, 138–143. https://doi.org/10.1016/j.msard.2017.07.008

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring Depression. *Archives of general psychiatry*, *4*(6), 561-571. https://doi.org/10.1001/archpsyc.1961.01710120031004

Bowen J. D. (2019). Highly Aggressive Multiple Sclerosis. *Continuum (Minneapolis, Minn.)*, *25*(3), 689–714. https://doi.org/10.1212/CON.0000000000000731

Brandstadter, R., & Katz Sand, I. (2017). The use of Natalizumab for multiple sclerosis. *Neuropsychiatric disease and treatment*, *13*, 1691–1702. https://doi.org/10.2147/NDT.S114636

Ciriaco, M., Ventrice, P., Russo, G., Scicchitano, M., Mazzitello, G., Scicchitano, F., & Russo, E. (2013). Corticosteroid-related central nervous system side effects. *Journal of pharmacology & pharmacotherapeutics*, *4*(Suppl 1), S94–S98. https://doi.org/10.4103/0976-500X.120975

Chwastiak, L. A., & Ehde, D. M. (2007). Psychiatric issues in multiple sclerosis. *The Psychiatric clinics of North America*, *30*(4), 803–817. https://doi.org/10.1016/j.psc.2007.07.003

Chwastiak, L., Ehde, D. M., Gibbons, L. E., Sullivan, M., Bowen, J. D., & Kraft, G. H. (2002). Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic

study of a large community sample. *The American journal of psychiatry*, *159*(11), 1862–1868. https://doi.org/10.1176/appi.ajp.159.11.1862

Ghasemi, N., Razavi, S., & Nikzad, E. (2017). Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. *Cell journal*, *19*(1), 1–10.

Gold, S. M., & Irwin, M. R. (2009). Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Immunology and allergy clinics of North America*, *29*(2), 309–320. https://doi.org/10.1016/j.iac.2009.02.008

Goldenberg M. M. (2012). Multiple sclerosis review. *P & T: a peer-reviewed journal for formulary management*, *37*(3), 175–184.

Heitmann, H., Andlauer, T. F. M., Korn, T., Mühlau, M., Henningsen, P., Hemmer, B., & Ploner, M. (2022). Fatigue, Depression, and pain in multiple sclerosis: How neuroinflammation translates into dysfunctional reward processing and anhedonic symptoms. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *28*(7), 1020–1027. https://doi.org/10.1177/1352458520972279

Iaffaldano, P., Viterbo, R. G., Paolicelli, D., Lucchese, G., Portaccio, E., Goretti, B., Direnzo, V., D'Onghia, M., Zoccolella, S., Amato, M. P., & Trojano, M. (2012). Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PloS one*, *7*(4), e35843. https://doi.org/10.1371/journal.pone.0035843

Johnson K. P. (2007). Natalizumab (Tysabri) treatment for relapsing multiple sclerosis. *The neurologist*, *13*(4), 182–187. https://doi.org/10.1097/01.nrl.0000263760.53418.5b

Lien, I. A., Bolstad, I., Lien, L., & Bramness, J. G. (2022). Screening for Depression in patients in treatment for alcohol use disorder using the Beck Depression Inventory-II and the Hopkins Symptom Checklist-10. *Psychiatry research*, *308*, 114363. https://doi.org/10.1016/j.psychres.2021.114363

Longinetti E, Frisell T, Englund S, Reutfors J, Fang F, Piehl F. (2022). Risk of Depression in multiple sclerosis across disease-modifying therapies. *Multiple Sclerosis Journal*, 28(4):632-641. https://doi.org/:10.1177/13524585211031128

Manian, N., Schmidt, E., Bornstein, M. H., & Martinez, P. (2013). Factor structure and clinical utility of BDI-II factor scores in postpartum women. *Journal of affective disorders*, *149*(1-3), 259–268. https://doi.org/10.1016/j.jad.2013.01.039

Marrie, R. A., Fisk, J. D., Tremlett, H., Wolfson, C., Warren, S., Tennakoon, A., Leung, S., Patten, S. B., & CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (2015). Differences in the burden of psychiatric comorbidity in MS vs the general population. *Neurology*, *85*(22), 1972–1979. https://doi.org/10.1212/WNL.0000000000002174

Mohr, D. C., Goodkin, D. E., Likosky, W., Gatto, N., Baumann, K. A., & Rudick, R. A. (1997). Treatment of Depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Archives of neurology*, *54*(5), 531–533. https://doi.org/10.1001/archneur.1997.00550170015009

Niknafs, A. (2022). A Pilot Study On the Side Effects of Using Atypical Antipsychotics in Patients with Schizophrenia On Developing Obsessive Compulsive Symptoms. *European Journal of Behavioral Sciences*, 5(2):15-27. https://doi.org/10.33422/ejbs.v5i2.845

Niknafs, A., Lavasani, M.G., Banijamali, S., & Afrooz, G. (2022). Investigating the relationship between creativity and mental health and spiritual happiness and the parent's popularity of high school students and designing a model of spiritual happiness. *Journal of Gifted Education and Creativity*, 9(3), 311-322.

Pandya, R., & Patten, S. (2002). Depression in multiple sclerosis associated with interferon beta-1a (Rebif). *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, *47*(7), 686. https://doi.org/10.1177/070674370204700720

Passamonti, L., Cerasa, A., Liguori, M., Gioia, M. C., Valentino, P., Nisticò, R., Quattrone, A., & Fera, F. (2009). Neurobiological mechanisms underlying emotional processing in relapsing-remitting multiple sclerosis. *Brain: a journal of neurology*, *132*(Pt 12), 3380–3391. https://doi.org/10.1093/brain/awp095

Patten, S. B., Beck, C. A., Williams, J. V., Barbui, C., & Metz, L. M. (2003). Major depression in multiple sclerosis: a population-based perspective. *Neurology*, *61*(11), 1524–1527. https://doi.org/10.1212/01.wnl.0000095964.34294.b4

Penner, I. K., Sivertsdotter, E. C., Celius, E. G., Fuchs, S., Schreiber, K., Berkö, S., Svenningsson, A., & TYNERGY trial investigators (2015). Improvement in Fatigue during Natalizumab Treatment is Linked to Improvement in Depression and Day-Time Sleepiness. *Frontiers in neurology*, *6*, 18. https://doi.org/10.3389/fneur.2015.00018

Polman, C. H., O'Connor, P. W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D. H., Phillips, J. T., Lublin, F. D., Giovannoni, G., Wajgt, A., Toal, M., Lynn, F., Panzara, M. A., Sandrock, A. W., & AFFIRM Investigators (2006). A randomized, placebo-controlled trial of Natalizumab for relapsing multiple sclerosis. *The New England Journal of medicine*, *354*(9), 899–910. https://doi.org/10.1056/NEJMoa044397

Rommer, P. S., & Zettl, U. K. (2018). Managing the side effects of multiple sclerosis therapy: pharmacotherapy options for patients. *Expert opinion on pharmacotherapy*, *19*(5), 483–498. https://doi.org/10.1080/14656566.2018.1446944

Rossi, S., Studer, V., Motta, C., Polidoro, S., Perugini, J., Macchiarulo, G., Giovannetti, A. M., Pareja-Gutierrez, L., Calò, A., Colonna, I., Furlan, R., Martino, G., & Centonze, D. (2017). Neuroinflammation drives anxiety and Depression in relapsing-remitting multiple sclerosis. *Neurology*, *89*(13), 1338–1347. https://doi.org/10.1212/WNL.0000000000004411

Skule, C., Ulleberg, P., Dallavara Lending, H., Berge, T., Egeland, J., Brennen, T., & Landrø, N. I. (2014). Depressive symptoms in people with and without alcohol abuse: factor structure and measurement invariance of the Beck Depression Inventory (BDI-II) across groups. *PLoS One*, *9*(2), e88321. https://doi.org/10.1371/journal.pone.0088321

Solaro, C., Gamberini, G., & Masuccio, F. G. (2018). Depression in Multiple Sclerosis: Epidemiology, Aetiology, Diagnosis and Treatment. *CNS drugs*, *32*(2), 117–133. https://doi.org/10.1007/s40263-018-0489-5

Stephenson, J. J., Kern, D. M., Agarwal, S. S., Zeidman, R., Rajagopalan, K., Kamat, S. A., & Foley, J. (2012). Impact of Natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study. *Health and quality of life outcomes*, *10*, 155. https://doi.org/10.1186/1477-7525-10-155

Svenningsson, A., Falk, E., Celius, E. G., Fuchs, S., Schreiber, K., Berkö, S., Sun, J., Penner, I. K., & Tynergy Trial Investigators (2013). Natalizumab treatment reduces fatigue in

multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PloS one*, *8*(3), e58643. https://doi.org/10.1371/journal.pone.0058643

Tobias, K. G., Lehrfeld, J., Rosenfeld, B., Pessin, H., & Breitbart, W. (2017). Confirmatory factor analysis of the Beck Depression Inventory-II in patients with advanced cancer: A theory-driven approach. *Palliative & supportive care*, *15*(6), 704–709. https://doi.org/10.1017/S1478951517000724

Treadaway, K., Cutter, G., Salter, A., Lynch, S., Simsarian, J., Corboy, J., Jeffery, D., Cohen, B., Mankowski, K., Guarnaccia, J., Schaeffer, L., Kanter, R., Brandes, D., Kaufman, C., Duncan, D., Marder, E., Allen, A., Harney, J., Cooper, J., Woo, D., … Frohman, E. M. (2009). Factors that influence adherence with disease-modifying therapy in MS. *Journal of neurology*, *256*(4), 568–576. https://doi.org/10.1007/s00415-009-0096-y

Vattakatuchery, J. J., Rickards, H., & Cavanna, A. E. (2011). Pathogenic mechanisms of depression in multiple sclerosis. *The Journal of neuropsychiatry and clinical neurosciences*, *23*(3), 261–276. https://doi.org/10.1176/jnp.23.3.jnp261