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The Rate and Causes of Non-Adherence to Disease Modifying Therapy among Patients with Relapsing Multiple Sclerosis Recorded in Sulaymani City Multiple Sclerosis Clinic

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Maysam Majeed Hama Murad 1 **Sarwer Jamal Al-Bajalan 2**

Abstract

Background: Multiple sclerosis (MS) is a chronic, inflammatory progressive demyelinating disease of the central nervous system. MS is one of the main causes of disability among young adults, and its management is a serious challenge for the healthcare system. And it is a debilitating disease that can partly be controlled with long-term use of disease-modifying therapy (DMT). Adherence of treatment in MS is essential for the benefits of therapies. However, although neurologists are aware of the consequences of non-adherence, they generally spend limited time discussing the importance of treatment adherence with their patients. Treatment for MS focuses on disease management to prevent and treat relapses, manage symptoms, and slow disease progression.

Objective: The aim of this study is to find out the rate and causes of non-adherence to disease modifying therapy (DMT) in relapsing multiple sclerosis patients recorded in Sulaimani city multiple sclerosis clinic.

Methods: cross-sectional study was conducted, in which about 350 MS patients with relapsing MS recorded in Sulaimani Shar teaching hospital Multiple Sclerosis clinic and 124 patients have been interviewed and evaluated by questionnaires regarding demoFigureic (age, sex, occupation and etc.), clinical data (type of DMT, duration of illness, side effects, missed injection, clinical course of patients, disease progression, missing dose and etc.), causes and barriers of non-adherence to treatment. During the interviews the questionnaire was filled out by the researcher. Data analyzed was performed using SPSS software version 22.0 and P- value.

Result: The mean age was 36.8±9.89 years. The majority of the gender was female (66.1%) and 64.5% of participant were married. The of the total respondents using (Betaferon) (41.1%). there were statistically significant differences between adherent and non-adherent group in type of DMT. However, patients taking (Betaferon) are more belonged to non-adherent group. The main cause for non-compliance was memory problem. The overall adherence was 72.5% according to the first criterion (missed $1 injection

1 University of Sulaimani / Faculty of Medical Sciences / School of Medicine

2 Neurologist / Lecturer at University of Sulaimani / Faculty of Medical Sciences / School of Medicine.

or tablet). The degree of adherence among MS patients treated with immunomodulatory drugs are high; however, some patients do not take medications regularly.
Conclusion: The adherence rate is acceptable. It is widely known that treatment satisfaction is related to adherence. In our study, patients' level of satisfaction was higher with oral treat¬ments. However, oral administration showed a greater lack of adherence. The main cause of lack of adherence was memory problem. In relation to other variables, Side effects of medication, Fear of needles and Tired of taking my medication showed a positive correlation with treatment adherence.
Key words: Multiple Sclerosis, Disease Modifying Therapy, Sulaimani, Shar Teaching Hospital

Introduction:

Multiple sclerosis (MS) is a chronic, progressive and disabling inflammatory disorder of the central nervous system and its treatment includes the continuous use of medications, especially immunomodulators (IM). Given that, adherence to treatment is essential to maximize the benefits of the therapy. (Antonia Corso Camara & Soares Gondim, 2017)

Multiple sclerosis (MS) affects approximately 2.5 million people worldwide and is the most common cause of neurological disability among young adults. Inflammation and demyelination of the CNS are the hallmarks of the disease, with the most common clinical course being acute inflammatory episodes superimposed on a background of progressive disability and impairment. (Woods, 2009)

The estimated prevalence of MS in Europe over the past three decades is 83 cases per 100,000 people, with higher rates in northern countries, and the mean annual incidence is 4.3 per 100,000 people. The number of MS patients worldwide exceeds 2.3 million of who approximately 600,000 live in Europe. (Brola et al., 2016).In Poland, on the basis of cohort studies, it is estimated that the prevalence rate is 149.8/100,000 for women and 66.5/100,000 for men (109/100,000 for the entire population). (Marrie et al., 2015)

The first symptoms of the disease typically appear in young adults between 20 and 40 years of age; these are mainly visual disturbances and difficulties in movement. (Sintzel et al., 2018).Due to the physical consequences of the disease, MS is one of the main causes of disability among young adults, and its management is a serious challenge for healthcare systems. (Kołtuniuk & Rosińczuk, 2018)

Disease-modifying therapies (DMTs) constitute the current first-line treatment option for relapsing-remitting and secondary progressive MS because they reduce the relapse rate and slow disability progression. (Parra et al., 2011)

Currently, the first-line drugs include interferon beta-1a (Avonex), which is injected sintramuscularly once a week, and Rebif , which is injected subcutaneously three times a week, interferon beta-1b (Betaferon)which is injected subcutaneously every other day), Gilenya (fingolimod) is an immunosuppressant which is once-a-day pill taken orally It works by keeping immune cells trapped in your lymph nodes so they can't reach the central nervous system (brain and spinal cord), Tysabri (natalizumab) as an intravenous infusion (drip) which is once every four weeks. However, in order to achieve the intended therapeutic effect in the form of reducing the number of relapses, slowing down the progression of the disease, and reducing disability and the number of hospitalizations, the patient must follow the treatment recommendations, such as taking the drug according to the prescribed dosage and for the complete duration of the treatment.(8,9)

The first disease-modifying therapies (DMTs) for the treatment of relapsing-remitting (RR) multiple sclerosis (MS) was approved in the mid-1990s, and continues to be used as first-line treatments for MS today. (Dargahi et al., 2017)

To date, MS is still an incurable disease. Treatments are designed to modify the natural evolution of the illness (reducing relapse and disability progression rates) with disease-modifying therapies (DMTs) or to alleviate symptoms (reducing inflammation) to improve the patient's quality of life.(Gold et al., 2016)

Treatment adherence, defined as a patient's acceptance of the need for a medication, persistence with the therapy, and compliance, is crucial for achieving optimal clinical outcomes. (Lugaresi, 2009)

Despite the indubitable benefits, there are several factors associated with DMTs that can impact patient adherence, including inconvenient methods and schedules of administration, long periods of therapy, side effects, or lack of direct relief of recurrent MS-related symptoms. Only long-term adherence to recommended DMT regimens ensures full treatment benefits. Health care professionals play a key role in the management of MS, encouraging the patients to persist with their therapies and providing education on the treatment-adherence benefits. This is the first survey to provide an overview of treatment adherence among Belgian patients with MS, as perceived by their neurologist in clinical practice.

In multiple sclerosis (MS), treatment discontinuation is common, especially during the first months of therapy, increasing the risk of relapse, disease progression, and hospitalization. Disease-modifying therapies (DMTs) aim to reduce the frequency and severity of MS relapses and slow disease progression.(Lim & Constantinescu, 2010)

Adherence to therapy, especially in chronic cases, is crucial in order for patients to obtain a clinical benefit, although adherence data for other chronic diseases were scarce. (Haase et al., 2016) Lack of adherence is associated with increased morbidity, mortality, and health care costs. In MS, therapy adherence varies widely (60%–90% with DMTs), and non-adherence has been associated with increased MS-related hospitalizations and relapse rates. (Herráiz & Fernández-del, 2019)

Several factors have been associated with therapy adherence, including age, sex, socioeconomic status, comorbidity, perceived lack of efficacy, MS type, patient attitude, adverse drug effects, forgetfulness, depression, anxiety, and cognitive difficulties.(McKay et al., 2017), therefore, a better understanding of these factors would increase understanding of MS-treatment adherence, providing useful information for treatment choice. The aim of this study is to evaluate the degree of adherence in MS patients in Spain, and the influence of several variables on this adherence. Secondary aims are to examine patients' satisfaction with their treatment and reasons for changing treatment.(Burks et al., 2017)

As recognized by the World Health Organization, "Adherence to therapies is a primary determinant of treatment success. Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems." In MS, non-adherence has been associated with increases in MS-related hospitalizations and relapse rates. (Faris et al., 2010) To improve adherence, an understanding of potentially modifiable factors that are associated with non-adherence is needed. (Aldeer et al., 2018)

Measuring self-reported missed doses is a practical, efficient, and commonly used method in research and clinical practice.(Herráiz & Fernández-del, 2019)Factors associated with missing doses in MS are varied, but include perceived lack of efficacy, adverse drug effects, and simply forgetting to inject.(20,21) Depression, anxiety, and cognitive Correspondence difficulties have also been associated with poor drug adherence in MS; however, findings have been inconsistent.(16,22,23) Less is known about the effect of MS symptoms such as pain, fatigue, and other comorbidities.

MS patients do not follow treatment recommendations for a wide range of reasons. The most important ones include occurrence of side effects,(24,25) lack of therapeutic effectiveness, and forgetting to take a dose of the drug.(Antonia Corso Camara & Soares Gondim, 2017) It should be emphasized that the duration of therapy also plays an important role. Six Studies have shown that two years after starting therapy, only 30%–40% of patients follow treatment recommendations.(26,27)It should be noted that

socio-demoFigureic factors may also significantly influence compliance; for example, people with lower economic status are characterized by lower adherence. (Woo et al., 2009)

Materials and methods

Study design and population:

This is a cross-sectional study using a questionnaire to assess adherence to MS treatments. The study was carried out during the period of time from 1st December of 2018 to 1st August 2019 at MS clinic of Shar teaching hospital with a questionnaire survey was used. Data were collected by direct interviews lasting 15–20 minutes.

The study's population consisted of MS patients (with diagnoses of RRMS, SPMS, and PPMS in accordance with the McDonald criteria 2010) aged ≥18 years, who had been receiving pharmacologic treatment for at least 1 year. In this descriptive cross-sectional study 124 patients (82 women and 42 men) with a mean age of **36.8±9.89** year evaluated with documented or recorded in MS clinic diagnosed of relapsing remitting multiple sclerosis. Written informed consent was obtained from all patients.

Qualification criteria:

inclusion criteria were 1) a confirmed diagnosis of relapsing-remitting MS (RRMS) based on medical records, 2) Old established patients on disease modifying therapy drugs (Betaferon, Rebif, Avonex, Tysabri and Gilenya) 3) treatment for at least 12 months prior to participation in the study 4) age over and equal 18 years, and 5) written informed consent prior to participation in the study. Exclusion criteria were 1) progressive forms of MS, 2) confirmed diagnosis of RR-MS but not taking first-line DMT drugs (Betaferon, Rebif, Avonex, Tysabri and Gilenya), 3) treatment initiated less than 12 months before participation in the study or newly diagnosed, 4) severe cognitive impairment (patients unable to follow the test instructions), 5) pregnant patients, and 6) lack of written consent to participate in the study.

Instruments:

Definition of adherence:

Non-adherence was defined as missing an injection or dose modification in the 4 weeks prior to completing the survey.In previous studies that used the MS-TAQ instrument, patients were identified as non-adherent if they missed one or more dose in the 28 days prior to completing the survey or if they missed at least 25% of the chosen DMT doses, that is, if they missed ≥1 injection of Avonex; ≥3 injections of Rebif; >3 injections of Betaferon, Tysabri if missed 3 or more injections per one year or 1 injection per month, In this study, non-adherent patients also included those taking Gilenya who missed more than 7 tablets in one month .

Variables and measurement instruments:

For the purposes of this study, the diagnostic survey method was applied, with the use of both a questionnaire designed by the author and the combination of some Polish version of MS-TAQ. The author's questionnaire was an original survey that included questions about socio-demoFigureic data that is, age, sex, place of residence, education, marital status, financial status, and duration of illness.

The MS-TAQ questionnaire is a self-administered tool to identify barriers to adherence for MS patients taking DMTs and also find our rate of compliance, but in our study we used only 2 subscales (DMT-BARR and DMT-SE) to reach our aims. DMT-Barriers (DMT-BARR) quantify the extent to which the patient rated 13 barriers to adherence as important reasons for non-adherence (asked only of patients who missed at least one dose in the previous 28 days; DMT-Side Effects (DMT-SE) describe the frequency of 10 side effects (asked of all patients; asked of all patients; binary yes/no response for "in the past four weeks [28 days] did you usually").

Statistical Methods:

All statistical computation is enhanced using statistical method (SPSS 21). The data had been coded, tabulated, and presented in a descriptive form. The statistical procedure that was applied

to determine the results of the present study included:

1. Alpha-cronbach has been used for testing the reliability of the questionnaire.
2. Descriptive statistical data analysis (Frequency, Percentage, Mean, Stander deviation)
3. Inferential data analysis:

A. Chi-square Test
B. Parried samples T-test:
There are criteria of the probability level of determining the significance of the test: P value as:

1. High significant (P< 0.001)
2. Significant (P< 0.05)
3. Non-significant (P> 0.05)
4. Very highly significant (P< 0.000)

Results3.1. Defining adherence In previous research with the MSTEQ instrument patients were identified as non-adherent if they missed 1 or more injections in the 28 days prior to completing the survey.(28,29)

Reliability of Questionnaire:
Reliability means accuracy, dependability, stability, and consistency of the research instrument. Reliability and validity are concepts used to evaluate the quality of research. They indicate how well a method, technique or test measures something. Reliability is about the consistency of a measure, and validity is about the accuracy of a measure. It's important to consider reliability and validity when you are creating your research design, planning your methods, and writing up your results, especially in quantitative research.

Table (1): Reliability and Validity:

Methods	Result
Alpha Cronbach	0.899
Validity	0.808

Table 1: It can be seen that alpha Cronbach was used to get the result of the reliability of the participations. As a result, the value of alpha Cronbach equals to (0.899) and the validity was (0.808), then the result of alpha Cronbach and validity shows the highly reliable of the questionnaire.

Results:

Table (2): Distribution of the Socio-demoFigureic characteristics of study participants

Characteristics	Frequency	%
Age		
<20	5	4
20-29 years old	26	21
30-39 years old	43	34.7
40-49	37	29.8
≥50	13	10.5
Total	124	100
Mean ± S.D	36.8±9.89	
Gender		
Male	42	33.9
Female	82	66.1
Total		
Marital Status		
Single	44	35.5
Married	80	64.5
Total	124	100
Educational level		
Illiterate	11	8.9
elementary school	32	25.8
High school	31	25
Diploma	19	15.3
University	31	25
Total	124	100
Occupation		
Employed	36	29
Unemployed/retired	28	22.6
Student	17	13.7
Housewife	43	34.7
Total	124	100
Residency		
City center	66	53.2
Outside of city	58	46.8
Total	124	100

It is clear from the table (2) givers demoFigureic characteristics: 34.7% were between 30-39 years old and 29.8% were between 40-49 years old and the mean and standard deviation were (36.8,9.89) respectively. The majority of the gender was female, which was 66.1% of the total, this means the most

participants wasn't male, the percentage of males was 33.9%.64.5% were married and 35.5% were single. The majority of the education level was elementary school which was 25.8%, while the University and

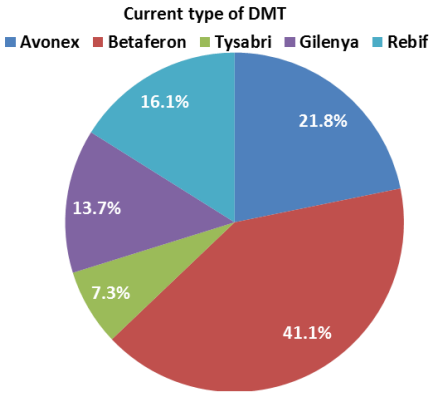
Characteristics	Frequency	%
Drugs taken for Multiple Sclerosis (MS)?		
Avonex	27	21.8
Betaferon	51	41.1
Tysabri	9	7.3
Gilenya	17	13.7
Rebif	20	16.1
Total	**124**	**100**
Disease duration(year)		
≤ 3	40	32.3
4-7	47	37.9
8-11	25	20.2
≥ 12	12	9.7
Total	**124**	**100**
DMT side effect		
No	51	41.1
Yes	73	58.9
Total	**124**	**100**
Clinical course of patient		
RRMS	79	63.7
SPMS	38	30.6
CIS	7	5.6
Total	**124**	**100**
Miss or forgot doses in last 4 weeks		
No	71	57.3
Yes	53	42.7
Total	**124**	**100**

Diploma were 25% and 15.3% by respectively and the minority of the educational level was illiterate which 8.9% was. Most of the participants, 34.7% was Housewife while the rate of the Student of the occupation was 13.7% which was the lowest rate among of the occupation levels. 53.2% of the total respondents were living in the City center place and 46.8% were living in Outside of city.

Table (3): Distribution of clinical data of study participants:

[Figure 1]: According to the study, 63.7% of the Clinical course of patient was (RRMS) which was the highest rate among all type of Clinical course and 30.6% and 5.6% was SPMS and CIS by respectively.

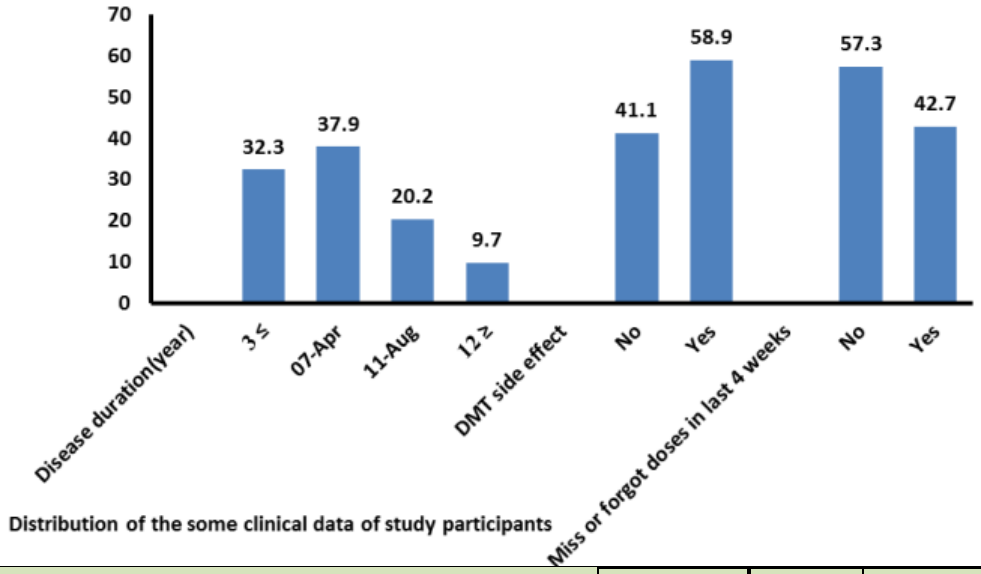
Table (3): shows some clinical data of study participants, According to the study. Figure 1 clarifies that the most frequently of the Multiple Sclerosis is (Betaferon) which 41.1% of the total respondents, 21.8% of the total participation were (Avonex). And the rate of the Tysabri was 7.3% which was the lowest rate among all Multiple Sclerosis. The majority of Disease duration was between (4-7 years) which was 37.9% of the total. Then 32.3% of the total respondents were (≤ 3years) and 9.7% was (≥ 12). The most participants, 58.9% of the total participations had DMT side effect and 41.1% of them did not have DMT side effect, 42.7% of the total participations were Miss or forgot doses in last 4 weeks**.**



[Figure 2]: Rate of M.S responds to type of DMT

Regarding disease duration Figure 2 presents the majority of Disease duration was between (4-7 years) which was 37.9% of the total. Then 32.3% of the total respondents were (≤ 3years) and 9.7% was (≥12). The most participants, 58.9% of the total participations had DMT side effect and 41.1% of them did not have DMT side

effect, 42.7% of the total participations were Miss or forgot doses in last 4 weeks [Figure 2].



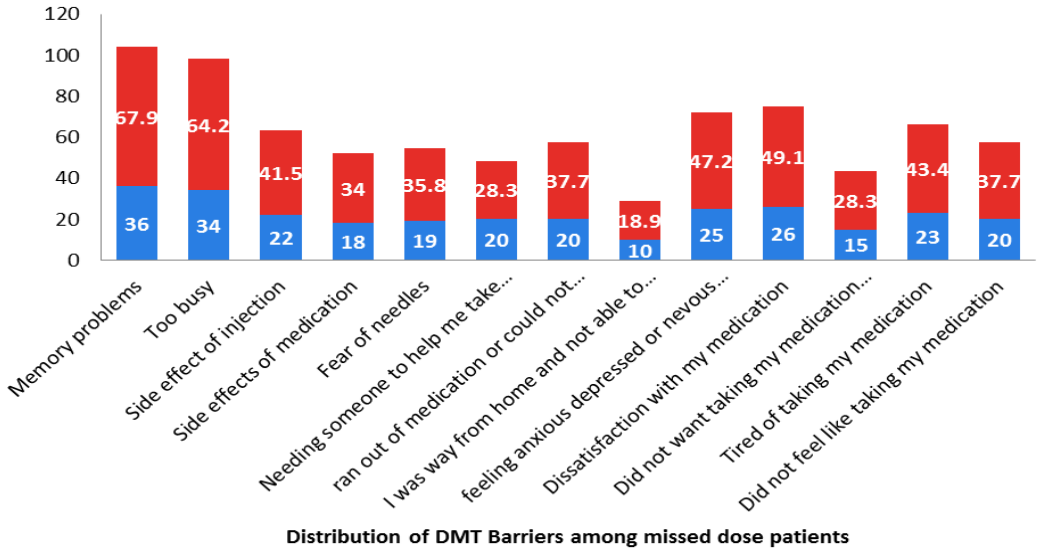
Distribution of the some clinical data of study participants

N	Questions	Scales	Total	Severity

[Figure 3] Distribution of the some clinical data of study participants

			No	Yes		Mean ± S.D
1	Memory problems	N	17	36	53	1.68±0.47
		%	32.1	67.9	100	
2	Too busy	N	19	34	53	1.64±0.48
		%	35.8	64.2	100	
3	Side effect of injection	N	31	22	53	1.42±0.5
		%	58.5	41.5	100	
4	Side effects of medication	N	35	18	53	1.34±0.48
		%	66	34	100	
5	Fear of needles	N	34	19	53	1.36±0.48
		%	64.2	35.8	100	
6	Needing someone to help me take my medication	N	38	20	53	1.28±0.45
		%	71.7	28.3	100	
7	Ran out of medication or could not refill my Prescription	N	33	20	53	1.38±0.49
		%	62.3	37.7	100	
8	I was away from home and not able to access my Medication	N	43	10	53	1.19±0.4
		%	81.1	18.9	100	
9	Feeling anxious, depressed, or nervous about taking my medication	N	28	25	53	1.47±0.5
		%	52.8	47.2	100	
10	Dissatisfaction with my medication	N	27	26	53	1.49±0.5
		%	50.9	49.1	100	
11	Did not want taking my medication to interfere with activities	N	38	15	53	1.28±0.45
		%	71.7	28.3	100	
12	Tired of taking my medication	N	30	23	53	1.43±0.5
		%	56.6	43.4	100	
13	Did not feel like taking my medication	N	33	20	53	1.38±0.49
		%	62.3	37.7	100	
Total		N	406	288	694	1.41±0.48
		%	58.5	41.5	100	

[Table 4]: Distribution of DMT Barriers among missed dose patients:

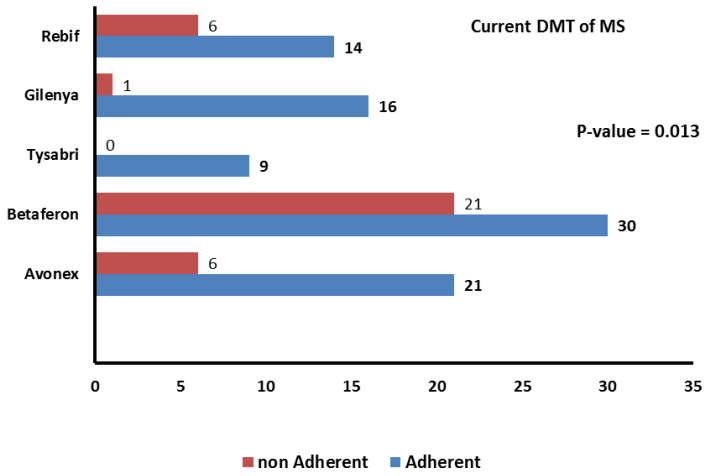


[Figure 4]: Distribution of DMT barriers among missed dose patients.

[Table 4]: Regarding DMT barrier among missed dose patients Table 7 shows that the mean and standard deviation of (Memory

problems) were (1.68±0.47) respectively which were the most interesting question from the participation and it more affected on respondents. Otherwise, the mean and standard deviation of (I was away from home and not able to access my Medication) were (1.19±0.4) which was the lowest result compared with other question. Moreover, 58.5% of the total respondents weren't DMT Barriers; 41.5% were DMT Barriers and the total mean score and standard deviation were (1.41±0.48) of DMT Barriers cause of non-adherence of study participants [Figure 4].

Table (5): The association between Rate of adherence and Clinical data of study participants:



[Figure 5]: showing the bar chart of adherent and non-adherent among current DMT users:

Variable	Items	Adherent		Non adherent		Severity	
		No	%	No	%	Chi-Square	P-value
Clinical course of patient	RRMS	57	63.3	22	64.7	0.659	0.719
	SPMS	27	30	11	32.4		
	CIS	6	6.7	1	2.9		
	Total	90	100	34	100		
Disease duration(year)	≤ 3	31	34.4	9	26.5	6.885	0.076
	4-7	36	40	11	32.4		
	8-11	13	14.4	12	35.3		
	≥ 12	10	11.1	2	5.9		
	Total	90	100	34	100		
Current EDSS	< 4	63	70	23	67.6	0.064	0.8
	≥ 4	27	30	11	32.4		
	Total	90	100	34	100		
Miss or forgot doses in last 4 weeks	No	71	78.9	0	0.0	62.754	0.000
	Yes	19	21.1	34	100		
	Total	90	100	34	100		
DMT side effect	No	45	50	6	17.6	10.668	0.001
	Yes	45	50	28	82.4		
	Total	**90**	**100**	**34**	**100**		

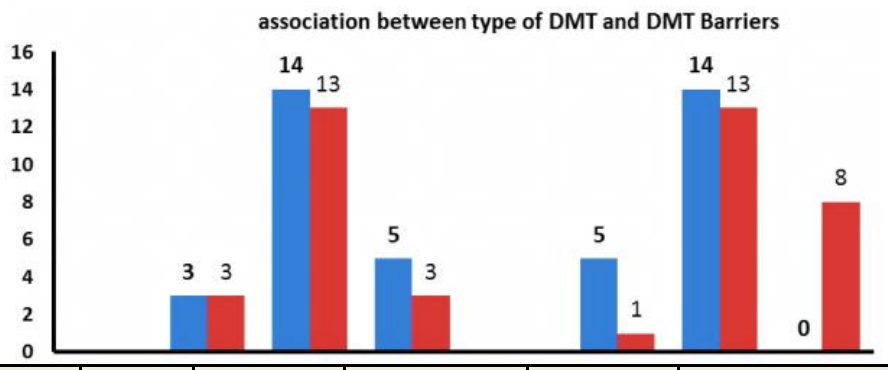
[Table 5]: illustrates that the association between Rate of adherence and some Clinical data. Then, the association between (Adherent and Non adherent) in related to some Clinical data, the result of the study shows that, there

were statistically significant differences between both groups of the Rate of adherence (Adherent) and (Non adherent) in Current DMT of MS p = 0.013, Miss or forgot doses in last 4 weeks p=0.000, DMT side effect p=0.001, because the result of p-value was less than the common alpha 0.05.In addition, Finally, there was no statistically significant difference between (Adherent) and (Non adherent) in related to Clinical course of patient p=0.719, Disease duration(year) p=0.076 , Current EDSS p=0.8 because the (p-value >0.05) Figure 5.

[Table 6]: Correlate between Rate of adherence and DMT Barriers:

Variables	Items	Adherent		Non adherent		Severity	
		No	%	No	%	Chi-Square	P-value
Memory problems	No	4	21.1	13	38.2	1.652	0.199
	Yes	15	78.9	21	61.8		
	Total	19	100	34	100		
Too busy	No	5	26.3	14	41.2	1.17	0.279
	Yes	14	73.7	20	58.8		
	Total	19	100	34	100		
Side effect of injection	No	15	78.9	16	47.1	5.105	0.024
	Yes	4	21.1	18	52.9		
	Total	19	100	34	100		
Side effects of medication	No	17	89.5	18	52.9	7.253	0.007
	Yes	2	10.5	16	47.1		
	Total	19	100	34	100		
Fear of needles	No	16	84.2	18	52.9	5.182	0.023
	Yes	3	15.8	16	47.1		
	Total	19	100	34	100		
Needing someone to help me take my medication	No	17	89.5	21	61.8	4.612	0.032
	Yes	2	10.5	13	38.2		
	Total	19	100	34	100		
Ran out of medication or could not refill my prescription	No	17	89.5	16	47.1	9.333	0.002
	Yes	2	10.5	18	52.9		
	Total	19	100	34	100		
I was away from home and not able to access my medication	No	19	100	24	70.6	6.888	0.009
	Yes	0	0.0	10	29.4		
	Total	19	100	34	100		
Feeling anxious, depressed, or nervous about taking my medication	No	12	63.2	16	47.1	1.268	0.26
	Yes	7	36.8	18	52.9		
	Total	19	100	34	100		
Dissatisfaction with my medication	No	12	63.2	15	44.1	1.768	0.184
	Yes	7	36.8	19	55.9		
	Total	19	100	34	100		
Did not want taking my medication to interfere with activities	No	16	84.2	22	64.7	2.285	0.131
	Yes	3	15.8	12	35.3		
	Total	19	100	34	100		
Tired of taking my medication	No	16	84.2	14	41.2	9.189	0.002
	Yes	3	15.8	20	58.8		
	Total	19	100	34	100		
Did not feel like taking my medication	No	16	84.2	17	50	6.071	0.014
	Yes	3	15.8	17	50		
	Total	19	100	34	100		

[Table 6]: Figured out that there were not statistically significance relation between questions (Memory problems, Too busy, Feeling anxious, depressed, or nervous about taking my medication, Dissatisfaction with my medication and did not want taking my medication to interfere with activities) with Rate of adherence because the p-value were greater than 0.05. However, other questions were statistically significance relationship between other questions with Rate of adherence (P<0.05).
[Table 7]: Correlate between Types of DMT and DMT Barriers:



Variables	Items	Avonex		Betaferon		Rebif		Severity	
		N	%	N	%	N	%	Chi- Square	P-value
Side effects of injection	No	3	50	13	48.1	3	37.5	0.319	0.852
	Yes	3	50	14	51.9	5	62.5		
	Total	6	100	27	100	8	100		
Fear of needles	No	1	16.7	13	48.1	8	100	10.541	0.005
	Yes	5	83.3	14	61.9	0	0.0		
	Total	6	100	27	100	8	100		

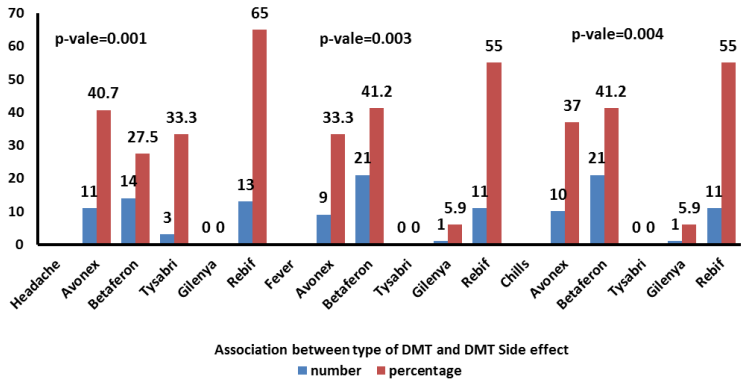
[Figure 6]: illustration of DMT barrier and types of DMT

[Table 7] shows that there was statistically significance relationship between Fear of needles with type of DMT (p=0.005) because the p-value was less than the common alpha 0.05. However, there were not statistically significant relationship between Side effects of injection with type of DMT (p=0.852) because the p-value were greater than 0.05 [Figure 6].

[Table 8]: the association between type of DMT and DMT Side effect

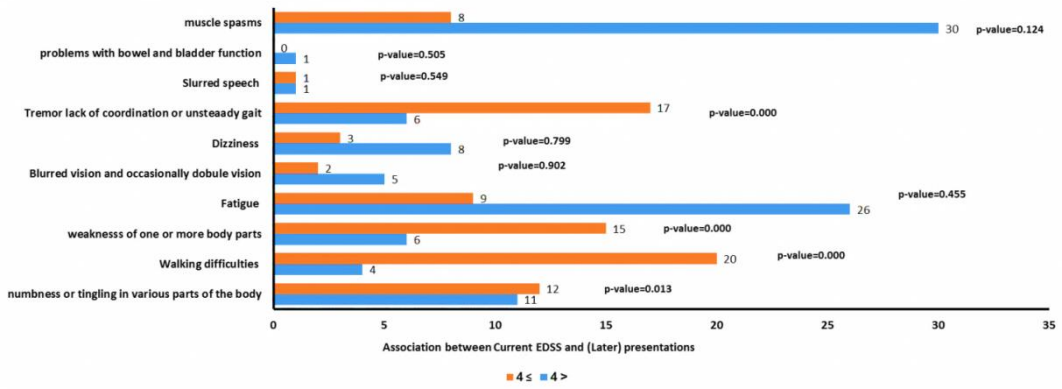
DMT side effect	Items	Avonex		Betaferon		Tysabri		Gilenya		Rebif		Severity	
		N	%	N	%	N	%	N	%	N	%	Chi-Square	P-value
DMT side effect	No	9	33.3	19	37.3	4	44.4	16	94.1	3	15	26.388	0.00
	Yes	18	66.7	32	62.7	5	55.6	1	5.9	17	85		
	Total	27	100	51	100	9	100	17	100	20	100		

Side effects	Headache	No	16	59.3	37	72.5	6	66.7	17	100	7	35	19.059	0.001
		Yes	11	40.7	14	27.5	3	33.3	0	0.0	13	65		
		Total	27	100	51	100	9	100	17	100	20	100		
	Increased fatigue	No	27	100	49	96.1	6	66.7	17	100	18	90	16.583	0.002
		Yes	0	0.0	2	3.9	3	33.3	0	0.0	2	10		
		Total	27	100	51	100	9	100	17	100	20	100		
	Fever	No	18	66.7	30	58.8	9	100	16	94.1	9	45	15.76	0.003
		Yes	9	33.3	21	41.2	0	0.0	1	5.9	11	55		
		Total	27	100	51	100	9	100	17	100	20	100		
	Mood changes/depression /anxiety	No	27	100	48	94.1	7	77.8	17	100	20	100	10.836	0.28
		Yes	0	0.0	3	5.9	2	22.2	0	0.0	0	0.0		
		Total	27	100	51	100	9	100	17	100	20	100		
	Sleep disturbance	No	25	92.6	47	92.2	8	88.9	17	100	20	100	3.338	0.503
		Yes	2	7.4	4	7.8	1	11.1	0	0.0	0	0.0		
		Total	27	100	51	100	9	100	17	100	20	100		
	High blood sugar	No	27	100	51	100	9	100	17	100	20	100	-----	-----
		Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0		
		Total	27	100	51	100	9	100	17	100	20	100		
	Chills	No	17	63	30	58.8	9	100	16	94.1	9	45	15.664	0.004
		Yes	10	37	21	41.2	0	0.0	1	5.9	11	55		
		Total	27	100	51	100	9	100	17	100	20	100		
	Muscle cramps	No	25	92.6	45	88.2	8	88.9	17	100	20	100	4.634	0.327
		Yes	2	7.4	6	11.8	1	11.1	0	0.0	0	0.0		
		Total	27	100	51	100	9	100	17	100	20	100		
	Nausea and/or vomiting	No	26	96.3	49	96.1	9	100	17	100	20	100	1.817	0.769
		Yes	1	3.7	2	3.9	0	0.0	0	0.0	0	0.0		
		Total	27	100	51	100	9	100	17	100	20	100		



[Figure 7]: Association between types of DMT and DMT side effect

[Table 8]: it illustrates that there was statistically significance relationship between DMT side effect with type of DMT (p=0.000) because the p-value was less than the common alpha 0.05.Howerver, Headache, Increased fatigue, Fever and Chills was statistically significance relationship with type of DMT because the (P<0.05).In addition, there were not statistically significance relationship between Mood changes/depression/anxiety , Sleep disturbance , Muscle cramps and Nausea and/or vomiting with type of DMT because the p-value were greater than the common alpha 0.05 [Figure 7].



[Figure 8] Association between current EDSS and later presentations

Discussion:

Compliance with treatment strategies is a key factor toward successful outcomes in disease management. While "compliance" refers strictly to the need for a patient to follow instructions, in the concept of "treatment adherence", the patient plays an active role, recognizing the need for medication, persisting with the therapy, and being compliant. The definitions of "compliance" and "adherence" are often misunderstood or are used interchangeably. It is thus the role of physicians to provide explanations and highlight the importance of treatment adherence to their patients.

The issue of treatment adherence among patients with MS is widely discussed in scientific research. Many researchers have attempted to identify the key factors that influence non-compliance with treatment recommendations in this group

Our study is the first performed in sulaymaniyah to assess the level of adherence among MS patient treated with injectable and oral of first line immunomodulatory drugs. prevoius study have indicated that the percentage of people referred to as non-adherents (if they have completed 1 day or 28 days prior to completing the survey) ranged from 49%(Kołtuniuk & Rosińczuk, 2018) to 85.4%.(Parra et al., 2011).

However, taking into account the medication possession ratio criterion, which is a percentage calculated from the number of doses dispensed in relation to the dispensing period of time, the percentage of adherents varied from 39.9%(Hansen et al., 2015) to 78%.(McKay et al., 2017) Moreover, in studies using the index of proportion of days covered (calculated by dividing the number of days of DMT supplied by the number of days of observation), the percentage of adherents ranged from 58.58% for injection patients and 61.39% for oral patients(Burks et al., 2017) to 76% after the first year of treatment.(Evans et al., 2017)In the present study, the percentage of adherents was 72.5%, which is similar to the results obtained by other researchers(7,32,33)who used a self-report questionnaire to determine the number of adherent patients by adopting the criterion of assessing all doses in the previous month.

With respect to socio-demographic variables, the analysis showed no statistically significant differences between adherent and non-adherent patients, which is consistent with the results of Ożura et al (Ożura et al., 2013) and Wicks et al.(Wicks et al., 2015) However, according to Burks et al,(Burks et al., 2017) women are 24% less likely to be adherent than men. Moreover, Higuera et al (Higuera et al., 2016) found that women had a 5.5% lower probability of being adherent than men.

The lower level of adherence among women should prompt researchers to identify factors that will improve their adherence level, and it should prompt healthcare providers to give women more support because women represent the majority of MS patients.

Devonshire et al (Devonshire et al., 2007) concluded that adherent patients had a significantly shorter duration of disease than non-adherent patients, which was confirmed by McKay et al.(McKay et al., 2017) Same like our study and studies have confirmed that the proportion of people regularly taking medication decreases with the duration of treatment

In our study, almost 95% of the patients who received treatment in the form of tablets belonged to the adherent group, which is in line with study of koltinuik et al(Kołtuniuk & Rosińczuk, 2018)and inconsistent with the data obtained by Burks et al,(Burks et al., 2017).Oral therapy for MS is a relatively new form of treatment. The ease of taking tablets compared with injections is a great incentive to follow treatment recommendations.(7,24,32,33)

Moreover, it has been shown that people taking Avonex (once a week) significantly more often belong to the adherent group, which was confirmed in our study(Testing the differences between the other DMT's showed that patients on Avonex were significantly more adherent then patients on other DMT's). This may be related to the fact that when a medication is used less often (and thus the difficulties associated with it are rarely experienced), it is easier to adhere to the therapeutic instructions.

Ana Oˇzura et al (Ožura et al., 2013)concluded that Side effects of treatment did not differ statistically significantly between the group of adherent and non-adherent, that is conflicted with our study, positive relationship seen between DMT side effect and both groups of adherent and non-adherent patients ,82% of non-adherent patients had DMT side effect it may be because of patients not regularly taking medication and then side effects appears than who received DMT drugs on time .(However the differencein side effects between the adherent and nonadherent group did notreach statistical significance. The study by Wicks et al.(Wicks et al., 2015) Using the same questionnaire as us also did not find significant differences, while other studies found side effects to be one)

Next we looked at the reasons for non-adherence. The most common reason for missing an injection was being memory problem (forgetting to take the injection) same with (16,31,33) and too busy(Ana Oˇzura et al).(Ožura et al., 2013) The third most common reason was Side effect of injection followed by the side effects of the medication, being tired of taking medication and Fear of needles. The least common reasons needed help of others and being out of medication. These results are somewhat different from the previous studies where patients as the most common reason for missing injections reported too busy and doing other activities (Ana Oˇzura et al) (Ožura et al., 2013) side effects of medication.(Fernández et al., 2012)

The present study showed that half of the non-adherent patients were dissatisfied with their treatment, whereas other authors(Finkelsztejn et al., 2016) have indicated that over 80% of patients perceived treatment as beneficial. A study by Mékiès et al(Mékiès et al., 2018) showed that for injections of interferon beta-1a administered subcutaneously, convenience and overall satisfaction with treatment were associated with decreased adherence. However, in our own study, there were no statistically significant differences in the degree of patient satisfaction among adherent and non-adherent patients.

Limitations of this study should be considered when interpreting its findings. Only one method to evaluate adherence was employed. Although this method is widely used, in order to confirm this result, it is necessary to use other methods. Due to the reduced sample size, these results should be treated with caution and considered as a first approach. In addition, the patients who agreed to participate and answer the questionnaire may represent a group of the population that is more actively engaged with their disease, leading to a higher level of adherence being observed in the present study. Another limitation definition of adherence in our study was described directly as not missing any doses during 28 days so this period of time might be too short to show any missed injections for medications dosed with larger intervals (eg, Avonex). Also the time frame of the questionnaire we used (MSTEQ) for measuring adherence was short (one month).Other studies with time frames of several months or even years reported lower rates of adherence (Wong et al., 2010); then studies using short time frames.(39,40)The described problem of under estimated non-adherence lead to a small number of identified non adherent patients. The comparison of groups (adherent vs. non-adherent) was therefore less reliable.

Conclusions

Our study shows an acceptable adherence rate (71%), associating several factors to an adherent patient profile (treatment, disease, and personal characteristics). Patients gave high importance to their disease and showed a reasonable level of satisfaction with their current treatment. Though

satisfaction is related to adherence (and satisfaction was higher with oral treatments), oral administration showed a lower level of adherence The findings of this study can be helpful to explain factors associated with adherence among patients with MS and warn health care services about the importance of the development of individual and collective strategies to offer educational support through the provision of information about the disease and treatment. Still, it suggests interventions that shall reduce the barriers related to forgetfulness and it encourages the inclusion of the patient's family in the treatment.

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