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Depression and Anxiety in Patients with Multiple Sclerosis: A Retrospective Study on the Impact of Glatiramer Acetate

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Abstract

Objective: *It has been reported that of disease-modifying therapies used in treatment of relapsing-remitting MS (RRMS) may affect mood of the patients. This study aims to investigate the impact of glatiramer acetate (GA) on depressive and anxiety symptoms in patients with RRMS.*

Methods: *The study included 31 patients who were admitted to the neurology clinic, and who were diagnosed with RRMS. To assess depressive and anxiety symptoms in the patients before and after the treatment with GA was used the Center Epidemiologic Studies Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale (HAD), respectively.*

Results: *Before the treatment, based on the scales CES-D and HAD-Depression scores, 18 (58.1%) and 17 (54.8%) patients had depression, respectively and based on HAD-Anxiety 15 (48.4%) patients had anxiety. After the treatment, the same numbers were 8 (25.8%), 9 (29.0%), and 7 (22.6%), respectively. The statistical analyses indicated that the mean scores of CES-D (t=4.51, P=0.000), HAD-Depression (t=2.91, P=0.007), HAD-Anxiety (t=2.78, P=0.009) and HAD-Total (t=3.15, P=0.004) significantly decreased from the onset of treatment to the end of treatment.*

Conclusion: *Results of the present study suggest that GA may be useful effects on depressive and anxiety symptoms rather than negative effects in RRMS patients.*

Keywords: Multiple sclerosis, glatiramer acetate, depression, anxiety

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating disorder of the central nervous system that is frequently observed in young adults between the ages of 20–45 and is characterized by episodic neurologic dysfunction[1]. MS causes not only physical disability but also fatigue, gait disorders, bladder and bowel dysfunction, cognitive dysfunction, nociceptive or neuropathic pain, depression, and anxiety.

Over the last decade, several studies have shown that comorbidity is common in MS, even at diagnosis, and its prevalence increases with age[2,3]. It has been reported that the prevalence of psychiatric disorders is 72% in MS, 54% of which is constituted by depressive disorders[4]. Prevalence of depression is 2–3-fold higher in MS patients than in the general population, while the lifetime prevalence is around 50% [5]. However, estimates regarding the prevalence of depression (4.98%–58.9%) and anxiety (1.2%–43.6%) in the MS population show significant differences[6]. Although depression is the leading psychiatric disorder associated with MS, prevalence of anxiety disorders also increases in MS.

Studies have shown that depression is not just an emotional disorder in MS patients; it can be a biological-based symptom[7]. In other words, many factors such as structural brain changes, immune-inflammatory, genetic and psychosocial factors can cause this. Depression and anxiety in MS are important because they frequently accompany the clinical presentation of MS, in addition to being major determinants of the quality of life, affecting cognitive functions, causing suicidal thoughts and suicide attempts, and affecting social relationships and adherence to disease-modifying treatments (DMTs) [8].

The most commonly used DMTs for the treatment of MS are interferon beta (IFNβ) −1a, IFNβ-1b and glatiramer acetate (GA). According to reports, prevalence of depression increased after IFNβ was introduced for the treatment of relapsing-remitting MS (RRMS) in the 1990s[9]. However, it is not possible to draw a definite conclusion from these studies that were conducted as case reviews. Although it is believed that IFNβ causes secondary depression due to the inhibition of serotonin, Patten and Metz reported that there was no such relationship in their study aiming to reveal the relationship between depression and IFNβ treatments[10]. Numerous controlled and uncontrolled clinical studies data on IFN-βwere evaluated in a common pool and there was no association with suicide attempts or with the increase in depression rating scale scores[7]. Long-term data have also failed to confirm the hypothesis that IFNβ treatment for RRMS causes depression.

The mechanism of action of GA, which has an approved safety and efficacy profile in the first-line treatment for RRMS, is different than that of IFNβ. GA is synthesized by a copolymer polypeptide structure that consists of glutamic acid, lysine, alanine, and tyrosine [11]. The drug was produced to compete with and mimic myelin basic protein. Although its mechanism of action is not entirely known, it was reported to induce suppressor T cells in animal studies [12]. Briefly, GA is a first-line therapeutic against the RRMS, in which it acts by immune modulatory mechanisms, which also touch T and B cells, interfering with the disease course. Glatiramer acetate is generally well tolerated by the patients. The most common side effects observed with GA are mild local injection site reactions, which can include pain, erythema, inflammation and induration. Systemic adverse event related to GA is rarely seen, but postinjection transient flushing, chest tightness, palpitations, and dyspnea can be observed. While IFNβ package insert information warns of depression and suicide, the GA package insert information does not carry such a warning. No adverse events associated with depression were reported in placebo-controlled or open-label studies with GA. In a study, the incidence of depression has been investigated in a clinical randomized trial involving patients receiving IFN-β or GA and no obvious differences were detected between the treatment groups in terms of Beck Depression Inventory scores[13]. However, Ziemssen et al. demonstrated that patients who were on GA had less severe depression and improved quality of life [14].

An ideal pharmacological agent should have a dual therapeutic action of being effective in the treatment for RRMS and reducing comorbid psychiatric symptoms. This study aims to investigate the effects of GA on depression and anxiety symptoms in RRMS patients.

Materials and Methods

This study was approved by the ethics committee of our institution, and a written informed consent was obtained from all participants. The present study was conducted under the good clinical practice guidelines of the declaration of Helsinki and its later amendments (Registration number of ethical approval: 2020/2899 by the ethics committee of Meram Medical Faculty, Necmettin Erbakan University).

Study population and data collection

The study data were obtained by retrospectively reviewing medical registers. Therefore, no interference of the natural treatment of the patients occurred because of this study. A total of 65 patients with MS who were examined between January 2016 and December 2019 at the Neurology Outpatient Clinic of a University Hospital were included in the study (Figure 1). Clinically definite

MS patients treated with GA from clinical site was retrospectively selected. Demographic characteristics (i.e. age, age at disease onset, gender, education status, employment status, marital status) and clinical characteristics (i.e. duration of disorder, number of previous MS attack, Expanded Disability Status Scale (EDSS) score) were obtained from hospital Enlil HBYS software (Table 1).

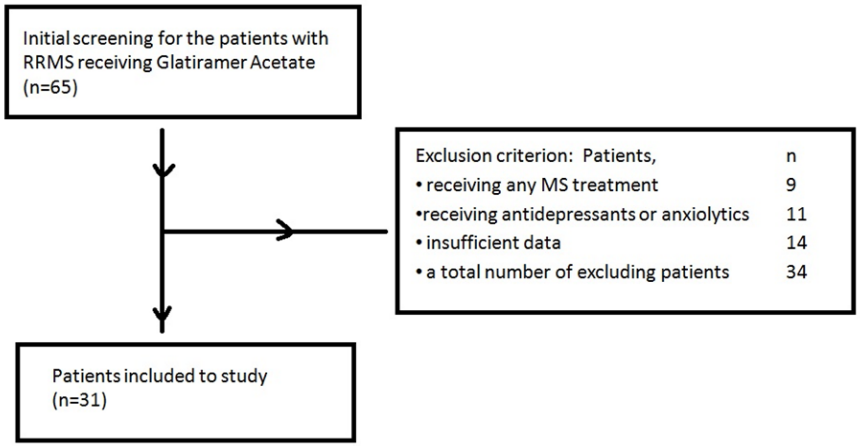

Figure 1. The flow chart of the patients

RRMS: Relapsing-Remitting Multiple Sclerosis

Table 1. Sociodemographic and clinical characteristics of the sample

Age at the assessment, mean±SD, years	33.90±7.15
Age at the onset, mean±SD, years	29.83±7.07
Duration of disorder, mean±SD, years	4.04±3.68
Number of previous MS attack, mean±SD	3.35±1.74
Gender, n(%)	
Female	25 (80.6)
Education, n (%)	
Primary school	14 (45.2)
Secondary school	8 (25.8)
University	9 (29.0)
Employment status, n (%)	
Unemployed	24 (77.4)
Marital status, n (%)	
Married	23 (74.2)
EDSS score, mean±SD	1.33 ± 0.75

SD: Standard Deviation - MS: Multiple Sclerosis -EDSS: Expanded Disability Status Scale

In our clinic, there is no specific protocol regarding which drug therapy will be selected for patients meeting MS diagnostic criteria. The choice of medication is determined according to accessibility, the experience of the physician and the characteristics of the patient. In addition, the Center for Epidemiologic Studies Depression Scale (CES-D) and Hospital Anxiety and Depression Scale (HADS) are used in our clinic before the injection treatments and during the 2nd month controls, as far as the polyclinic facilities allow. In subsequent controls, scales are applied in case of psychiatric complaints, although not periodically.

Methods

The inclusion and exclusion criteria were as follows:

Inclusion criteria

• Patients diagnosed according to McDonald criteria

• To have a relapsing–remitting course

• Patients treated with GA (subcutaneously once daily 20 mg/mL solution)

• Those who did not receive DMTs before GA (naïve patients)

• Those that were evaluated in terms of depression and anxiety symptoms before the GA treatment and 2 month after starting the treatment using CES-D and HADS

Exclusion criteria

• Incomplete medical history and data (n=14)

• Those who received any MS treatment prior to GA treatment (n = 9)

• Those who used antidepressants or anxiolytics (n = 11) for any reason

On the basis of the exclusion criteria, 34 patients were excluded from the study. As a result, the study data include the results of 31 patients.

Center for Epidemiologic Studies Depression Scale

The CES-D is a self-report questionnaire that has been developed to measure depression symptoms and to identify people at risk of having a depressive disorder[15]. The Turkish version of the CES-D, developed by Spijker et al., was used in this study. CES-D contains 20 items that can be responded to on a four-point Likert scale, with response categories ranging from “rarely or none of the time” (0 points) to “most or all of the time” (3 points). These items are then summed to obtain a total score, with higher scores indicating more severe depression symptoms. A cut-off score of ≥16 is generally accepted as an indicator for clinically significant depression [16].

Hospital Anxiety and Depression Scale

HADS is used to determine a patient's risk of developing anxiety and depression, and to also measure its severity and the resulting change in the severity. It has two sub-scales that separately evaluate anxiety and depression. Cut-off scores used in the Turkish version of the scale are 10 and 7 for the anxiety and depression sub-scales, respectively [17].

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 16.0, for Windows (SPSS Inc., Chicago, IL). For sociodemographic data of the sample was used descriptive analyses. The scores of CES-D, HAD-depression and HAD-anxiety before and after the treatment were compared with t test for dependent variables. Correleations between CES-D and HAD subscales and EDSS scores were assessed with Pearson's correlation test.

Result

Mean age of the patients (n = 31) was 33.90 ± 7.15. Patients were mostly female (n = 25, 80.6%), married (n = 23, 74.2%), and unemployed (n = 24, 77.4%). Nearly half of the sample (n = 14, 45.2%) included elementary school graduates. Average duration of the disease was 4.04 ± 3.68 years (range = 0.5–16 years), the mean number of MS attacks was 3.35 ± 1.74 (range = 2–10), and the mean EDSS score was 1.33 ± 0.75 (range = 0–3).

According to the pretreatment CES-D and HADS-Depression scores, 18 (58.1%) and 17 (54.8%) patients had depression, respectively. In addition, HADS-Anxiety scores showed that 15 (48.4%) patients had anxiety. The same numbers were 8 (25.8%), 9 (29.0%), and 7 (22.6%), respectively, 2 month after the treatment.

Statistical analyses show that CES-D (t = 4.51, p = 0.000), HADS-Depression (t = 2.91, p = 0.007), HADS-Anxiety (t = 2.78, p = 0.009), and HADS-Total (t = 3.15, p = 0.004) scores exhibited a significant decrease in the second month of treatment (Table 2). In addition, EDSS score was not associated with baseline scores of CES-D (r=0.077, p=0.685), HADS-Depression (r=0.137, p=0.470), HADS-Anxiety (r=0.048, p=0.800) and HADS-Total (r=0.096, p=0.614) scales.

Table 2. Anxiety and depression symptom levels before and after glatiramer acetate in patients with multiple sclerosis

	Before treatment, mean ± SD	***After treatment, mean ± SD***	***t***	***P***
HADS-Depression	7.74±4.87	5.42±4.23	2,91	0.007
HADS-Anxiety	9.81±5.72	7.16±4.36	2,78	0.002
HADS-Total	17.55±9.60	12.58±7.88	3,15	0.003
CES-Depression	17.03±12.37	9.19±11.03	4,51	0.000

HADS: Hospital Anxiety and Depression Scale, CES: Center Epidemiologic Studies, SD: Standard Deviation

Discussion

MS is a disorder that can significantly impact physical, mental, and social wellbeing. There are several reasons for MS affecting the psychological state of the patients. They are as follows: MS has direct effects on the central nervous system; there is no clear diagnosis and prognosis in MS; it has an episodic and unpredictable clinical course; it affects work and family life; there are several concomitant symptoms and other chronic diseases that accompany it; and the most important thing there is no cure for MS. In addition, prolonged use of drugs in the treatment and protection against attacks also has many psychiatric side effects.

Estimates regarding the prevalence of depression (4.98%–58.9%) and anxiety (1.2%–43.6%) in the MS population show significant differences[4]. According to the CES-D and HADS-Depression scores in our study, 18 (58.1%) and 17 (54.8%) patients had depression, respectively. In addition, HADS-Anxiety scores showed that 15 (48.4%) patients had anxiety. The fact that nearly half of these 31 patients showed symptoms of depression and anxiety underlines the necessity and importance of investigating psychiatric comorbidities in MS patients. The presence of depression and anxiety in a majority of MS patients also increases the importance of DMTs that will be administered. Thus, the treatment of choice should not elicit symptoms of depression and anxiety or increase existing psychiatric symptoms, and should, at the very least, have no impact on these symptoms. When starting MS treatment, most neurologists believe that IFNβ will increase depression more in the course of the disease than GA. For this reason, newly diagnosed patients with signs of depression or psychiatric history are usually given GA treatment from the beginning of MS treatment. This approach clearly shows itself in the treatment preferences of the patient group included in the study. Thus, we think that GA treatment is preferred more because approximately half of MS patients have depression and anxiety symptoms.

CES-D, HADS-Depression, HADS-Anxiety, and HADS-Total scores displayed a considerable decrease in the second month of treatment, which was also statistically significant. Therefore, it was shown that such a GA treatment modality not only prevented an increase in the symptoms of depression and anxiety in RRMS but was also may be effective in reducing psychiatric symptoms. The results obtained are interesting when it is considered that the efficacy of GA in MS treatment occurs at the earliest 2nd month, mean 4th and / or 6th month. Despite the uncertainty of the future caused by the disease, the difficulty of daily self-administered injection treatment, side effects of treatment and fear of injection, the decrease in psychiatric symptoms after 2 months of treatment makes the success of GA treatment even more interesting. According to the results of the study, considering that GA treatment was preferred in a patient group more prone to depression and

anxiety, it can be said that the positive effect of GA on psychiatric symptoms started earlier than its effect on MS. Since a 4-6 week waiting period is predicted for the onset of efficacy in an antidepressant drug, the application of clinical scales at the second month control visits seems appropriate to evaluate psychiatric symptoms. Similar to our findings in a study by Nagy et al., it was found that GA treatment reduced depression and improved the quality of life[18]. Additionally, in a 2016 study[14] involving more than 750 patients, 96% of whom were RRMS, patients had either did not receive disease-modifying therapy (de novo, n = 481) or previously treated with subcutaneous 20mg / mL GA once daily (n=237). In this study, patients have been evaluated in terms of disease progression, relapse rate, general functionality, quality of life (QoL), cognition, fatigue, and depression for 2 years. MS Inventory Cognition Scale scores showed a significant improvement between previously treated patients and de novo cohorts. In the same study, General Depression Scale scores also decreased significantly. These data show that MS patients benefit from GA treatment in QoL parameters beyond relapse and disease severity measures. In contrast, two different studies that compared patients who were on IFNβ-1b and GA found no difference in terms of depression. According to a retrospective study by Kirzenger et al., patients who were on GA and IFNβ had similar antidepressant use and depression scores[19]. In another study by Schippling et al., it was reported that IFNβ-1b and GA did not provide different results in terms of depression[20]. EDSS score was not correlated with baseline scores of CES-D, HADS-Depression, HADS-Anxiety, and HADS-Total. The most important reason for this result was thought to be that the patient group consisted of individuals with low EDSS scores and suitable for first line MS treatment. Such a patient group is an advantage for our study. Because, we think that determining and evaluating the positive effects of GA on depression and anxiety will be more difficult due to additional problems in the patient group with high EDSS scores.

Both preclinical and clinical studies have shown that peripheral GA administration can increase central brain-derived neurotrophic factor (BDNF) activity or serum BDNF levels[21]. GA possibly exhibits antidepressant effects by increasing central BDNF either by stimulating neurogenesis or by exhibiting anti-inflammatory effects[21]. The anti-inflammatory effect of GA has also been demonstrated by its ability to induce Th2 cells that cross the blood–brain barrier, accumulate in the brain, and increase IL-10 and BDNF expression. Considering all its aspects, GA is, in addition to its efficacy in MS treatment, also effective in the first-line treatment of RRMS due to its positive impact on the comorbid depression and anxiety symptoms. Thus, it can be safely used in RRMS patients who exhibit comorbid depression and anxiety symptoms.

There are some inherent limitations of the present study. First, the sample size of our study population is small. Secondly, due to the retrospective nature of our study, the fact that it did not evaluate common conditions in MS such as fatigue, pain and cognitive dysfunction that coincide with depression and anxiety is an important limitation. Furthermore, there were a few limitations of this study, including the fact that one-to-one psychiatric interviews were not conducted to evaluate the psychiatric state of the patients, and the CES-D and HAD scales were not periodically used during the treatment period. Considering these features in prospective study planning will be beneficial in revealing the positive effects of GA on psychiatric symptoms.

Conclusion

Neither IFNβ nor GA treatment appears to exacerbate depression and anxiety symptoms in patients with RRMS. However, the results of this study suggest that RRMS patients can benefit from GA in terms of their depression and anxiety symptoms. While depression and anxiety are the most prevalent psychiatric disorders in MS patients, GA can show dual therapeutic effect in RRMS patients with depression and anxiety.

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