Factors Affecting the Adherence to Disease-Modifying Therapy in Patients With Multiple Sclerosis

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ABSTRACT

Background: Adherence to medication treatment in patients with multiple sclerosis (MS) is important to increase its effectiveness, reduce patient disability, prevent attacks, and increase the quality of life. **Aim:** This study investigated factors that influence adherence to disease-modifying therapy in patients with MS. **Methods:** This descriptive study was conducted with 198 patients with MS who met the inclusion criteria and agreed to participate between July 2016 and February 2017. Data were collected using an Individual Identification Form that included sociodemographic characteristics, the Multiple Sclerosis Treatment Adherence Questionnaire, the Fatigue Severity Scale, the Self-Efficacy Scale, and the Brief COPE. **Results:** We found that 59.6% of the patients were adherent to therapy. Patients were significantly more adherent to Avonex than other treatments, and ''memory problems'' was the most common reason for missing or forgetting medication in nonadherent patients. There was a significant difference between medication adherence and some sociodemographic characteristics and disease characteristics ($P < .05$). There was no significant difference between coping attitudes, fatigue, and self-efficacy level and medication adherence ($P > .05$). **Conclusion:** Patients' adherence to medication treatment was low and may be associated with social, physical, and cognitive measures.

Keywords: coping, fatigue, medication adherence, multiple sclerosis, nursing, self-efficacy

Multiple sclerosis (MS) is a chronic, progressive, and disabling inflammatory disorder of the central nervous system that targets the myelin sheaths around nerves, leading to inflammation, myelin loss, and axonal destruction.[1] The MS patient prevalence is between 1 and 2.5 million worldwide with approximately 400 000 in the United States. Multiple sclerosis occurs twice as frequently in women and most commonly between the ages of 20 and 50 years.[1] The number of studies on the prevalence of MS in Turkey is insufficient; however, it is thought to affect 34 to 101 per 100 000 people.[2]

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Just as no certainty exists as to the cause of MS, no definite treatment exists for it.[3] The medications used to treat the signs and symptoms of the disease do not produce a cure but can substantially improve symptoms, decrease disability progression, and improve quality of life. Recurrences are controlled by disease-modifying therapy (DMT) including the first-line treatments with interferon β-1a (Avonex and Rebif), interferon β-1b (Betaferon and Extavia), and glatiramer acetate (Copaxone). Early treatment using DMT reduces recurrence frequency, disabilities' progression, and hospitalization frequency.[3]

Adherence, as used in chronic disorders, was defined by the World Health Organization as the extent to which a person's behavior with respect to taking medication, following a diet, and/or executing lifestyle changes corresponds with recommendations from a healthcare provider.[4] Medication adherence is required for patients to benefit fully from the treatment. Nonadherence or poor medication adherence may lead to unsuccessful treatments and increased costs.[5] Patients receiving DMT have nonadherence rates of 6% to 46%, and patients are most likely to quit therapy in the first 6 months.[3]

Many factors contribute to medication nonadherence in patients with MS. A study of 157 patients who missed at least 1 injection during overall DMT duration showed that patients' main reasons for missed injections were as follows: had to travel abroad (33.1%),

forgetfulness (26.1%), and adverse effects (25.5%).[6] Although no criterion standard exists, the 3 main assessment methods for medication adherence are patient self-reports, other people's reports, and clinical observations.[7] Nonadherence to medication is imprecisely defined, ranging from less than 80% or 90% of the prescribed doses to missing even a single dose.[8]

Poor adherence to MS medication has negative outcomes. Long interruptions in MS medication increase the recurrence risk. Nonadherence or poor adherence is widely observed in MS as in other chronic diseases; therefore, improving adherence should be a significant treatment objective. The purpose of this study was to examine adherence to DMT in patients with MS and potential factors that could influence it. We were also interested in attitudes such as coping, fatigue, and self-efficacy that patients have regarding the disease and treatment and their possible connection with adherence.

Materials and Methods

This is a descriptive and cross-sectional study. This study was conducted in the MS clinic of the Faculty of Medicine, Department of Neurology of a university in Izmir, Turkey, between July 2016 and February 2017. The sample consisted of 198 patients with MS 18 years and older followed at the clinic who agreed to participate, received DMT for at least 1 month, had their last seizure at least 30 days ago, had an Expanded Disability Status Scale score of 6.5 or less as assessed by a neurologist, and could read, speak, and write in Turkish. The data were collected through face-to-face interviews using an Individual Identification Form, Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ), Fatigue Severity Scale (FSS), Self-Efficacy Scale, and Brief COPE.

An Individual Identification Form was developed based on previous research[3,4,9,13,15–17] and included questions about the patients' sociodemographic and disease-related characteristics. The MS-TAQ was used to assess DMT adherence and treatment obstacles in patients with MS.[9] It evaluates situations hindering patients from disease and treatment adherence through self-reports to minimize adverse effects and develop coping strategies. Wicks et al[9] also assessed missed doses using the missing dose rate (MDR) formula, where the missed or missed dose number is divided into the total dose number that should be taken in 1 month (accepted as 28 days). The questionnaire has 3 subscales: DMT-Barriers, DMT-Side Effects, and DMT-Coping Strategies. Reliability of the tool was supported in a study by Wicks et al[9] with a Cronbach's α of .86. In this study,

> Married patients with children showed statistically lower treatment adherence levels.

the instrument was given to 10 patients with MS, who were eligible for the study but not part of the study subjects, and its reliability was supported at a Cronbach's α of .83.

The FSS has 9 items. Each question is scored using a Likert-type scale that, for each question, the patient is asked to choose a number from 1 to 7 that indicates how much the patient agrees with each statement, where 1 indicates strong disagreement and 7 indicates strong agreement. A score of 4 or higher generally indicates severe fatigue.[10] Armutlu et al[10] examined validity and reliability in Turkey with a Cronbach's α of .94.[10]

The Self-Efficacy Scale was adapted to Turkish in 1999 with a Cronbach's α of .81.[11] It is a 5-point Likert-type self-report scale with 23 items where 1 means "does not describe me at all" and 5 means "describes me very well." The minimum and maximum total scores are 23 and 155, respectively. The scale has 4 subscales. Higher total scores indicate higher levels of self-efficacy perception. The long form of the Brief COPE was developed in 1989.[12] The short form includes 14 factors with 2 items each. The Likert-type scale is scored from 1 ("I never do this") to 4 ("I mostly do this"). Each subscale is assessed separately for both forms. A high score on each subscale indicates more use of that particular coping strategy, and a low score indicates less use of that coping strategy. The short form translated into Turkish has a Cronbach's α coefficient of subscales that ranged from .39 (restraint coping) to .92 (humor).[12]

Permission to use the MS-TAQ and other scales was obtained from the authors. Ethical approval from the ethics committee of the university and written permission from the university medical faculty hospital were received. Patients who met the inclusion criteria were informed of the purpose of the research and invited to take part as volunteers by the researchers. Statistical analysis was performed using SPSS for Windows version 21.0. Normality of distribution was tested using Kolmogorov-Smirnov test. Because all the statistics were not normally distributed, we used nonparametric tests for further analysis. Group comparisons were examined using Mann-Whitney U test for 2 independent samples with ordinal and interval

variables and with χ^2 test for nominal variables. Statistical significance was set at $P < .05$.

Results

The patient mean age was 44 ± 2.4 years, 77.8% were female, 40.4% completed primary school, and 72.2% were married with children (Table 1). Married patients with children showed statistically lower treatment adherence levels ($P < .05$; Table 2). No relationship was found between the other sociodemographic characteristics and medication adherence ($P > .05$).

Disease-Related Characteristics and Medication Adherence

Of the participants, 83.8% had been diagnosed more than 10 years ago, 93.4% had relapsing-remitting MS, and 35.4% received Copaxone treatment (Table 1). Adherent patients were significantly more likely to have another chronic disease, report being forgetful, and be more satisfied with the treatment (Table 2). Patients showed the highest and lowest adherence to Avonex and Betaferon, respectively. Adherence and medications showed no significant association ($P = .131$) (Table 2). No relationship was found between the other disease-related characteristics and medication adherence ($P > .05$).

According to MDR scores, 59.6% of the patients were adherent to their medication. The patients who did not miss or forget their medication were considered adherent (MDR = 0), whereas those who missed or forgot at least once were considered nonadherent (MDR > 0). The most common reason for nonadherence was "memory problems" (Supplemental Digital Content 1, available at http://links.lww.com/JNN/A136).

Medication Adherence, Fatigue, Self-Efficacy, and Coping

The mean FSS score was 4.74 for adherent and 5.17 for nonadherent patients, both of which higher than 4. Among the patients with FSS scores of 4 or greater, 70.4% of the adherent patients and 81.3% of the nonadherent patients reported fatigue. Medication adherence or nonadherence did not differ by the patients' FSS score ($P = .06$). The mean score on the Self-Efficacy Scale was 91.0 for adherent and 89.2 for nonadherent patients. No significant difference was found between the mean self-efficacy score and medication adherence ($P = .25$). Adherent and nonadherent patients obtained similar mean scores on the Brief COPE inventory. No significant difference was found between the mean Brief COPE score and medication adherence ($P = .74$) (Supplemental Digital Content 2, available at http://links.lww.com/JNN/A137).

TABLE 1. Patient Demographic and Disease Characteristics (N= 198)

Gender, %	Age, M (SD)	Marital Status, %	Having Children, %	Education, %	Disease Type,%	DMT Type, %	Disease Duration, %	Forgetfulness Problem, %	Having Another Chronic Disease, %	Satisfied With Treatment, %
Male: 22.2;	44	Married: 72.2	Yes: 74.7	Primary: 40.4	RRMS: 93.4	Copaxone: 35.4	>10 years: 83.8	Yes: 58.6	Yes: 6.6	Not satisfied at all: 2.5
Female:77.8	(2.4)	Single: 27.8	No: 25.3	High: 29.8	SPMS: 6.6	Avonex: 10.6	<10 years: 16.2	No: 41.4	No: 93.4	A little satisfied: 4.0
				University: 29.8		Rebif: 25.8				Moderately satisfied: 17.7
						Betaferon: 28.3				Very satisfied: 56.6
										Completely satisfied: 19.2

Abbreviations: DMT, diseasemodifying treatment; M, mean; RRMS, relapsing-remitting multiple sclerosis; SD, standarddeviation; SPMS, secondary progressive multiple sclerosis.

TABLE 2. Differences in Demographic and Disease Variables Between Adherent and Nonadherent Groups

	Nonadherent (N=80)	Adherent (N=118)	Testing Differences	
	%	%	χ^2	*p*
Sex				
Woman	39.6	60.4	0.181	0.670
Man	43.2	56.8		
Age				
18–40 years old	41.9	58.1	0.259	0.611
41–65 years old	38.3	61.7		
Marital status				
Married	45.8	54.2	6.317	0.010
Single	26.8	73.2		
Having children				
Yes	46.6	53.4	9.409	0.000
No	22.0	78.0		
Education				
Primary	37.5	62.5		
High	30.0	61.0	1.033	0.597
University	45.8	54.2		
Disease type				
RMS	41.1	58.9	0.536	0.464
SPMS	30.8	69.2		
DMT type				
Copaxone	38.6	61.4		
Avonex	28.6	71.4	43.188	0.131
Rebif	35.3	64.7		
Betaferon	51.8	48.2		
Disease duration				
>10 years	38.6	61.4	1.460	0.227
<10 years	50.0	50.0		
Forgetfulness problem				
Having	48.3	51.7	7.208	0.007
Not having	29.3	70.7		
Having another chronic disease				
Yes	84.6	15.4	11.294	0.001
No	37.3	62.7		
Satisfied with treatment				
Not satisfied	20.0	80.0		
A little satisfied	37.5	62.5		
Moderately satisfied	62.9	37.1	15.960	0.003
Very satisfied	42.0	58.0		
Completely satisfied	18.4	81.6		

Abbreviations: DMT, disease modifying treatment; *p*, signifiance value; ^{2}, Chi square test.

Discussion

Overall, our study show a high self-reported non-adherence rate (40.4%). Other studies using self-report measures and the same a criterion (missing 1 or more injections) show similar rates of nonadherence—around 18.5%,[3] 24.9%,[13] 17.6%,[14] 35.3%,[6] and between 16% and 51%.[8] Our study showed that medication adherence had a significant relationship with the patients' marital status ($P < .05$), but not with the other sociodemographic characteristics ($P > .05$). Married patients and patients with children showed increased nonadherence to medication. However, some studies reported that married patients had higher medication adherence than single patients because they received help/support from their spouses.[15] In this study, the significant difference between the adherent and nonadherent patients may have arisen because married patients had more responsibilities than single patients. Besides, cultural differences between countries may cause these different results. Similar studies found no significant relationship between medication adherence and sociodemographic characteristics, particularly marital status.[6,9,13,14]

Our results also show that patients on Avonex were significantly more adherent than patients on other DMTs. The same was also found in other studies.[3,13,16] There is no general agreement up to date on whether the type of DMT actually influences adherence. We believe that the results show this difference in adherence due to different frequencies of DMT administration. Avonex is taken only once weekly, whereas other therapies are taken more often. Patients on Avonex therefore had to take the therapy only 4 times to be adherent, which is 3 to 7 times less often than patients on other DMTs. Therefore, adherence could be higher in patients on Avonex because they had to take the medication less often.

Medication adherence was significantly related to comorbid chronic disease and satisfaction with the treatment ($P < .05$). Most patients contract complex chronic diseases requiring long-term treatment late in adulthood. Patients may have difficulty maintaining treatment because of complicated treatment regimens and therefore show poor adherence.[17,18] The lower adherence levels by those who had another chronic disease may be because occupation and loads increase as the treatment becomes more complex. Although patient satisfaction is a treatment adherence indicator, it also affects decisions about health, behaviors regarding the treatment, and treatment results, and generally, adherent patients are highly satisfied.[19] These results indicate a significant relationship between patients' medication adherence and satisfaction levels; adherent patients were more satisfied with treatment than nonadherent patients ($P < .05$).

In most studies, patients with MS report fatigue.[4,20,21] Donze et al[22] indicated that fatigue (57%) is among the top 3 reasons for discontinuing treatment of patients with MS. Of the patients with an FSS mean score of 4 or greater, 81.3% of the nonadherent patients and 70.4% of the adherent patients reported fatigue. This may be due to the high possibility of MS-induced fatigue, independent from adherence.

Most patients with MS experience some disabilities at late disease stages, which negatively affect their independence. Disability negatively affects patients' self-efficacy.[23] Self-efficacy is a psychological term meaning individuals' self-confidence to complete tasks and achieve objectives. Low self-efficacy is associated with less physical activity, lower adherence, and lower quality of life.[23] Self-efficacy plays an important role in maintaining patient functions. It is a significant indicator of medication adherence.[24] In this study, both adherent and nonadherent patients obtained high mean Self-Efficacy Scale scores. Thus, patients had high self-efficacy, which was statistically independent from their medication adherence.

Patients with MS may have difficulty adapting to their disease because of DMT. Patients' coping attitudes play an important role in controlling this situation. Existence of one or more coping styles may shape patients' adaptation to medication.[25] In this study, patients obtained the highest mean Brief COPE scores on the Using Instrumental Social Support, Focusing on and Venting of Emotions, Acceptance, Turning to Religion, Positive Reinterpretation, and Planning subscales, indicating that patients used these coping methods more than others. Zengin et al[26] analyzed the coping styles of patients with MS and found that they used the Planning, Focusing on and Venting of Emotions, and Using Instrumental Social Support methods the most. In our study, the adherent and nonadherent patients' mean scores on the subscales and the entire scale were similar (adherent patients, 69.08; nonadherent patients, 69.41). No significant difference for the mean scores on the Brief COPE and its 13 subscales (except for the Substance Use) was found with medication adherence ($P > .05$). Questions 12 and 19 in the Substance Use subscale examined whether the patients used alcohol or tranquillizers to forget or think less about a problem. This significance may have arisen from the higher level of positive answers and higher scores of the nonadherent patients.

Finally, we looked at the reasons for nonadherence. The most common self-reported reasons for missing an injection were "memory problems" and "away from home and could not access medication." The third most common reason was "side effects of injection." These results are similar from the previous studies where patients reported memory problems as the most

common reason for missing injections.[4,9,14,27,28] Because MS patients with cognitive impairments are less likely to be adherent, it is logical that the most likely reason for nonadherence is forgetting to administer treatment. Patients with cognitive impairments may also forget to rotate their injection site, making them more vulnerable to injection site reactions.

The reasons of nonadherence in MS are complex but can be addressed through interventions. The goals of the healthcare professional could be to motivate the patient to take the medication correctly, to adhere to the prescribed schedule, and to keep follow-up appointments. Other support strategies might include sending reminders, providing information that the patient can consult after the appointment, helping the patient understand the importance of adherence, listening to individual concerns, and offering praise and encouragement.[29] Remington et al[30] provide a thorough list of interventions needed to improve for adherence in MS. In addition, some studies have reported an association between improved adherence and nurse-based telephone counseling and motivational interviewing.[31,32]

Conclusion

Multiple sclerosis is a complex disease primarily managed by parenterally administered DMTs. Adherence to injectable MS therapies needs to be addressed from the time of diagnosis throughout the disease. Access to and communication with healthcare providers are key elements in the promotion of adherence. This study shows that social, physical, and cognitive factors affect low medication adherence by patients with MS. Healthcare professionals, particularly nurses, should be sensitive to the patients' status and aware of the situations hindering treatment adherence to support the patients. The unique position of nurses presents a valuable opportunity for helping patients develop practices and behaviors that facilitate adherence. A considerable patient population with MS in Turkey exists, and medication adherence is important to increase treatment effectiveness, reduce disability rates, prevent attacks, and increase quality of life. This study will help health professionals identify factors affecting medication adherence of patients with MS and determine appropriate patient strategies.

Acknowledgments

References

1. Higuera L, Carlin CS, Anderson S. Adherence to disease-modifying therapies for multiple sclerosis. *J Manag Care Spec Pharm*. 2016;22(12):1394–1401.

2. Heydarpour P, Khoshkish S, Abtahi S, Moradi-Lakeh M, Sahraian MA. Multiple sclerosis epidemiology in Middle East and North Africa: a systematic review and meta-analysis. *Neuroepidemiology*. 2015;44(4):232–244.

3. Ozura A, Kocav L, Sega S. Adherence to disease-modifying therapies and attitudes regarding disease in patients with multiple sclerosis. *Clin Neurol Neurosurg*. 2013;115(1):6–11.

4. Camara NAAC, Gondim APS. Factors associated with adherence to immunomodulator treatment in people with multiple sclerosis. *Braz J Pharm Sci*. 2017;53(1):e16132.

5. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1):e016982.

6. 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;13:107–111.

7. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *Int J Clin Pharm*. 2014;36(1):55–69.

8. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int*. 2015;2015:217047.

9. Wicks P, Massagli M, Kulkarni A, Dastani H. Use of an online community to develop patient-reported outcome instruments: the multiple sclerosis treatment adherence questionnaire (MS-TAQ). *J Med Internet Res*. 2011;13(1):e1–e12.

10. Armutlu K, Korkmaz NC, Keser I, et al. The validity and reliability of the fatigue severity scale in Turkish multiple sclerosis patients. *Int J Rehabil Res*. 2007;30(1):81–85.

11. Yildirim F, Ilhan IO. The validity and reliability of the general self-efficacy scale-Turkish form. *Turk Psikiyatri Derg*. 2010;21(4):301–308.

12. Bacanlı H, Sürücü M, İlhan T. An investigation of psychometric properties of coping styles scale brief form: a study of validity and reliability. *Educ Sci Theory Pract*. 2013;13(1):90–96.

13. Köşkderelioğlu A, Gedizlioğlu M, Ortan P, Öcek Ö. Evaluation of the adherence to immunmodulatory treatment in patients with multiple sclerosis. *Arch Neuropsychiatr*. 2015;52(4):376–379.

14. Arroyo E, Grau C, Ramo-Tello C, Parra J, Sanchez-Solino O. 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(2):59–67.

15. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269–286.

16. Arroyo E, Grau C, Ramo C, Parra J, Sánchez-Soliño O. Global adherence project to disease-modifying therapies in patients with relapsing multiple sclerosis: 2-year interim results. *Neurologia*. 2010;25(7):435–442.

17. Tavares NU, Bertoldi AD, Mengue SS, et al. Factors associated with low adherence to medicine treatment for chronic diseases in Brazil. *Rev Saúde Pública*. 2016;50(2):10s.

18. Rafii F, Fatemi NS, Danielson E, Johansson MC, Modanloo M. Compliance to treatment inpatients with chronic illness: a concept exploration. *Iran J Nurs Midwifery Res*. 2014;19(2):159–167.

19. Becker V, Heeschen V, Schuh K, Schieb H, Ziemssen T. Patient satisfaction and healthcare services in specialized multiple sclerosis centres in Germany. *Ther Adv Neurol Disord*. 2018;11:1–12.

20. Coyle PK, Cohen BA, Leist T, et al. Therapy optimization in multiple sclerosis: a prospective observational study of therapy compliance and outcomes. *BMC Neurol*. 2014;14:49.

21. Nagaraj K, Taly AB, Gupta A, Prasad C, Christopher R. Prevalence of fatigue in patients with multiple sclerosis and its effect on the quality of life. *J Neurosci Rural Pract*. 2013; 4(3):278–282.

22. Donze C, Malapel L, Kwiatkowski A, et al. Treatment discontinuation in multiple sclerosis: the French Web-based survey ALLIANCE. *Mult Scler J Exp Transl Clin*. 2015;1:1–10.

23. Jongen PJ, Ruimschotel R, Heerings M, et al. Improved self-efficacy in persons with relapsing remitting multiple sclerosis after an intensive social cognitive wellness program with participation of support partners: a 6-months observational study. *Health Qual Life Outcomes*. 2014;12:40.

24. Munsell M, Frean M, Menzin J, Philips 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*. 2017;11:55–62.

25. Milanlioglu A, Ozdemir PG, Cilingir V, et al. Coping strategies and mood profiles in patients with multiple sclerosis. *Arq Neuropsiquiatr*. 2014;72(7):490–495.

26. Zengin O, Erbay E, Yildirim B, Altındag O. Quality of life, coping, and social support in patients with multiple sclerosis: a pilot study. *Turk J Neurol* 2017;23:211–218.

27. Di Battista G, Bertolotto A, Gasperini C, Ghezzi A, Maimone D, Solaro C. Multiple sclerosis state of the art (SMART): a qualitative and quantitative analysis of therapy's adherence, hospital reliability's perception, and services provided quality. *Mult Scler Int*. 2014;2014:752318.

28. Saiz A, Mora S, Blanco J. Therapeutic compliance of first line disease-modifying therapies in patients with multiple sclerosis. COMPLIANCE Study. *Neurologia*. 2015;30(4):214–222.

29. Rieckmann P, Boyko A, Centonze D, Elovaara I, Giovannoni G, Havrdová E. 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.

30. Remington G, Rodriguez Y, Logan D, Williamson C, Treadaway K. Facilitating medication adherence in patients with multiple sclerosis. *Int J MS Care*. 2013;15(1):36–45.

31. Schapiro RT. Adherence to interferon beta-1b: BETA Nurse Program. *Int J MS Care*. 2004;6:66.

32. Bombardier CH, Cunniffe M, Wadhwani R, Gibbons LE, Blake KD, Kraft GH. The efficacy of telephone counseling for health promotion in people with multiple sclerosis: a randomized controlled trial. *Arch Phys Med Rehabil*. 2008;89(10): 1849–1856.