

Adherence to disease-modifying therapies among patients with multiple sclerosis in Bulgaria – A real world study

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Abstract

Introduction: The purpose was to assess the level of medication adherence (MA) and related factors among individuals with multiple sclerosis (MS) in Bulgaria.

Materials and methods: A prospective one-year study was conducted among 54 patients with MS diagnosed, treated, and monitored in Clinic of Neurology, University Hospital “Alexandrovska”, Sofia in 2022/2023. Clinical data, patients reported outcomes, patients’ characteristics such as age, gender and reduced work capacity, and other data were collected to define the predictors of non-adherence to medicines. MA level was assessed through a free Morisky–Green 4-item questionnaire.

Results: Most of the observed patients were rated with high and moderate adherence to MS therapy (n = 44; 81.48%). The remaining 18.52% of the patients with poor adherence to therapy were women. There was no statistical basis for asserting differences in adherence levels among the various factors considered.

Conclusion: The current study demonstrates the importance of MA assessment and provides insights into MA among patients with MS in Bulgaria. Still, there are low-adherent patients, and the responsible factors should be further investigated.

Keywords

medication adherence, Morisky, multiple sclerosis, neurology

Introduction

More than 2,8 million people suffer from multiple sclerosis (MS) worldwide (Soiza et al. 2018; Magyari and Sorensen 2020; Aslam et al. 2022). Every day about 300 people receive a diagnosis of multiple sclerosis and every five minutes someone in the world is diagnosed with MS. Europe has the highest prevalence rate of MS of all WHO regions, with approximately 133 per 100 000

people affected. It is assumed that the number of MS patients in Bulgaria is about 5 000 (Smart MS) (Magyari and Sorensen 2020).

Until now, a definitive cure for MS remains elusive, underscoring the complex nature of this autoimmune condition (Soiza et al. 2018; Kołtuniuk and Chojdak-Łukasiewicz 2022). The treatment is based on an interdisciplinary approach (Feinstein et al. 2015; Axisa and Hafler 2016; Doshi and Chataway 2016; Baldassari and Fox 2018; Izquierdo

et al. 2019; Villoslada and Steinman 2020). The primary objective is to slow down disease progression and reduce the long-term patients' disability. Treatment approaches vary based on the specific course of the disease, whether the disease is in relapse phase or in remission. Treatment is generally divided into 3 main categories: management of relapses, disease-modifying therapy and symptomatic management (Milanov 2023). Improving patients' quality of life and slowing their progression need good cooperation between patients and medical professionals and the key to effective therapy is good adherence and compliance by the patient. Non-adherence to disease-modifying therapies (DMTs) is associated with higher rates of relapse and risk of disease progression (Cunningham et al. 2010; Rolnick et al. 2013; Soiza et al. 2018; Kołtuniuk and Chojdak-Iukasiewicz 2022; Kołtuniuk et al. 2022).

Medication adherence refers to how well a patient follows the recommended dosing schedule, including timing and dosage. Persistence, on the other hand, measures the duration of time in which a patient continues to take the medication from the start to the end of their treatment. Discontinuation refers to stopping of medication, which can be initiated either by the healthcare provider or the patients themselves (Mardan et al. 2021).

Suboptimal medication adherence can be intentional or unintentional. Intentional suboptimal adherence is when patients knowingly deviate from the prescribed regimen due to reasons such as perceiving the medication as ineffective, concerns about the cost, experiencing unwanted side effects or injection side reactions for injectable medications. Unintentional suboptimal adherence is primarily attributed to forgetfulness and can be influenced by factors like physical disabilities, cognitive impairments, or depression, which are often presented in patients with multiple sclerosis (Mardan et al. 2021).

It was still questionable whether the oral DMTs might offer better adherence to injectable ones, but recent studies suggest that real-world adherence and persistence with both once- and twice-daily oral maintenance DMTs (fingolimod, dimethyl fumarate, and teriflunomide) may be like self-injectable DMTs. Despite the proven effectiveness of these therapies, many patients with MS still struggle with adherence to their treatment plans (Cutter et al. 2019).

The aim of this study is to assess adherence to therapy of patients with multiple sclerosis in Bulgaria.

Materials and methods

Study design

A prospective one year-study was conducted among patients with multiple sclerosis in Bulgaria. A questionnaire survey was performed in Clinic of Neurology at the University Hospital "Alexandrovska" in Sofia, Bulgaria, where those diagnosed with multiple sclerosis, including treated, and monitored patients self-report their medication adherence.

Patient characteristics

According to the legislative requirement each patient gave their informed consent to participate and fill a declaration for participation. Patients were examined during their regular consultations to assign treatment protocols. The Clinic of Neurology at the University Hospital "Alexandrovska" has three departments, diagnostic offices, and laboratories, which provide high-quality specialized inpatient, outpatient-consultative, planned and emergency neurological care to patients from all over the country. The study period was from 1st April 2022 until 1st April 2023. A questionnaire about patients' demographic, clinical characteristics, treatment satisfaction and standardized instruments (EQ-5D, VAS and Morisky test) to evaluate quality of life and to assess patients' MA were applied.

Adherence

One of the most commonly self-reported measures of medication non-adherence was used – a four-item Morisky Green Levine Medication Adherence test which includes four questions with yes or no response options. The results are presented in scores from 0 to 4 and there are three levels of medication adherence based on this score: good (score = 0), moderate (score = 1–2) and poor (score = 3–4) (Table 1).

Table 1. Questions in four-item Morisky Green Levine Medication Adherence test (Beyhaghi et al. 2017).

Measures	
Did you ever forget to take medicines?	
Were you ever careless about taking medicines?	Yes = 1
Did you stop taking medicines when feeling better?	No = 0
Did you stop taking medicines if you feel worse?	

Statistics

We employed a range of statistical methods to analyze and evaluate the relationships within the data of interest. These methods included descriptive statistics, non-parametric tests such as Kruskal-Wallis and Mann-Whitney tests, the odds ratio test, and regression analysis. We utilized the MedCalc statistical software version 22.014, tailored for biomedical research.

Clinical and demographic variables to identify predictors of medication non-adherence were explored. The associations between these variables were assessed using the odds ratio (OR), which was estimated through logistic regression analysis, adjusted for confounding factors ($p < 0.05$ indicated statistical significance). The odds ratio (OR) for high or low adherence was calculated for each demographic characteristic of the observed patients, including gender, age, and more.

Ethics

All patients with multiple sclerosis appointed for a regular examination at the Clinic of Neurology, University Hospital "Alexandrovska" in Sofia, Bulgaria, who agreed

to participate, were recruited for this study. All patients, with no exception, provided signed written informed consent at their appointment authorizing the use of their anonymized (pseudonymized) data for scientific purposes.

Results

Patients' characteristics

Fifty-four patients were examined during their regular consultations to assign treatment protocols and participated in the study. Forty-two of them (77.78%) were females ($p < 0.0001$). They were divided into five age groups: 18–30, 30–40, 40–50, 50–60 and over 60 years. Most of the patients were in the age group 30–40 (19, 35.19%), followed by age groups 40–50 (17, 31.48%), 18–30 (8, 14.81%), 50–60 (8, 14.81%) and only 2 of the patients were over 60 years old (3.70%) ($p = 0.0010$). All participants in the study were with relapsing remitting multiple sclerosis and on active treatment with disease-modifying drugs. Nearly half of the patients, 48.15%, exhibit decreased work capacity ($p = 0.7855$). Patients' characteristics are shown in Table 2.

Table 2. Patients' Characteristics.

Gender	
Females	42 (77.78%)
Males	12 (22.22%)
Age groups	
18–30	8 (14.81%)
30–40	19 (35.19%)
40–50	17 (31.48%)
50–60	8 (14.81%)
Over 60	2 (3.70%)
Reduced work capacity	
Yes	26 (48.15%)
No	28 (51.85%)

Clinical characteristics

All individuals enrolled in the study have been diagnosed with relapsing-remitting MS and are currently receiving active treatment with disease-modifying medications. 50% of them were treated with interferons ($p < 0.0001$). A majority (55.56%) have been living with multiple sclerosis for over a decade ($p = 0.0329$). Although most of the patients did not report concurrent medical conditions (33.33%) did have other medical issues ($p = 0.0143$). A significant proportion of patients (96.30%) expressed satisfaction with the effectiveness of their therapy ($p < 0.0001$) and 51.85% have noticed improvements in their medical condition over time ($p = 0.0002$). 22 of the patients (40.74%) were with Expanded Disability Status Scale (EDSS) score 0–1.5 (no disability or minimal signs in one or in more than one FS) and 32 (59.26%) were with EDSS score 2.0–4.5 (minimal, mild, moderate or significant disability). No patients with EDSS score above 5.0 were reported ($p = 0.0342$) (Table 3).

Table 3. Clinical characteristics.

Therapy effectiveness	
Sufficiently effective therapy	52 (96.30%)
Insufficiently effective therapy	2 (3.70%)
Individual perception on the treatment effect	
Improvement in MC	28 (51.85%)
Deterioration in MC	4 (7.41%)
Unable to assess	22 (40.74%)
MS duration	
<10 years	30 (55.56%)
>10 years	24 (44.44%)
DMDs	
dimethyl fumarate	10 (18.52%)
Teriflunomide	7 (12.96%)
Interferons	27 (50.00%)
Ocrelizumab	1 (1.85%)
glatiramer acetate	8 (14.81%)
Fingolimod	1 (1.85%)
EDSS score	
0–1.5	22 (40.74%)
2.0–4.5	32 (59.26%)
5.0–10.0	0 (0.00%)

Abbreviations: DMD – Disease-modifying drugs; EDSS - Expanded Disability Status Scale; MC – Medical condition.

Medication adherence level

Most of the observed patients have high and moderate adherence to MS therapy ($n = 44$; 81.48%) (Table 4, Fig. 1). The remaining 18.52% of the patients with poor adherence to therapy were women. The study did not report any male participant with low medication adherence. The absence of reduced work capacity and advancing age were linked to enhanced therapy adherence. 95.83% of the patients in the study believe that their current treatment is sufficiently effective ($p = 0.0001$). The percentage of patients with better adherence (high and moderate level of adherence) to therapy was statistically significant ($p = 0.0046$). The results of the logistic regression analysis are presented in Table 4.

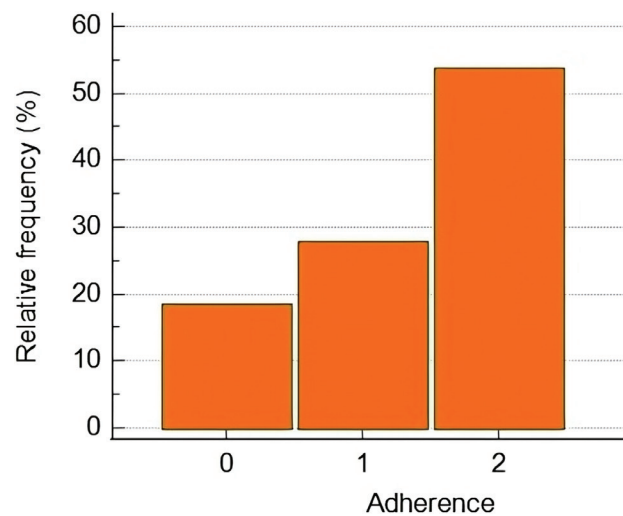


Figure 1. Adherence level. Legend: 0 – low adherence; 1 – moderate adherence; 2 – high adherence.

Table 4. Logistic regression results.

Determinant	High and moderate level of adherence (N)	Low level of adherence (N)	OR, 95% CI, p
Gender			OR = 0.1238
Male	12	0	95% CI 0.006737–2.2753
Female	32	10	P = 0.1596
Therapy effectiveness			OR = 1.2353
Sufficiently effective therapy	42	10	95% CI 0.05506–27.7144
Insufficiently effective therapy	2	0	P = 0.8941
Coexisting diseases			OR = 1.4286
Yes	14	4	95% CI 0.3469–5.8826
No	30	6	p = 0.6213
Type of therapy (Samjoo et al. 2021)			OR = 0.7241
High efficacy	0	1	95% CI 0.275–19.0692
Moderate efficacy	10	43	p = 0.8466
Age			OR = 2.8000
18–40 years	20	7	95% CI 0.6393–12.2632
>40 years	24	3	p = 0.1718
Reduced work capacity			OR = 3.0702
Yes	19	7	95% CI 0.7001–13.4636
No	25	3	P = 0.1369
EDSS score			OR = 3.333
0–1.5	2	20	95% CI 0.6343–17.5181
2.0–9.5	8	24	p = 0.1550

* statistically significant test result $p < 0.05$.

A low level of adherence was reported only in women (OR = 0.1238, 95% CI 0.006737–2.2753 $p = 0.1596$) as well as individuals who believe that therapy is sufficiently effective (OR = 1.2353 95% CI 0.05506–27.7144 $p = 0.894$) and patients treated with DMDs with moderate efficacy (OR = 1.3810 95% CI 0.05244–36.3655 $p = 0.8466$) but without statistical significance. The likelihood of therapy adherence was 70% lower for patients with an EDSS score below 2.0 compared to those with a higher score (OR = 0.3000 95% CI 0.05708–1.5766 $p = 0.1550$). Patients with reduced work capacity (OR = 3.0702 95% CI 0.7001–13.4636 $p = 0.1369$) and those aged 18–40 (OR = 2.8000 95% CI 0.6393–12.2632 $p = 0.1718$) had roughly three times higher odds of showing better adherence.

Hence, it can be asserted that there is no statistical basis for asserting differences in adherence levels among the various factors considered.

Discussion

There is a lack of studies that assess in detail medication adherence in patients with multiple sclerosis in Bulgaria. To the best of our knowledge, this is the first study in Bulgaria focused on medication adherence and the factors leading to non-adherence in patients with multiple sclerosis. The study was performed in a real-world clinical setting by using the most commonly measure of adherence

to therapy used both in research and medical practice capacities. Considering that multiple sclerosis is a chronic autoimmune disease with a treatment primarily focused on symptoms management and slowing disease progression, MA is critical to be assessed and improved.

There are a lot of validated and specific questionnaires and other methods for measuring medical adherence in patients with multiple sclerosis. In the current study we applied four-item Morisky Green Levine Medication Adherence test as a validated choice for measuring adherence to therapy in multiple sclerosis and many other chronic diseases (Fernandez-Lazaro et al. 2019; Fayet et al. 2020; Qiao et al. 2020).

The results showed that most patients had high or moderate adherence to MS therapy, with only 18.52% exhibiting poor adherence. Factors such as gender, therapy effectiveness, coexisting diseases, type of therapy, age, and reduced work capacity were assessed for their association with medication adherence. The conducted logistic regression analysis shows that low levels of medication adherence were primarily observed in women, individuals who believed therapy was more effective, and patients treated with moderately effective medications, although these patterns did not show significant statistical differences. On the other hand, patients with an EDSS score below 2.0 were 70% less likely to adhere to therapy. Patients with reduced work capacity and those aged 18–40 had approximately three times higher odds of showing better adherence. However, there is no statistically significant evidence to confirm variations in adherence levels among the factors studied.

There are various studies published regarding adherence to therapy in patients with multiple sclerosis. A cross-sectional study evaluated MS patients' adherence in Latin America using the multiple sclerosis treatment adherence questionnaire (MS-TAQ). The authors found that the prevalence of non-adherence was similar to others previously reported. The study reported 78.1% overall adherence (79.7% in Argentina and 76% Ecuador, $p = 0.23$) and results are close to those in our study (84.18%). The authors found that patients using infusion therapies significantly more often belonged to the adherent group (Alonso et al. 2022). Another study used IMS Health World Data Adjudicated Claims – US and measured the adherence by medication possession ratio (MRI). The results showed that male sex and age older than 18–34 years are significantly associated with a higher likelihood of adherence. While in our study, we reported only female with poor adherence to therapy, and those with the highest odds of adherence were patients between 18–40 years of age (Munsell et al. 2017). There is a lack of available studies evaluating therapy adherence in individuals with multiple sclerosis in Bulgaria. In contrast to other areas such as Ontario, patients with multiple sclerosis in Bulgaria demonstrate high adherence to therapy. A retrospective cohort study evaluated poor adherence to disease-modifying drugs in patients with multiple sclerosis in Ontario which is compatible with previously reported rates of

adherence in this region (Wong et al. 2011). Our research establishes a connection between the severity of disability and adherence to therapy, indicating that individuals with a lower EDSS score are more assessed patients with primary progressive multiple sclerosis and did not incorporate individuals with secondary progressive MS, unlike other studies. A German study revealed that the main reasons for nonadherence are adverse events, a physician's recommendation, lack of treatment effect, dependence on a wheelchair and a secondary progressive MS (Twork et al. 2007). We did not incorporate the influence of adverse drug reactions on adherence in our study, unlike other studies that have explored this aspect. In Saudi Arabia 598 adult MS patients were recruited and their medication adherence was assessed using the Arabic version of the eight-item Morisky Medication Adherence Scale (MMAS-8). The authors revealed that the medication adherence among MS patients in Saudi Arabia is low due to changing prescribed drugs because of presence of attack, substandard response to treatment or adverse events (Alhazzani et al. 2019). The Moriyski's green test is widely used, and numerous studies have been conducted to assess therapy adherence among patients with various diseases using this test (Gutie et al. 2016; Parente et al. 2020; Lara-morales et al. 2022; Portela et al. 2022; Dinkova et al. 2023; Kamusheva et al. 2023). Therapeutic adherence in 120 Spanish patients with MS under interferon b-1a was assessed with Morisky-Green test and with the percentage of doses received and the results showed that 68% of the patients are adhered to the treatment. Relying solely on one method for assessing medication adherence (Morisky Green Levine Medication Adherence) in our study yields elevated results in Bulgaria compared to Spain (Fernández et al. 2012).

Various factors influence the level of medication adherence. Some studies found that males and older patients have better treatment adherence. People with higher education are more likely to be less adherent than patients who did not go to college or finish their degree. Longer disease duration and insufficient information about the condition and treatments are associated with non-adherence. Mostly the higher EDSS score has a negative effect on treatment adherence but there are studies which prove otherwise. Psychological and behavioral problems such as memory loss, forgetfulness, and depression are associated with poorer treatment adherence. Commonly reported reasons for non-adherence are problems with administration and the occurrence of adverse events. Many studies have revealed that adherent patients have a better quality of life (Mékiés et al. 2018; Buja et al. 2021; Koftuniuk et al. 2022; Soria et al. 2023).

Adherence to therapy is essential for an effective treatment, especially when a patient is dealing with a chronic disease like multiple sclerosis (Pagès-Puigdemont et al. 2016; Losi et al. 2021; Burnier 2023). Also, it is extremely important to assess the level of treatment satisfaction because patients who are more satisfied adhere to the treatment plan better (Haase et al. 2016; Jacobs et al. 2017).

All healthcare professionals should provide the necessary knowledge about a patient's disease and risks and encourage him to adhere to the treatment regimen. Therefore, the additional training of medical professionals and patients, as well as the introduction of new technologies for monitoring patients' adherence are of utmost importance.

Multiple sclerosis is a complex neurological disorder that requires a multifaceted approach to treatment and management. Correct management is essential for ensuring high adherence to therapy in individuals diagnosed with multiple sclerosis (Milanov 2023).

Limitations of the study

One potential weakness of the study is the relatively small sample size, with only 54 patients included. This limited sample size may affect the generalizability of the findings to a larger population of patients with MS. Additionally, the study relied on self-reported measures of medication adherence, which may be subject to recall bias or social desirability bias. We have not evaluated the probable adverse drug reactions and their influence on adherence to medication therapy. We included only actively treated MS patients.

Another constraint arises from the absence of a thorough examination of the factors impacting medication adherence. The medication adherence test's purpose is to determine if patients follow their treatment or not, rather than delving into the underlying factors. Future research should involve a dedicated questionnaire designed to explore the predictors of medication adherence.

Strengths

This is the first study concentrating on adherence to medication and on the factors that affect it in Bulgarian patients diagnosed with multiple sclerosis. Strengths of the study include the use of various statistical methods to analyze the data and the inclusion of multiple clinical and demographic variables. The study also utilized a standardized medication adherence test, which provides a quantitative measure of adherence. The Clinic of Neurology at the University Hospital "Alexandrovska" serves patients from across the country, providing both inpatient and outpatient care, as well as planned and emergency services.

Conclusion

The research contributes to our understanding of medication adherence in the context of multiple sclerosis in Bulgaria, offering a foundation for future studies to delve deeper into the intricacies of patient behavior and treatment outcomes. These insights are essential for healthcare practitioners and policymakers aiming to optimize therapeutic interventions and improve patient outcomes in the management of multiple sclerosis. It is crucial to persist in research in this field and create approaches to assist

patients in their efforts to adhere more effectively to their multiple sclerosis treatment regimens. This will ultimately enhance their quality of life and slow the progression of the disease. Such measures could encompass individualized education, addressing psychological and cognitive aspects, and delivering information customized to the patient's disease duration and lifestyle.

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