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Treatment Adherence in Multiple Sclerosis: The Effect of Drug Administration Methods and Neuropsychiatric Comorbidities

Multipl Sklerozda Tedaviye Uyum: İlaç Uygulama Yöntemlerinin ve Nöropsikiyatrik Eşlik Eden Durumların Etkisi

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ABSTRACT

Objectives: Multiple sclerosis (MS) is a chronic neurodegenerative disease affecting young adults. While disease-modifying drugs (DMDs) help manage and decelerate disease progression, adherence to these treatments is a significant challenge. This study aimed to investigate the relationship between treatment adherence and different drug administration methods in MS patients in the context of neuropsychiatric evaluations.

Methods: A prospective cohort study was conducted at the University Hospital of Neurology Clinic using the 2017 revised McDonald criteria for MS diagnosis. Demographic data, MS-related metrics, and DMDs were recorded. Participants were stratified based on their DMDs into oral, injectable, and infusion treatments. The MS Treatment Adherence Questionnaire, Beck Depression Inventory, and State-Trait Anxiety Inventory were administered.

Results: Of the 89 patients, treatment adherence was 45%. There were significant differences in side effect scores between the non-adherent and adherent groups for both oral and injectable DMDs. The Beck Depression Inventory average score was 12.49±9.81, while the State-Trait Anxiety Inventory average scores for STAI1 and STAI2 were 38.95±10.41 and 47.89±10.66, respectively. Significant differences were observed in disease duration, the average expanded disability status scale score, and the average STAI score.

Conclusion: Adherence rates varied with the method of drug administration, with oral treatments having 34.4% adherence and injectable treatments having 53.4%. Factors like perceived efficacy, depression, and anxiety influenced treatment adherence. No significant correlations were found between demographic factors like age, gender, or education and adherence rates. Treatment adherence is crucial in managing MS. This study highlights the role of drug administration methods and neuropsychiatric comorbidities in influencing adherence. A comprehensive assessment considering these factors is vital in choosing an appropriate DMD for MS patients.

Keywords: Infusion; injection; multiple sclerosis; oral; treatment adherence and compliance

ÖZET

Amaç: Multipl skleroz (MS), genç yetişkinleri etkileyen kronik bir nörodejeneratif hastalıktır. Hastalığı modifiye eden ilaçlar (DMD'ler) hastalığın ilerlemesini yönetmeye ve yavaşlatmaya yardımcı olmasına rağmen, bu tedavilere uyum büyük bir sorundur. Bu çalışmada, nöropsikiyatrik değerlendirmeler bağlamında MS hastalarında tedaviye uyum ve farklı ilaç uygulama yöntemleri arasındaki ilişkinin araştırılması amaçlandı.

Yöntem: Bir üniversite hastanesi nöroloji kliniğinde, MS tanısı için 2017 yılında gözden geçirilmiş McDonald kriterleri kullanılarak prospektif bir kohort çalışması gerçekleştirildi. Demografik veriler, MS ile ilgili ölçütler ve DMD'ler kaydedildi. Katılımcılar DMD'lerine göre oral, enjektabl ve infüzyon tedavileri olmak üzere kategorilere ayrıldı. MS Tedavi Uyumu Anketi, Beck Depresyon Envanteri ve Sürekli-Kişilik Kaygı Envanteri uygulandı.

Bulgular: Seksen dokuz hastanın %45'inde tedaviye uyum vardı. Oral ve enjektabl DMD'ler için uyumsuz ve uyumlu gruplar arasında yan etki puanlarında anlamlı farklar vardı. Beck Depresyon Envanteri ortalaması 12,49±9,81 iken, STAI1 ve STAI2 için Sürekli-Kişilik Kaygı Envanteri ortalamaları sırasıyla 38,95±10,41 ve 47,89±10,66 idi. Hastalık süresi, ortalama EDSS puanı ve ortalama STAI puanları arasında anlamlı farklar gözlendi.

Sonuç: Uyum oranları ilaç uygulama yöntemine göre değişiklik gösterdi; oral tedavilerde %34,4 uyum, enjektabl tedavilerde %53,4 uyum bulundu. Algılanan etkinlik, depresyon ve anksiyete gibi faktörler tedaviye uyumu etkiledi. Yaş, cinsiyet veya eğitim gibi demografik faktörlerle uyum oranları arasında anlamlı bir korelasyon bulunamadı. Tedaviye uyum, MS'nin yönetilmesinde kritik önem taşımaktadır. Bu çalışma, ilaç uygulama yöntemlerinin ve nöropsikiyatrik komorbiditelerin MS tedavisine uyum üzerindeki rolünü vurgulamaktadır. Bu faktörleri göz önünde bulunduran kapsamlı bir değerlendirme, MS hastaları için uygun bir DMD seçiminde hayati öneme sahiptir.

Anahtar sözcükler: Multipl skleroz; tedavi uyumu; oral; enjeksiyon; infüzyon.

Multiple sclerosis (MS) is a chronic, immunologically-based neurodegenerative disease affecting the central nervous system.[1] Typically starting between the ages of 20 and 40, MS predominantly affects young adults and has a higher prevalence in women. It is estimated that over 2.8 million individuals worldwide are affected by MS.[2,3] MS ranks among the most common diseases causing neurological sequelae globally, and in some countries, it is the primary cause of non-traumatic disability among young adults.[4] The disease is associated with a range of neurological symptoms, including impairments in sensory, motor, and cognitive functions.[5] Treatment goals for MS not only encompass managing symptoms and treating relapses and complications but also hindering disease progression.[6] Disease-modifying drugs (DMDs) have been shown to prevent relapse rates and halt disease progression.[7] Currently, there are at least 15 DMDs approved by the food and drug administration for the treatment of MS, and these DMDs differ in their mode of application, dosage, mechanism of action, efficacy, safety, and tolerability.[8-12]

The World Health Organization defines treatment adherence as "the extent to which a person's behavior-in terms of taking medications, following diets, and/or executing lifestyle changes-corresponds to the recommendations agreed on by a healthcare provider." Adherence to treatment regimens is fundamental for patients to derive maximum benefit from their treatments and, simultaneously, to ensure the cost-effectiveness of the treatment. Non-adherence or poor adherence can result in negative results, treatment failure, and higher expenditures.[13] Studies have found that, depending on different methods and definitions, adherence to DMDs among MS patients ranges between 49% and 93%.[14-16] Factors that contribute to reduced adherence to DMDs include drug side effects, cognitive impairment, frequent dosing regimens, depression, and anxiety.[17-20]

Given the established effectiveness of disease-modifying medications, a better knowledge of the factors influencing treatment adherence in MS might help doctors build tailored treatment regimens that improve adherence and thereby minimize MS relapses. The purpose of this study was to look at the link between treatment adherence and various drug delivery modalities in MS patients as part of neuropsychiatric assessments.

Methods

Data Collection

Our study is a prospective cohort study conducted with patients who received a definitive MS diagnosis based on the 2017 revised McDonald criteria at the University Hospital of Neurology Clinic. Demographic data of patients with MS, such as age, gender, and education, as well as MS disease duration, the expanded disability status scale (EDSS), and their current DMDs, were recorded. The Beck Depression Inventory and the State-Trait Anxiety Inventory were administered for the neuropsychiatric evaluation of the patients. Patients included in the study were those aged 18 years or older, diagnosed with definitive MS, and on the same DMD for at least 12 months. Patients with severe cognitive impairments who had difficulty completing the surveys and those with a history of any psychopathological diagnosis or treatment were excluded. Informed consent was obtained from all patients participating in the study. Patients were divided into three groups based on the DMDs they used: those on oral medications (teriflunomide, dimethyl fumarate, and fingolimod), those on injectable treatments (interferons, glatiramer acetate), and those on infusion treatments (natalizumab and ocrelizumab). Patients treated with alemtuzumab and cladribine, which are not continuous-use treatments, were excluded from the study. After neurological examinations, patients were administered the MS treat-

ment adherence questionnaire (MS TAQ), Beck Depression Inventory, and State-Trait Anxiety Inventory (STAI1 and STAI2). The study received ethical approval from the local ethics committee.

Questionnaire and Definitions

Patients' treatment adherence was assessed using the MS-TAQ. This questionnaire was developed in 2009 by Paul Wicks and Michael Massagli, and reliability and validity study in Turkish was conducted by Usta Yeşilbakan, Erbay, and Yüceyar in 2019. The MS-TAQ consists of three subgroups: DMD barriers, DMD side effects, and DMD coping strategies. The first section (DMD-Barriers) is administered to patients who have missed at least one medication dose in the last 28 days. It includes factors causing dose omissions. The second section (DMD-side effects) evaluates the frequency of 10 possible side effects related to DMDs. The third section (DMD-Coping Strategies) includes seven coping mechanisms used by patients to mitigate side effects. Patients" anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI1, STAI2). These scales were developed by Spielberger et al.[21] in 1970 and adapted to the Turkish community by Ner and Le Compte in 1985. The state anxiety scale (STAI1) is a sensitive tool for assessing immediate emotional reactions, whereas the trait anxiety scale (STAI2) measures the persistence of general anxiety shown by an individual. In the survey assessing state and trait anxiety levels, consisting of 20 questions each, a higher score indicates higher anxiety, whereas a lower score indicates lesser anxiety. The Beck Depression Inventory, developed by Beck et al.[22] in 1961, was used to evaluate patients" depressive states.

Patients who forgot or skipped their required dose once or more in 28 days were considered non-adherent to treatment, whereas those who did not miss any dose in 28 days were considered adherent. The medication possession ratio (MPR) is calculated by dividing the total number of days treated by the total number of days required for treatment. An MPR ≥0.8 represents treatment adherence and an MPR <0.8 represents non-adherence. The missed dose ratio is calculated by dividing the number of missed or skipped doses by the total required doses.

Statistical Analysis

Statistical analysis of the study data was conducted using the Statistical Package for Social Sciences version 22.0 for Windows. The methods used included descriptive statistics such as mean, standard deviation, and frequency distributions. To compare proportions within categorical variables, the chi-square test was employed. For data with a non-normal distribution, the Mann–Whitney U test was utilized to compare the means of two independent groups. When comparing more than two groups, the Kruskal–Wallis analysis of variance, a non-parametric test, was used. A $p<0.05$ was considered statistically significant for all results.

Results

A total of 89 patients, with an average age of 39.97±11.41 (73% female ratio), were included in the study. The mean EDSS score of the study group was 1.97±2.01, and the average disease duration was 9.01±6.46 years. Demographic data are provided in Table 1.

Among the patients participating in the study, treatment adherence was found to be 45%. When the groups using oral DMDs and those receiving injectable treatments were evaluated separately in terms of treatment adherence, only the side effect scores were statistically significantly different in both groups. In both groups, the side effect score was higher in the non-adherent group, whereas the coping scores were significantly higher in those who adhered to the treatment (respectively, oral group; $p<0.001$, $p=0.004$; injectable group; $p<0.001$, $p<0.001$).

The depression and anxiety levels of the study group were assessed using designated scales, and the average Beck depression score was 12.49±9.81. The average scores for

Table 1. Demographic and clinical characteristics of the study participants

Demografic features	The study of all groups (n=89)
Age (mean±SD); years	39.97±11.41
EDSS score (mean±SD)	1.97±2.01
Disease duration (mean±SD); years	9.01±6.46
Marial status	77.5% (married)
	22.4% (single)
Income status	4.516±3.181 TL
Status of having children	69.7%
DMDs	Enjectables; 48.3%
	Oral tablets; 32.6%
	Infusion therapy; 19.1%

DMD: Disease-modifying drugs; EDSS: Expanded disability status scale.

STAI1 and STAI2 were determined to be 38.95±10.41 and 47.89±10.66, respectively. When the study group was evaluated according to the treatments used and based on demographic and clinical characteristics, there were differences between the groups in terms of disease duration, average EDSS score, and average STAI scores (respectively, p<0.001, p<0.001, p=0.009), but no significant difference was observed in limitation scores (Table 2). No correlation has been observed between treatment adherence parameters and depression. The relationship between nonparametric numerical data was evaluated with Spearman correlation analysis.

Discussion

In our study, the rate of patients showing treatment adherence was found to be 56% (when patients receiving infusion therapy were not included in this rate). When looking at the treatment adherence of patients using oral treatment and those using injection treatments separately, they were found to be 34.4% and 53.4%, respectively. According to the results of the MS TAQ survey, although there was no difference between the groups in terms of the limitation parameter, there were differences between the groups in terms of DMD side effects and DMD coping methods.

In our study, when patients were grouped according to MS treatment administration, age, EDSS, and disease duration, they were found to be higher in the group receiving infusion treatment than in the group receiving oral or injection treatment (Fig. 1). High-efficacy infusion treatments, such as natalizumab and ocrelizumab, are not the first line of MS treatment and are generally initiated in the later stages of the disease.[23-25] An increase in the EDSS score is expected with an increase in neurodegeneration in the advanced stages of MS.[26] Therefore, findings such as the higher average age, longer disease duration, and higher EDSS scores in the group receiving infusion treatment are consistent with the literature.

The MS-TAQ is a tool that measures treatment adherence in patients with MS. In MS patients, as the total scores for DMD barriers and DMD side effects increase, adherence to treatment decreases. However, as the DMD-Coping score increases, treatment adherence also increases.[27] In a study conducted, the effects of the method of treatment application on treatment adherence in MS patients were demonstrated. Adherence is 63% in oral treatments, whereas it is 68% in injection treatments. In the infusion treatments, adherence was found to be 100%. This high adherence to infusion treatments may stem from the fact that these treatments are administered by health professionals through medical appointments.[15] In a study conducted with rheumatoid patients, it was shown that, apart from the method of appli-

Table 2. Comparison of treatment adherence, depression, anxiety, and clinical metrics among treatment groups

	The oral tablet group (n=29)	The enjectables group (n=43)	The infusion group (n=17)	p
Age (mean±SD); years	34.27±8.83	38.83±9.68	51.29±11.62	*<0.001 **0.003
EDSS (mean±SD)	0.79±0.66	1.29±0.79	5.73±1.09	*<0.001 **<0.001
Disease duration; years	5.93±4.55	8.87±5.63	14.61±7.70	*<0.001 **0.026
Beck depression score (mean±SD)	10.48±10.50	12.04±9.03	17.05±9.62	0.204
STAI 1 score (mean±SD)	36.79±10.72	38.34±9.33	44.17±11.33	0.177
STAI 2 score (mean±SD)	45.89±10.37	47.30±9.91	52.82±12.05	*p=0.009
Treatment adherence	34.4%	53.4%	100%	***0.150
MDR (mean±SD)	0.14±0.10	0.05±0.05	-	***0.002
DMD-barriers (mean±SD)	29.94±10.72	33.5±9.23	-	0.260
DMD-coping strategies (mean±SD)	3.17±1.62	3.44±1.77	4.41±1.46	*0.016 **0.047
DMD-side effects (mean±SD)	23.06±11.29	22.65±11.32	10.35±0.60	*<0.001 **<0.001

*Oral versus infusion. **Injectable versus infusion. ***oral versus injectable. DMD: Disease-modifying drugs, MDR: Missed dose ratio.

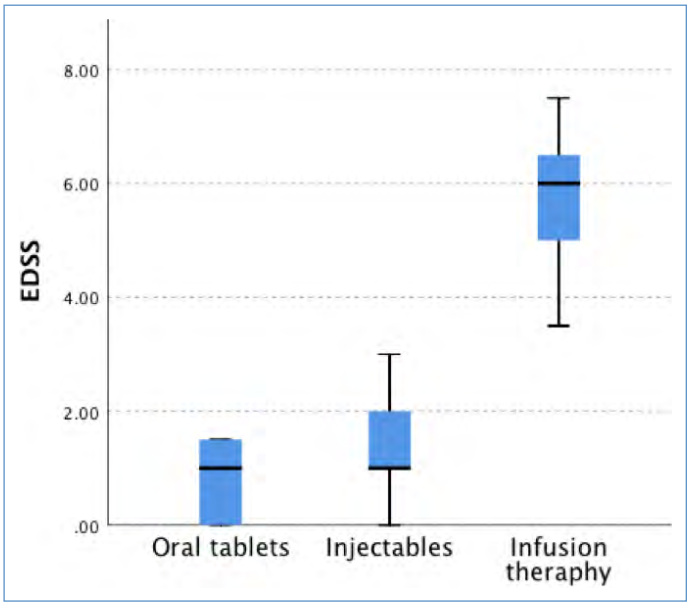

Figure 1. Comparison of expanded disability status scale scores, and multiple sclerosis treatment modalities.

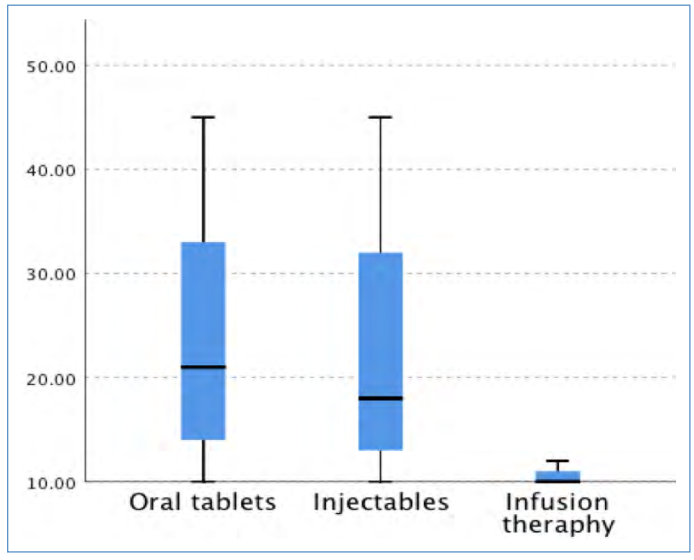

Figure 2. Comparison of disease-modifying drugs side effects across multiple sclerosis treatment modalities.

cation, the frequency of application also affects treatment adherence. Treatments with a lower frequency of application have been shown to increase adherence.[28] The high adherence to infusion treatments could also be due to the lower frequency of application. In our study, consistent with the literature, while adherence in infusion treatments is 100%, this rate decreases in oral and injection treatments. In a study by Munsell et al.,[29] MPR was found to be significantly higher in the group receiving injection treatment than in the group receiving oral treatment.

In our study, there was a generally high rate of treatment non-adherence (43.8%). In the literature, rates of treatment non-adherence have varied across different studies, showing results such as 18.5%, 24.9%, 17.6%, 35.3%, 16%, and 51%.[30-34] In our study, we found no correlation between treatment non-adherence and factors such as age, gender, education, or the duration of the disease. A study in the literature suggested that being married and having children increases medication non-adherence.[27] The lack of correlation between these factors and treatment adherence in our study may be attributed to our relatively small sample size.

When examining the subgroups of MS TAQ in our study, no correlation was observed between DMD-barriers and DMD-coping scores and the methods of treatment application. However, DMD side effects were found to be higher in the group receiving oral and injection treatments, whereas they were significantly lower in the group undergoing infusion therapy (Fig. 2). One reason for the higher treatment adherence in the group receiving infusion therapy compared with other drug application methods might be the differences in side effects. Oral DMDs offer advantages over injectable DMDs, such as ease of application; however, the factors that might affect the adherence and persistence of oral DMDs are not clear.[35] One of the most often mentioned reason for stopping treatment is a perceived lack of effectiveness.[36-38] Although the ease of use of oral drugs is an advantage, the lower perceived efficacy of oral medications increases non-adherence.[13]

Depression is commonly observed in MS patients and can negatively impact adherence. A study by Bruce et al.[39] demonstrated a strong connection between treatment adherence and emotional functioning in MS patients. The same study also indicated that MS patients with mood or anxiety disorders showed nearly 5 times more DMD treatment non-adherence than MS patients without a psychiatric diagnosis. In addition, approximately 35% of MS patients suffer from chronic anxiety. It is estimated that the lifetime prevalence of generalized anxiety disorder in MS is 20.[40] Köşkderelioğlu et al.[31] showed that higher scores on the Beck Depression Inventory were associated with treatment non-adherence. Treadaway et al.[19] pointed out that the group with treatment non-adherence had higher scores on the Beck Depression Inventory. Neuropsychiatric comorbidities are common in people with MS; a recent meta-analysis has shown that the prevalence of depression (31%) and anxiety (22%) in MS patients is high.[41] In our study, although no significant correlation was found between the

Beck Depression Inventory scores and the groups according to the drug administration, the average score for the group receiving infusion therapy was consistent with moderate depressive symptoms. The situational anxiety scale showed no difference between the groups receiving oral therapy, injection therapy, or infusion therapy. However, the chronic anxiety scale was higher in the infusion therapy group and was statistically significant. Considering that the EDSS scores of the infusion therapy group were higher and they were in a more advanced stage of the disease, this situation can be explained by their higher disability levels. These results emphasize the importance of comprehensively assessing and treating depressive symptoms and anxiety disorders in MS.

In MS, adherence to disease-modifying therapy is one of the key factors determining therapeutic success. To date, there are only a few studies in our country examining the factors affecting treatment adherence in MS patients. In assessing MS treatment adherence, this study also evaluated the neuropsychiatric comorbidities of the patients and the formation of subgroups according to drug administration. This is of great importance and contributes to the literature in terms of considering these criteria when choosing a DMD for patients. A limitation of the study is that it did not separately evaluate the DMDs used by each patient when forming subgroups based on drug administration.

Conclusion

Adherence to treatment in MS is a significant factor affecting the course of the disease. This study discusses the factors affecting treatment adherence in MS. The impact of drug administration and the frequency of drug administration on treatment adherence have been clearly demonstrated. Furthermore, it has been emphasized that neuropsychiatric comorbidities, frequently observed in MS patients, could also affect treatment adherence, and patients need to be evaluated in detail in this regard.

Disclosures

Ethics Committee Approval: Approved based on the decision numbered GOKAEK-2023/13.39 for the project with the code 2023/263. Approval date: 14.08.2023.

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Conflict of Interest: None declared.

References

1. Sánchez Martínez I, Cerdán Sánchez M, López Román J, Iniesta Martínez F, Carreón-Guarnizo E, Meca Lallana JE, et al. Possible influence of the route of treatment administration on treatment adherence in patients with multiple sclerosis. Clin Ther 2020;42:e87–e99.
2. Greer JM, McCombe PA. Role of gender in multiple sclerosis: Clinical effects and potential molecular mechanisms. J Neuroimmunol 2011;234:7–18.
3. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler 2020;26:1816–21.
4. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 2014;83:1022–4.
5. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D; University of British Columbia MS Clinic Neurologists. Early onset multiple sclerosis: A longitudinal study. Neurology 2002;59:1006–10.
6. Haase R, Kullmann JS, Ziemssen T. Therapy satisfaction and adherence in patients with relapsing-remitting multiple sclerosis: The THEPA-MS survey. Ther Adv Neurol Disord 2016;9:250–63.
7. Hauser SL, Cree BAC. Treatment of multiple sclerosis: A review. Am J Med 2020;133:1380–90.e2.
8. Margoni M, Preziosa P, Filippi M, Rocca MA. Anti-CD20 therapies for multiple sclerosis: Current status and future perspectives. J Neurol 2022;269:1316–34.
9. Freeman L, Longbrake EE, Coyle PK, Hendin B, Vollmer T. High-efficacy therapies for treatment-naïve individuals with relapsing-remitting multiple sclerosis. CNS Drugs 2022;36:1285–99.
10. Cree BAC, Hartung HP, Barnett M. New drugs for multiple sclerosis: New treatment algorithms. Curr Opin Neurol 2022;35:262–70.
11. Travers BS, Tsang BK, Barton JL. Multiple sclerosis: Diagnosis, disease-modifying therapy and prognosis. Aust J Gen Pract 2022;51:199–206.
12. Cross A, Riley C. Treatment of multiple sclerosis. Continuum (Minneap Minn) 2022;28:1025–51.
13. Patti F. Optimizing the benefit of multiple sclerosis therapy: The importance of treatment adherence. Patient Prefer Adherence 2010;4:1–9.
14. Lugaresi A, Rottoli MR, Patti F. Fostering adherence to injectable disease-modifying therapies in multiple sclerosis. Expert Rev Neurother 2014;14:1029–42.
15. Morillo Verdugo R, Ramírez Herráiz E, Fernández-Del Olmo R, Roig Bonet M, Valdivia García M. Adherence to disease-modifying treatments in patients with multiple sclerosis in Spain. Patient Prefer Adherence 2019;13:261–72.
16. Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. Adv Ther 2011;28:51–61.
17. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. J Manag Care Pharm 2013;19(1 Suppl A):S24–40.
18. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.

19. Treadaway K, Cutter G, Salter A, Lynch S, Simsarian J, Corboy J, et al. Factors that influence adherence with disease-modifying therapy in MS. J Neurol 2009;256:568–76.
20. Beer K, Müller M, Hew-Winzeler AM, Bont A, Maire P, You X, et al. The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: An observational study. BMC Neurol 2011;11:144.
21. Spielberger CD, Gonzalez-Reigosa F, Martinez-Urrutia A, Natalicio LFS, Natalicio DS. The state-trait anxiety inventory. Interam J Psychol1971.
22. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
23. Bigaut K, Kremer L, Fabacher T, Ahle G, Goudot M, Fleury M, et al. Ocrelizumab versus fingolimod after natalizumab cessation in multiple sclerosis: An observational study. J Neurol 2022;269:3295–300.
24. Jaber A, Patel M, Sylvester A, Yarussi M, Kalina JT, Mendoza JP, et al. COVID-19 vaccine response in people with multiple sclerosis treated with dimethyl fumarate, diroximel fumarate, natalizumab, ocrelizumab, or ınterferon beta Therapy. Neurol Ther 2023;12:687–700.
25. Bigaut K, Cohen M, Durand-Dubief F, Maillart E, Planque E, Zephir H, et al. How to switch disease-modifying treatments in multiple sclerosis: Guidelines from the French Multiple Sclerosis Society (SFSEP). Mult Scler Relat Disord 2021;53:103076.
26. Cadavid D, Cohen JA, Freedman MS, Goldman MD, Hartung HP, Havrdova E, et al. The EDSS-Plus, an improved endpoint for disability progression in secondary progressive multiple sclerosis. Mult Scler 2017;23:94–105.
27. Yeşilbalkan ÖU, Erbay Ö, Yüceyar AN. Translation and validation of the Turkish version of Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ). Noro Psikiyatr Ars 2018;56:191–4.
28. Huynh TK, Ostergaard A, Egsmose C, Madsen OR. Preferences of patients and health professionals for route and frequency of administration of biologic agents in the treatment of rheumatoid arthritis. Patient Prefer Adherence 2014;8:93–9.
29. Munsell M, Frean M, Menzin J, Phillips AL. An evaluation of adherence in patients with multiple sclerosis newly initiating treatment with a self-injectable or an oral disease-modifying drug. Patient Prefer Adherence 2016;11:55–62.
30. Ožura A, Kovač L, Sega S. Adherence to disease-modifying therapies and attitudes regarding disease in patients with multiple sclerosis. Clin Neurol Neurosurg 2013;115(Suppl 1):S6–11.
31. Köşkderelioğlu A, Gedizlioğlu M, Ortan P, Öcek Ö. Evaluation of the adherence to immunmodulatory treatment in patients with multiple sclerosis. Noro Psikiyatr Ars 2015;52:376–9.
32. Arroyo E, Grau C, Ramo-Tello C, Parra J, Sánchez-Soliño O; GAP Study Group. Adherence to disease-modifying therapies in spanish patients with relapsing multiple sclerosis: Two-year interim results of the global adherence project. Eur Neurol 2011;65:59–67.
33. Duchovskiene N, Mickeviciene D, Jurkeviciene G, Dirziuviene B, Balnyte R. Factors associated with adherence to disease modifying therapy in multiple sclerosis: An observational survey from a referral center in Lithuania. Mult Scler Relat Disord 2017;13:107–11.
34. Lam WY, Fresco P. Medication adherence measures: An overview. Biomed Res Int 2015;2015:217047.
35. Johnson KM, Zhou H, Lin F, Ko JJ, Herrera V. Real-world adherence and persistence to oral disease-modifying therapies in multiple sclerosis patients over 1 year. J Manag Care Spec Pharm 2017;23:844–52.
36. Tremlett HL, Oger J. Interrupted therapy: Stopping and switching of the beta-interferons prescribed for MS. Neurology 2003;61:551–4.
37. Río J, Porcel J, Téllez N, Sánchez-Betancourt A, Tintoré M, Arévalo MJ, et al. Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. Mult Scler 2005;11:306–9.
38. Clerico M, Barbero P, Contessa G, Ferrero C, Durelli L. Adherence to interferon-beta treatment and results of therapy switching. J Neurol Sci 2007;259:104–8.
39. Bruce JM, Hancock LM, Arnett P, Lynch S. Treatment adherence in multiple sclerosis: Association with emotional status, personality, and cognition. J Behav Med 2010;33:219–27.
40. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler 2007;13:67–72.
41. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, van Oppen P, Dekker J, et al. Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. J Neurol Sci 2017;372:331–41.