ORIGINAL RESEARCH

Bagcilar Med Bull 2024;9(3):156-161
DOI: 10.4274/BMB.galenos.2024.2024-02-022

Evaluation of the Quality of Life and Psychiatric Comorbidities of Oral and Injectable Therapy Users with Multiple Sclerosis

Multipl Skleroz Hastalarında Hastalık Modifiye Edici Enjekte Edilebilir ve Oral Tedavi Kullanıcılarının Yaşam Kalitesi ile Psikiyatrik Komorbiditelerinin Değerlendirilmesi

Hasan Gökçay[1], Sami Ömerhoca[2], Hasan Belli[3], Mehmet Yertürk[2], Kübra Nur Ustabaş[2], Nilüfer Kale İçen[2]

[1]Şarkışla State Hospital, Clinic of Psychiatry, Sivas, Turkey
[2]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Neurology, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Department of Psychiatry, İstanbul, Turkey

Abstract

Objective: Considering inconsistent findings and the absence of published longitudinal studies on large-scale community cohorts, this study aimed to assess the relationship between treatment modalities (injectable vs. oral therapy) and psychiatric symptoms and quality of life (QoL) in individuals with multiple sclerosis.

Method: This cross-sectional study involved 42 patients with multiple sclerosis diagnosed according to McDonald's 2017 criterion. Participants were grouped into those receiving injectable disease-modifying therapies (DMTs) (19 patients), oral DMTs (22 patients), and healthy controls (20 patients). The Expanded disability status scale, Hamilton depression rating scale (HAM-D), 36-item short form survey (SF-36), Hamilton anxiety rating scale (HAM-A), and headache impact test were applied.

Results: The healthy control group exhibited statistically higher SF-36 total scores than the oral and injectable therapy groups ($p<0.05$). The HAM-D and HAM-A scores were significantly lower in the healthy control group than in both the oral and injectable therapy groups ($p<0.05$). HAM-D and HAM-A scores were negatively correlated with the SF-36 total ($p<0.01$).

Conclusion: Our study contributes to the field by investigating the QoL and psychiatric symptoms in patients receiving both oral and injectable disease-modifying therapy. Our findings show that the effects of oral and injectable DMT use on QoL and psychiatric symptoms are similar.

Keywords: Anxiety, depression, injectable therapy, multiple sclerosis, oral therapy

Öz

Amaç: Tutarsız bulgular ve büyük topluluk kohortlarında yayımlanmış uzunlamasına çalışmaların olmaması dikkate alındığında, bu çalışma multipl sklerozlu bireylerde tedavi yöntemleri (enjekte edilebilir vs. oral tedavi) ile psikiyatrik belirtiler ve yaşam kalitesi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntem: Bu kesitsel çalışma, McDonald'ın 2017 kriterlerine göre tanı almış çoklu multipl sklerozlu 42 hastayı içeriyordu. Katılımcılar, enjekte edilebilir hastalık modifiye edici tedavi (DMT) alanlar (19 hasta), oral DMT alanlar (22 hasta) ve sağlıklı kontrol grubu (20 hasta) olarak gruplandırılmıştır. Genişletilmiş özürlülük durum ölçeği, Hamilton depresyon değerlendirme ölçeği (HAM-D), sağlık durumu anketi kısa form-36 (SF-36), Hamilton anksiyete değerlendirme ölçeği (HAM-A) ve baş ağrısı etki testi uygulanmıştır.

Bulgular: Sağlıklı kontrol grubuna kıyasla, oral tedavi grubu ve enjekte edilebilir tedavi grubu arasında SF-36 toplam puanları açısından anlamlı düşük bulunmuştur ($p<0,05$). HAM-D ve HAM-A puanları, sağlıklı kontrol grubunda hem oral tedavi grubundan hem de enjekte edilebilir tedavi grubundan istatistiksel olarak daha düşüktü ($p<0,05$). HAM-D ve HAM-A puanları, SF-36 toplamı ile negatif olarak korelasyon göstermiştir ($p<0,01$).
Sonuç: Çalışmamız hem oral hem de enjekte edilebilir hastalık modifiye edici tedavi alan hastalarda yaşam kalitesi ve psikiyatrik belirtileri değerlendirerek literatüre katkıda bulunmaktadır. Bulgularımız, oral ve enjekte edilebilir DMT kullanımının yaşam kalitesi ve psikiyatrik belirtiler üzerinde benzer etkilere sahip olduğunu göstermektedir.

Anahtar kelimeler: Anksiyete, depresyon, enjekte edilebilir tedavi, multipl skleroz, oral tedavi

Address for Correspondence: Hasan Gökçay, Şarkışla State Hospital, Clinic of Psychiatry, Sivas, Turkey
E-mail: hasangkcy@yahoo.com **ORCID:** orcid.org/0000-0002-5720-1888 **Received:** 28.02.2024 **Accepted:** 06.06.2024

Cite this article as: Gökçay H, Ömerhoca S, Belli H, Yertürk M, Ustabaş KN, Kale İçen N. Evaluation of the Quality of Life and Psychiatric Comorbidities of Oral and Injectable Therapy Users with Multiple Sclerosis. Bagcilar Med Bull. 2024;9(3):156-161

Introduction

Multiple sclerosis (MS) is an autoimmune disorder that is a leading cause of disability, particularly among young adults. MS is increasingly recognized as a disease with modifiable lifestyle components that significantly impair the quality of life (QoL), affecting development and progression (1-3). Since the early 1980s, QoL has been a crucial component of health status, initially defined in chronic diseases and later adapted for specific conditions like MS (4,5). QoL is a crucial outcome in MS that should be measured in clinical trials (6), predicting disability progression (7,8), and should be more widely utilized by clinicians (9), potentially as a primary disease management goal (10).

For many patients with MS, QoL decreases as the condition advances and the burden of psychiatric symptoms increases (11). Psychiatric comorbidity's adverse impact on QoL is well established, yet it is often overlooked or inadequately treated (12). Prior research has demonstrated that both psychological and physical aspects of QoL can be affected by disease progression, disability level, lifestyle choices, socio-economic factors, and the use of disease-modifying therapies (DMTs) (13,14).

Although there is no known cure for MS, the primary treatment goals are prevention of relapses, regaining function post-relapse, and impeding disability progression (15). Various DMTs have been effective in achieving these goals (16). In Turkey, seven oral DMTs have legal approval for MS treatment: Teriflunomide, dimethyl fumarate, fingolimod, monomethyl fumarate, cladribine, siponimod, and ozanimod (teriflunomide, dimethyl fumarate, fingolimod, cladribine) (17). Injectable treatments like glatiramer acetate and interferon β were considered primary medications before oral DMT approval (11). Some patients prefer transitioning from injectable to oral DMTs because of inadequate disease control, side effects, or diminished QoL (11).

Limited research has explored patient-reported QoL and psychiatric symptoms during the switch from injectable to oral medications. Existing studies evaluating the QOL among various DMT users have shown varying results (11). Given inconsistent findings and lack of literature, this study aims to assess the relationship between treatment modalities (injectable vs. oral therapy) and psychiatric symptoms and QOL in individuals with multiple sclerosis.

Materials and Methods

This cross-sectional study included patients diagnosed with multiple sclerosis. Patients diagnosed with MS according to McDonald's 2017 criteria (18) who applied to the Neurology clinic outpatient unit at the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between March 2023 and August 2023 were included. The study groups were as follows: Patients receiving injectable therapy, patients receiving oral DMTs, and healthy controls. Patients aged between 18 and 65 years, literate, and with no treatment changes for at least 1 year will be included in the study. Patients with a history of another neurological disease, such as head trauma that would prevent the interview, mental retardation, dementia, and other neurological diseases that could lead to organic mental disorders, such as epilepsy, using another immunosuppressive drug, and patients with psychiatric diagnosis or treatment were excluded. Healthy controls consisted of individuals aged 18-65 years that were literate and without neurological and psychiatric disease diagnoses and treatment.

Initially, 90 MS patients were included in the study. However, 22 patients were excluded because of irregular medication use, 12 patients because of treatment changes related to unresponsiveness, and 14 patients because of the addition of steroids to their treatment.

Informed consent was obtained verbally and in writing from all participants. We administered the semi-structured socio-demographic and clinical data form, Hamilton depression rating scale (HAM-D), 36-item short form survey (SF-36), Hamilton anxiety rating scale (HAM-A), and headache impact test (HIT-6) to consenting patients participating in the study. Expanded disability status scale (EDSS) scores were calculated during the neurological examination of the patients by a clinician.

Ethical Approval

The research protocol underwent scrutiny and approval from the Scientific Research Ethics Committee of the University of Health Sciences Turkey, Hamidiye Faculty of Medicine (IRB: 30.12.2022-28/1), strictly adhering to the principles outlined in the Declaration of Helsinki.

Measures

The anxiety scale, developed by Beck et al. (19), evaluates the frequency of anxiety symptoms using a 21-item self-assessment scale with scores ranging from 0 to 3. A higher score signifies a greater level of anxiety experienced. A Turkish validity and reliability study for this scale was conducted by Ulusoy et al. in 1996.

The Beck depression scale (BDI) is a self-report instrument that gages emotional, cognitive, somatic, and motivational

states using a Likert-type scale with 21 items. Each question is scored between 0 and 3, and a higher score indicates a more pronounced level of depression. The Turkish validity and reliability study for the BDI was carried out by Teğin in 1987 and Hisli (20).

The SF-36 is a generic instrument that assesses health-related QoL over the past four weeks across eight dimensions: Physical functioning (PF), role physical (RP), bodily pain (P), general health (GH), vitality (V), social functioning (SF), role emotional (RE), and mental health (MH). All items related to each dimension (excluding health transition) are aggregated and transformed into a scale ranging from 0 to 100, where a higher score indicates a better state of health or well-being (21,22).

The six-item headache impact test (HIT-6) offers a comprehensive assessment of adverse headache impact and is designed for both clinical practice and research. It evaluates the impact on social functioning, role functioning, vitality, cognitive functioning, psychological distress, and headache pain severity. The HIT-6 score, ranging from 36 to 78, indicates impact severity, with larger scores indicating greater impact. Severity categories are as follows: Little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78). HIT-6 exhibits excellent internal consistency, test-retest reliability, construct validity, and responsiveness in general headache patients (23).

Statistical Analysis

Statistical analysis was performed using IBM SPSS. Descriptive statistical methods such as mean, standard deviation, frequency, and percentage were used to analyze the study data. The normality of quantitative data was assessed using the Shapiro-Wilk test. Non-normally distributed quantitative variables were compared between groups using the Kruskal-Wallis test, and post-hoc analysis was conducted using the Mann-Whitney U test. The chi-square (χ^2) test was employed to compare qualitative variables across groups. Correlations between parametric variables were assessed using Pearson's test, with statistical significance set at $p<0.05$.

Results

Table 1 compares the socio-demographic and clinical data of the participants in the current study. Grouping of the patients (n=61) according to their current drug regimen indicated that 22 patients were using oral therapy, 19 were using injectable therapy, and 20 were using healthy controls. The average age for oral therapy was 38.95±9.56, injectable therapy was 39.61±10.57, and healthy control was 39.55±11.73. 54.5% of oral therapy, 68.4% of injectable therapy, and 45% of healthy controls were female. No notable statistical distinction was detected across the three groups concerning age and gender ($p>0.05$). The educational level (measured in years) significantly differed, with higher levels observed in the healthy control group compared with both the oral therapy and injectable therapy groups ($p<0.001$). No significant differences were found in marital status, smoking habits, duration of disease, and history of psychiatric disorders among the oral therapy, injectable therapy, and healthy control groups ($p>0.05$). Individuals receiving oral and injectable therapies exhibited a higher frequency of "no/irregular" employment status compared with the healthy control group ($p<0.05$). The average EDSS score of the oral therapy group was 2.17±1.38 and the injectable therapy group was 2.25±1.35, and no statistically significant variation was noted between the groups.

Both HAM-D and HAM-A scores were significantly lower in the healthy control group than in the oral therapy group and the injectable therapy group ($p<0.05$). HIT-6 scores did not show statistically significant differences among the three groups ($p>0.05$). Physical functioning, general health subscales, and SF-36 total scores were significantly higher in the healthy control group than in the oral therapy and injectable therapy group ($p<0.05$). The pain and social functioning subscale scores were notably lower in the injectable therapy group than in the healthy control group, with statistical significance ($p<0.05$).

Table 2 presents the correlation values between socio-demographic and clinical data. HAM-A ($r=-0.607$, $p<0.01$) and HAM-D ($r=-0.560$, $p<0.01$) scores exhibited a negative correlation with SF-36 total scores. Moreover, a negative correlation was noted between the HIT-6 score and the SF-36 total score ($r=-0.313$, $p<0.05$). The correlation data for the SF-36 subscales and other variables can be found in Table 2.

Discussion

Evaluating the QoL in patients with MS has become integral to diagnosis, aiming to minimize its negative impact on daily functioning through treatment (24). Our study contributes to the literature by assessing QoL and psychiatric symptoms in patients receiving both oral and injectable disease-modifying therapy (DMT). Our findings show that the effects of oral and injectable DMT use on QoL

Table 1. Comparative evaluation of socio-demographic and clinical data

All participants (n=61)	Oral therapy (n=22)	Injectable therapy (n=19)	Healthy control (n=20)					
	Mean ± SD/n (%)	Mean ± SD/n (%)	Mean ± SD/n (%)	df/χ^2	p^1	p^2	p^3	p^4
[a]Age	38.95±9.56	39.61±10.57	39.55±11.73	2	0.882			
[a]Education (years)	10.27±4.90	12.11±3.66	16.9±6.52	2	**0.000**			
[b]Gender (female)	12 (54.5)	13 (68.4)	9 (45.0)	2.186	0.335			
[b]Marital status (not married)	8 (36.4)	8 (42.1)	3 (15.0)	3.775	0.151			
[b]Employment (no/ irregular)	13 (59.1)	11 (57.9)	1 (5.0)	16.976	**0.002**	OT>HC, IT>HC		
[b]Smoking (yes)	2 (9.1)	6 (31.6)	8 (40.0)	5.581	0.061			
[b]History of psychiatric disorders (yes)	5 (22.7)	4 (21.1)	1 (5.0)	2.839	0.242			
[a]Duration of disease (years)	8.47±3.98	7.31±5.08	-	1	0.211			
[a]EDSS	2.17±1.38	2.25±1.35	-	1	0.727			
[a]HAM-D	15.27±8.04	11.38±7.45	5.20±5.69	2	**0.000**	0.221	**0.000**	**0.010**
[a]HAM-A	14.00±8.34	13.0±9.24	6.05±5.08	66	**0.003**	0.656	**0.001**	**0.014**
[a]HIT-6	53.68±8.13	54.66±10.08	49.45±8.39	2	0.152			
[a]SF-36 total	491.35±134.14	491.78±149.16	593.98±116.53	2	**0.024**	0.937	**0.018**	**0.018**
[a]Physical functioning	76.81±21.90	75.78±24.79	92.00±12.29	2	**0.006**	1.00	**0.001**	**0.030**
[a]Role limitations due to physical health	62.50±38.38	59.21±37.46	80.00±32.03	2	0.142			
[a]Role limitations due to emotional problems	51.51±39.47	68.42±40.78	73.33±36.83	2	0.125			
[a]Energy/fatigue	51.13±19.87	50.26±23.24	57.25±23.47	2	0.358			
[a]Emotional well-being	57.45±18.20	54.94±21.03	65.40±17.47	2	0.209			
[a]Social functioning	68.18±19.94	64.47±18.75	77.50±18.40	2	**0.043**	0.421	0.096	**0.015**
[a]Pain	72.61±23.97	63.15±23.00	79.50±12.23	2	0.078	0.180	0.460	**0.019**
[a]General health	51.13±16.47	55.52±22.16	69.00±14.47	2	**0.003**	0.377	**0.000**	**0.035**

p^1: Oral therapy vs. injectable therapy vs. healthy control, p^2: Oral therapy vs. injectable therapy, p^3: Oral therapy vs. healthy control, p^4: Injectable therapy vs. healthy control, $p<0.05$ statistically significant (bold values). χ^2: Chi-square, SD: Standard deviation, OT: Oral therapy, IT: Injectable therapy, HC: Healthy control, EDSS: Expanded disability status scale, HAM-D: Hamilton depression rating scale, HAM-A: Hamilton anxiety rating scale, HIT-6: Headache impact test, SF-36: 36-Item short form survey, [a]: Kruskal-Wallis and Mann-Whitney U tests as post-hoc tests were used, [b]: Chi-square test was used. p^3 p^4 Mann-Whitney tests as post-hoc tests were

Table 2. Correlation analysis of socio-demographic data and clinical characteristics

r	Age	Duration of the illness	EDSS	HAM-D	HAM-A	HIT-6
Physical functioning	-0.414**	-0.229	-0.228	-0.149	-0.239	-0.260
Role limitations due to physical health	-0.480**	-0.238	-0.373*	-0.421**	-0.368*	-0.290
Role limitations due to emotional problems	-0.361*	-0.359*	-0.419**	-0.295	-0.399**	-0.032
Energy/fatigue	-0.217	-0.060	-0.112	-0.544**	-0.501**	-0.309
Emotional well-being	-0.030	0.066	-0.185	-0.500**	-0.415**	-0.173
Social functioning	-0.201	-0.008	-0.057	-0.582**	-0.488**	-0.127
Pain	-0.216	-0.244	-0.092	-0.180	-0.586**	-0.306
General health	-0.342*	-0.060	-0.041	-0.538**	-0.379*	-0.305
SF-36 total	-0.446**	-0.248	-0.343*	-0.560**	-0.607**	-0.313*

r: Pearson correlation coefficient, EDSS: Expanded disability status scale, HAM-D: Hamilton depression rating scale, HAM-A: Hamilton anxiety rating scale, HIT-6: Headache impact test, SF-36: 36-Item short form survey, *: The correlation is significant (two-tailed) at the 0.05 level, **: Correlation is significant at the 0.01 level (two-tailed)

and psychiatric symptoms are similar. Moreover, although the patients were under treatment, they had poor QoL and more psychiatric symptoms than the healthy control group.

Clinical outcomes in MS result from a complex interplay of immune-mediated inflammation and neurodegeneration (25). Inflammatory demyelinating lesions in the CNS's white matter are the recognized hallmark, leading to symptomatic relapses. While these white matter lesions are well identified, it is increasingly acknowledged that gray matter lesions, though harder to detect with magnetic resonance imaging, may be more extensive (25). Moreover, gray matter plays a pivotal role in enabling normal daily functioning in humans (26). However, current disease-modifying treatments have primarily been assessed on the basis of their impact on white matter lesions and licensed for their effect on relapses (25). In our study, we found that depression and anxiety scores were higher in patients with MS than in healthy controls, regardless of the treatment modality. Perhaps this is because DMTs have more pronounced effects on white matter lesions than on gray matter lesions, regardless of the route of administration.

In our study, no notable differences were found in both QoL and clinician-reported disability status between patients using oral and injectable DMTs. Previous studies comparing QoL among users of injectable and oral DMTs, as well as those switching between them, have shown conflicting results (27-31). In agreement with our findings, Stuchiner et al. (11) observed no significant differences in the impact of transitioning to oral disease-modifying therapies on patient QoL. For instance, the evaluate patient outcomes trial found improved outcomes when patients switched from injectable to oral DMT fingolimod, including enhanced QoL and reduced fatigue and depression (29-31). In contrast, a study on patients switching to teriflunomide found sustained stable QoL. In another study comparing the QoL among relapsing MS patients using different DMTs, no significant differences were noted between users of fingolimod, interferon β-1b, and natalizumab (27).

Major depressive disorder and anxiety disorders are frequently found in individuals with MS and are linked to decreased treatment adherence, poorer functional status, and lower QoL (32). In our study, we found that depression and anxiety scores were higher in patients with MS than in healthy controls, regardless of the treatment modality. Moreover, we observed that the presence of both anxiety and depression symptoms is related to poor QoL in MS patients. While depression in MS has been extensively studied, anxiety disorders have received less attention (32). Studies using self-report scales indicate a point prevalence of clinically significant anxiety in MS ranging from 25% to 41% (33,34). Anxiety symptoms had a more pronounced negative impact on the QoL subparameters than depression symptoms in our study.

Study Limitations

Our study had several limitations. Although we grouped drugs by the type of use, we did not consider potential effects based on their pharmacological properties and doses. In addition, we did not evaluate MS severity. The cross-sectional design and limited number of participants restrict the generalizability of our study's results.

Conclusion

The approval of new oral drugs for MS offers benefits and more convenient administration routes. However, concerns arise because of the lack of long-term efficacy data and the potential for several adverse events. Oral DMT use may not be superior to injectable DMT use in terms of QoL, disability, and psychiatric symptoms. Moreover, despite effective treatments, psychiatric disorders in MS are under-detected and under-treated. Hence, determining the optimal treatment for each patient requires comprehensive assessments of safety, efficacy, monitoring needs, tolerability, and cost-effectiveness.

Ethics

Ethics Committee Approval: The research protocol underwent scrutiny and approval from the Scientific Research Ethics Committee of the University of Health Sciences Turkey, Hamidiye Faculty of Medicine (IRB: 30.12.2022-28/1), strictly adhering to the principles outlined in the Declaration of Helsinki.

Informed Consent: Informed consent was obtained verbally and in writing from all participants.

Authorship Contributions

Concept: H.G., S.Ö., H.B., K.N.U., Design: H.G., S.Ö., H.B., K.N.U., Data Collection or Processing: H.G., S.Ö., H.B., M.Y., K.N.U., N.K.İ., Analysis or Interpretation: H.G., S.Ö., H.B., M.Y., K.N.U., N.K.İ., Literature Search: H.G., S.Ö., M.Y., K.N.U., Writing: H.G., S.Ö., H.B., M.Y., K.N.U., N.K.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Grant WB, Riise T. Multiple sclerosis: A lifestyle disease? Neurology. 2016;86(14):1275-1276.
2. Ford HL, Gerry E, Johnson MH, Tennant A. Health status and quality of life of people with multiple sclerosis. Disabil Rehabil. 2001;23(12):516-521.
3. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. Mult Scler. 2000;6(2):91-98.
4. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-629.
5. Kaplan RM, Ganiats TG, Sieber WJ, Anderson JP. The Quality of Well-Being Scale: Critical similarities and differences with SF-36. International Journal for Quality in Health Care. 1998;10(6):509-520.
6. Rudick RA, Miller DM. Health-related quality of life in multiple sclerosis: current evidence, measurement and effects of disease severity and treatment. CNS Drugs. 2008;22(10):827-839.
7. Baumstarck K, Pelletier J, Butzkueven H, Fernández O, Flachenecker P, Idiman E, et al. Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. Eur J Neurol. 2013;20(6):907-e979.
8. Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the Quality of Life in Patients with Multiple Sclerosis in Clinical Practice: A Necessary Challenge. Mult Scler Int. 2013;2013:1-8.
9. Rieckmann P, Boyko A, Centonze D, Elovaara I, Giovannoni G, Havrdová E, et al. Achieving patient engagement in multiple sclerosis: A perspective from the multiple sclerosis in the 21st Century Steering Group. Mult Scler Relat Disord. 2015;4(3):202-218.
10. Lysandropoulos AP, Havrdova E. "Hidden" factors influencing quality of life in patients with multiple sclerosis. Eur J Neurol. 2015;22(Suppl 2):28-33.
11. Stuchiner T, Lucas L, Baraban E, Spinelli KJ, Chen C, Smith A, et al. Quality of life among injectable and oral disease-modifying therapy users in the Pacific Northwest Multiple Sclerosis Registry. BMC Neurol. 2020;20(1).
12. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. Nat Rev Neurol. 2014;10(9):507-517.
13. Jelinek GA, De Livera AM, Marck CH, Brown CR, Neate SL, Taylor KL, et al. Lifestyle, medication and socio-demographic determinants of mental and physical health-related quality of life in people with multiple sclerosis. BMC Neurol. 2016;16(1).
14. Janzen W, Turpin KVL, Warren SA, Marrie RA, Warren KG. Change in the Health-Related Quality of Life of Multiple Sclerosis Patients over 5 Years. Int J MS Care. 2013;15(1):46-53.
15. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359(9313):1221-1231.
16. Martinelli Boneschi F, Vacchi L, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. Cochrane Database Syst Rev. 2013;2013(5).
17. Sosyal Güvenlik Kurumu. Erişim Adresi: https://www.sgk.gov.tr/Duyuru/Detay/20231-Donem-Ilac-Geri-Odeme-Komisyonu-Kararlarina-Istinaden-Bedeli-Odenecek-Ilaclar-Listesinde-Yapilan-Duzenlemeler-Hakkinda-Duyuru-2023-08-11-11-36-24
18. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173.
19. Beck AT, Epstei N, Brow G, Steer R. Beck anxiety inventory. J Consult Clin Psychol. 1993.
20. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi. 1989;7(23):3-13.
21. Hobart J, Freeman J, Lamping D, Fitzpatrick R, Thompson A. The SF-36 in multiple sclerosis: why basic assumptions must be tested. J Neurol Neurosurg Psychiatry. 2001;71(3):363.
22. McHorney CA, Ware JE, Rachel Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32(1):40-66.
23. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: The HIT-6TM. Quality of Life Research. 2003;12(8):963-974.
24. Brola W, Sobolewski P, Fudala M, Flaga S, Jantarski K, Ryglewicz D, et al. Self-reported quality of life in multiple sclerosis patients: preliminary results based on the Polish MS Registry. Patient Prefer Adherence. 2016;10:1647.
25. Chard D, Trip A, Chataway J. New oral drugs for the treatment of multiple sclerosis. Br J Hosp Med (Lond). 2016;77(9):502-503.
26. Dolz J, Desrosiers C, Wang L, Yuan J, Shen D, Ben Ayed I. Deep CNN ensembles and suggestive annotations for infant brain MRI segmentation. Comput Med Imaging Graph. 2020;79.
27. Yahya RN, Kasim AA, Al Gawwam GA. Comparing the Quality of Life among Patients with Relapsing Remitting Multiple Sclerosis in Iraq Using Different Disease Modifying Therapies. Iraqi Journal of Pharmaceutical Sciences. 2018;27(2):102-114.
28. Hunter SF, Agius M, Miller DM, Cutter G, Barbato L, McCague K, et al. Impact of a switch to fingolimod on depressive symptoms in patients with relapsing multiple sclerosis: An analysis from the EPOC (Evaluate Patient OutComes) trial. J Neurol Sci. 2016;365:190-198.
29. Fox E, Edwards K, Burch G, Wynn DR, Laganke C, Crayton H, et al. Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. Mult Scler Relat Disord. 2014;3(5):607-619.
30. Coyle PK, Khatri B, Edwards KR, Meca-Lallana JE, Cavalier S, Rufi P, et al. Patient-reported outcomes in patients with relapsing forms of MS switching to teriflunomide from other disease-modifying therapies: Results from the global Phase 4 Teri-PRO study in routine clinical practice. Mult Scler Relat Disord. 2018;26:211-218.
31. Calkwood J, Cree B, Crayton H, Kantor D, Steingo B, Barbato L, et al. Impact of a switch to fingolimod versus staying on glatiramer acetate or beta interferons on patient- and physician-reported outcomes in relapsing multiple sclerosis: post hoc analyses of the EPOC trial. BMC Neurol. 2014;14(1).
32. Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. Psychiatr Clin North Am. 2007;30(4):803-817.
33. Janssens ACJW, Van Doorn PA, De Boer JB, Kalkers NF, Van Der Merché FGA, Passchier J, et al. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. Mult Scler. 2003;9(4):397-403.
34. Zorzon M, De Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G, et al. Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. J Neurol. 2001;248(5):416-421.