The Effectiveness of Mindfulness-Integrated Cognitive Behavior Therapy on Depression, Anxiety, and Stress in Females with Multiple Sclerosis: A Single Blind Randomized Controlled Trial

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Abstract

Background: Previous studies have shown the effectiveness of cognitive behavior therapy in improvement of psychological symptoms such as depression, anxiety, and stress. Recent studies suggest that mindfulness-based interventions (MBI) are effective in reducing these psychological symptoms in chronic diseases. The present study was the first study to examine the effects of mindfulness-integrated cognitive behavior therapy (MiCBT) on common comorbid psychological symptoms in patients with multiple sclerosis (MS).

Objectives: The present study aimed at examining the effect of mindfulness-integrated cognitive behavior therapy on depression, anxiety, and stress in females with multiple sclerosis.

Methods: This research was a quasi-experimental study conducted on female patients with MS who referred to Fars MS Society, Shiraz, Iran, in 2015. A total of 56 patients with MS were selected by convenience sampling method and randomly assigned into intervention and control groups. The intervention group received eight 2-hour sessions of MiCBT, while the control group was only given the usual treatment (TAU). The patients in both groups filled out a demographic questionnaire along with depression, anxiety and stress scales (DASS-21) in pre- and posttest.

Results: In the current study, no statistically significant differences were found between the study groups in demographic variables (P > 0.05). Analysis of covariance revealed significant differences between the study groups in all the 3 variables in posttest compared to the pretest. The mean scores of depression, anxiety, and stress in the MiCBT group were significantly lower than the control group (P < 0.001). The mean score of depression was 16.69 ± 7.1 in the experimental group before the intervention, which decreased to 6.17 ± 5.7 after the intervention (P < 0.001). In addition, the mean score of anxiety was 13.2 ± 7.25 in pre-intervention, which significantly reduced to 6.09 ± 5.2 in post-intervention (P < 0.001). The mean score of stress also decreased from 22.09 ± 6.07 to 10.87 ± 6.3 compared to the pretest (P < 0.001).

Conclusions: The results of the present study suggested that mindfulness-integrated cognitive behavior therapy is an effective and affordable treatment in reducing depression, anxiety, and stress for patients with MS.

Keywords: Multiple Sclerosis, Mindfulness, Cognitive Behavior Therapy, Depression, Anxiety, Stress

1. Background

Multiple sclerosis (MS) is an inflammatory disease, where myelin sheaths of nerve cells are damaged in the central nervous system (CNS). Usually, MS begins at a young age between 20 to 40 years (1) and affects females more frequently than males (2). According to the Atlas of MS, about 2.3 million people were affected by MS worldwide in 2013, with varying degrees in different regions. The average global prevalence of MS was reported to be 33 per 100,000 in 2013 (3). In the same year, the prevalence of MS was 51.54 per 100,000 in Iran, which has been spreading in the recent years (4).

Most patients with MS (approximately 85% - 90%) are diagnosed with relapsing-remitting MS (PRMS) on the outset, which is accompanied by complete or partial acute recurrent remissions. Many of these patients are later diagnosed with progressive secondary MS (PSMS) (5). The disease progresses with a series of physical and psychological problems affecting the daily activities and self-care among patients, which eventually curtails personal independence, psychological well-being, and quality of life (6). Research has shown that psychological problems, particularly high levels of depression and anxiety, are common in these patients (7), even higher than the general population (8). In fact, 48% of patients with MS experience certain levels of

anxiety, depression, and distress in the first year after diagnosis and need clinical attention (9).

Depression is one of the most common psychiatric symptoms diagnosed in patients with MS (10), the prevalence of which was reported to be 23.7% in a recent review study (11). Moreover, some previous researches reported that the lifetime prevalence of depression in patients with MS is over 50% (12). Anxiety is another common symptom in about 19% to 45% of patients with MS (8, 10, 13), which has 22% prevalence, based on the finding of a recent study (11).

Therefore, depression and anxiety are considered as 2 important and common comorbid disorders in patients with MS (8). In fact, these symptoms are so disabling that severely affect the general health and quality of life of patients with MS (14). Depression is one of the most important factors related to suicidal ideation and suicide attempts in patients with MS (15). In addition, some studies indicated that anxiety plays a considerable role in suicide and self-harm (16). If not treated, anxiety leads to problems in commitment to therapy (17) and exacerbation of symptoms in the patients (18).

Moreover, stress is known as a factor contributing to recurrence of MS. Research has shown that stress (19) and stressful events are effective in the outset and relapse of MS symptoms (18). Studies have also indicated that stress can lead to lower immunity (20) and brain inflammation (21), which in turn may contribute to development of MS in patients (22).

Considering the high prevalence and negative effects of psychological symptoms in patients with MS, it is crucial to efficiently and timely manage and treat these symptoms. The results of Goldman consensus group's study on depression in patients with MS revealed that emotional disorders and depression are not usually diagnosed by doctors, and they are not properly treated in most cases (23).

Furthermore, some studies reported that antidepressants are effective in treating psychological symptoms such as depression in patients with MS even though these drugs are associated with significant side effects and lead to a high rate of discontinuation (24). Nevertheless, previous studies indicated that psychological interventions can be helpful and effective in curtailing depression and improving the quality of life among patients with MS (25). One of the most effective psychotherapies is cognitive behavior therapy (CBT), which was proven to have moderate effects on psychological symptoms such as depression in patients with MS (25, 26).

In the recent years, there has been a growing interest in adopting mindfulness-based interventions (MBI) to relieve patients from chronic pain, cancer, heart disease (27), and most recently to enhance well-being and quality of life in patients with MS (28). The results of a meta-analytic review revealed that mindfulness-based interventions are effective in improving anxiety and depression in clinical population (27). One of such interventions is mindfulness-integrated cognitive behavior therapy (MiCBT) as a systematic approach, where mindfulness treatment is combined with foundational elements of cognitive and behavioral techniques. This integration serves to train patients to regulate their emotions and attention through internalization of attention. Later, they can learn to externalize and apply these skills to contexts that cause or maintain disorders and problems. In addition, one of the major objectives of this program is to treat comorbid psychological problems such as anxiety and depression (29). This therapy has attracted the attention of some researchers in the recent years. Studies demonstrated the effectiveness of MiCBT in reducing depression and greater adherence to treatment in patients with Type II diabetes (30), lower procrastination, perfectionism and concerns among students (31), and lower depression and anxiety in pregnant women (32). However, no studies, whether in Iran or other countries, investigated the effects of MiCBT on patients suffering from chronic diseases like multiple sclerosis and stress. In addition, the research on the effectiveness of MiCBT is generally in its infancy.

According to review studies, the prevalence and incidence of MS is increasing worldwide (2) and Iran is no exception (4). MS leads to various disabling problems including psychological troubles that can result in relapse of disease symptoms and increased suicide rates among these patients. Therefore, studying the effects of new inexpensive treatments like MiCBT in patients with MS seems necessary.

2. Objectives

This study aimed at examining the effect of mindfulness-integrated cognitive behavior therapy on depression, anxiety, and stress in females with multiple sclerosis.

3. Materials and Methods

3.1. Participants and Procedure

This study was a single blind randomized controlled trial with an intervention group and a control group (IRCT2015041321722N1). The participants were selected from all female patients with MS who had referred to Fars MS Society, Shiraz, Iran, from October to December 2015.

The minimum sample size for measuring the effectiveness of the study was calculated using the Cohen's formula. With an alpha of 0.05 (α = 0.05), an effect size of 0.80 (d

= 0.80) (33), and a power of 0.90, the Cohen's formula revealed that 15 patients were needed for each study group. However, 28 participants were recruited for each group to prevent probable attrition from affecting the findings.

After the sample size was determined, 94 patients were assessed according to the inclusion criteria. In the first meeting, medical history, current symptoms, medication, and duration of disease were examined under the supervision of a neurologist who decided whether the participants were adequately qualified for the study or not. The participants were also interviewed for psychiatric disorders. Among 94 available patients, 56 who met the inclusion criteria were selected by convenience sampling method and were asked to fill out an informed consent form, followed by a pretest. Then, the patients were assigned into 2 groups (intervention and control) using permuted block randomization method. There were 14 blocks and 4 people in each block. This randomization method was done by an individual external to the study to ensure that the main researchers were blind to the random assignment of the patients. The control group received their usual treatment, while the intervention group participated in MiCBT sessions as well as drug therapy. Finally, the participants took the posttest and filled out the questionnaires again. The anonymous data were collected by a research assistant who was blind to the assignment of patients to groups and the intervention procedure.

The inclusion criteria were as follow: the diagnosis of relapsing-remitting multiple sclerosis (the most common type of MS, which is characterized by recurrent relapses followed by partial or complete recovery) by a neurologist at least one year prior to the study; being under treatment; aged 20 to 45 years with an educational level of high school diploma or higher; expanded disability status scale (EDSS) score of ≤ 5.5 (no to moderately severe disability); and willingness to participate in the study. The exclusion criteria were as follow: having a history of psychotic disorders, mania, hypomania or personality disorders: having a history of cognitive impairments like dementia; having a history of substance abuse; having a history of epilepsy or seizure over the last 6 months prior to the first meeting; having a history of hearing or speech problems; being pregnant; having received psychotherapies during the month before the study; and being absent for more than 2 sessions. The research procedure is demonstrated in the flowchart in Figure 1.

3.2. Study Instruments

The instruments used in the current study were 2 sets of self-report questionnaires. The first included 6 questions about the patient's demographic information including age, education, marital status, age at onset, dis-

ease duration, and family history. The second was depression, anxiety, and stress scale (DASS-21), which is a 21-item structured questionnaire developed by Lovibond and Lovibond in 1995 (34). DASS-21 includes depression, anxiety, and stress subscales, each consisting of 7 items. Items 3, 5, 10, 13, 16, 17 and 21 concern depression; Items 2, 4, 7, 9, 15, 19 and 20 concern anxiety; and Items 1, 6, 8, 11, 12, 14 and 18 concern stress. Each item has a 4-point Likert scale between 0 (never) and 3 (almost always). Higher scores in each subscale indicate higher levels of depression, anxiety, and stress. Evidence suggests that DASS possesses adequate convergent and discriminant validity (34). The reliability and validity of the questionnaire was studied previously for the Iranian population. The reliability of DASS-21 subscales was calculated through Cronbach's alpha to be 0.80 for depression, 0.76 for anxiety, and 0.77 for stress (35).

3.3. Intervention

MiCBT is a structured group- training program held in eight 120-minute sessions once a week involving 4 stages: personal (attention regulation and emotion regulation); exposure (behavioral regulation); interpersonal relations; and empathy and relapse prevention. In this approach, the participants are trained to become self-aware of their bodies; eg, movements and behavior, physical sensations, mental and emotional states, and mental contents (29).

In our study, each MiCBT session consisted of a formal meditation and an educational component. Meditation practices involved mindful breathing, body scanning, and loving-kindness meditation. The participants were encouraged to practice meditation exercises every day between MiCBT sessions (between 15 to 45 minutes a day). The intervention was based on a protocol established by Bruno Cayoun (29, 36). The participants were trained by a competent clinical psychologist experienced in administering meditation exercises. The intervention was conducted in eight 2-hour weekly sessions, where most of the members in the intervention group participated. Additional sessions were arranged for those who had missed 1 or 2 sessions. All participants in the intervention group were handed a 25-page booklet, which included information about weekly sessions and instructions on each exercise such as mindful breathing, body scanning, and loving-kindness meditation. They were also given a CD containing audio instructions on how to perform the exercises. Table 1 displays the content of each MiCBT session.

3.4. Data Analysis

Data were analyzed using the SPSS software (version 18.0). All analyses were performed based on a per protocol analysis. Descriptive statistics (mean, standard deviation,
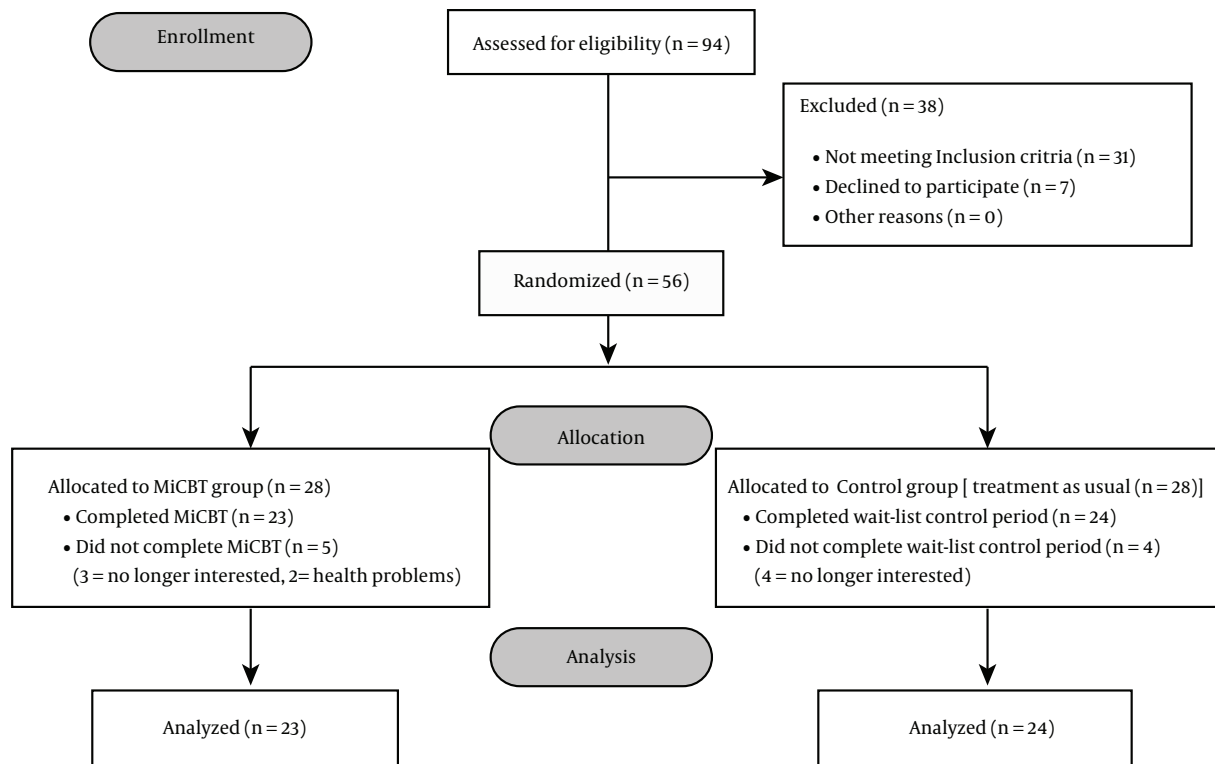
Figure 1. Study Flowchart

Table 1. The Curriculum for MiCBT Sessions

Session	Content
1	Introductory presentation about the sessions and rules, an overview of MiCBT, the concept and principles of mindfulness, mindful breathing
2	Mindful breathing (continued), an overview of a few MiCBT concepts (such as situation, sensory perception, evaluation, body sensations and reaction), the internal causes of intrusive thoughts and their extinction, part-by-part body scanning
3	Part-by-part body scanning (continued), explaining about body sensations , informal practice
4	Body scanning exercises (continued), introducing some CBT components in MiCBT (like exposure methods), encountering unpleasant sensations using Subjective Units of Distress Scale (SUDS) (a kind of form that is used for exposure to target events) through bipolar exposure (imaginary exposure to unpleasant situations)
5	Body scanning exercises (continued), review of SUDS
6	Body scanning exercises (continued), interpersonal skills, assertiveness and role-playing
7	Introducing the concepts of compassion and empathy, loving-kindness meditation
8	Review and evaluation

frequency, and percentage) were calculated for the demographic variables and the mean difference of depression, anxiety, and stress. Chi-square test was used to compare the marital status and family history of patients with MS in the study groups. Fisher's exact test was used to evaluate education levels. The independent samples t test was used to compare the significant differences between the mean scores of age, age at onset, and disease duration between the 2 groups. In addition, the normal distribution of the data was checked using Kolmogorov- Smirnov test, and analysis of covariance (ANCOVA) was performed to compare MiCBT and control groups for depression, anxiety, and stress.

3.5. Ethical Considerations

This research project was approved by the ethics committee of Kashan University of Medical Sciences, Kashan, Iran (code: IR.KAUMS.REC.1394.20) as well as the ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.SUMS.REC.1394.64). This study was also registered in the Iranian registry of clinical trials (IRCT code: IRCT2015041321722N1). All participants were asked to sign an informed consent form and were assured of the confidentiality of their personal data. They were also informed

that their participation in the study was voluntary and that they could withdraw from the study at any time. In addition, the control group was invited to attend the same MiCBT sessions after the study was completed.

4. Results

From the 56 patients with MS who had been randomly assigned into MiCBT and control groups (28 in each group), 47 (23 in the intervention group and 24 in the control group) completed the posttest at the end of the intervention, and their data were included in the final analysis (Figure 1). The means of the participants' age in the intervention and control groups were 36.78 ± 6.12 and 36 ± 7.08 years, respectively. Table 2 demonstrates the demographic characteristics of the participants. There were no statistically significant differences between the study groups at baseline in demographic variables including marital status, education, family history, age, age at onset, and disease duration (P > 0.05; Table 2).

Dependent variables were analyzed separately using analysis of covariance (ANCOVA) test with pretest scores included as covariates. Before using ANCOVA, the main assumptions of this statistical method were checked. The results of Kolmogorov-Smirnov test revealed that all variables of depression, anxiety, and stress in both intervention and control groups were normally distributed (P > 0.42). Moreover, the results of the Levene's test showed that the null hypothesis about the homogeneity of variances of the dependent variables including depression (F = 3.54, P = 0.084), anxiety (F = .273, P = 0.604), and stress (F = 2.78, P = 0.102) was confirmed. In addition, the slopes of the regression lines were the same in both study groups (P > 0.2).

Table 3 shows the participants' mean scores in depression, anxiety, and stress in the pre- and posttest. In the pretest, the mean scores of depression, anxiety, and stress of the experimental and control groups were 16.96 (7.1) versus 14.58 (10.93), 13.2 (7.25) versus 11.08 (7.9), and 22.09 (6.07) versus 20 (8.46), respectively. Therefore, no significant differences were found between the 2 groups in the pretest mean scores of depression, anxiety, and stress (P > 0.05). The results of ANCOVA indicated significant differences between the groups in depression (F (1, 44) = 42.16, P < 0.001), anxiety (F (1,44) = 20.63, P < 0.001), and stress (F (1,44) = 73.01, P < 0.001) after the intervention. The mean scores of all variables in the experimental group were significantly lower compared to those in the control group (P < 0.001; Table 3).

5. Discussion

The present research was the first study to assess the effects of MiCBT on patients with MS. Our findings revealed that MiCBT had positive effects on reducing depression, anxiety, and stress in patients with MS. This finding is consistent with the results of a research by Sohrabi et al. (2014) in which they reported a reduction in symptoms of depression in patients with Type II diabetes mellitus following the implementation of an 8-session MiCBT program (30).

Yazdanimehr et al. (2016) conducted a study to determine the effect of MiCBT on depression and anxiety among pregnant women. They studied 80 pregnant women, 40 in the experimental and 40 in the control groups. The results revealed that MiCBT was efficient in alleviating depression and anxiety even 1 month after the intervention. This finding is in compliance with the results of our study. Nevertheless, they used the Edinburg Postnatal Depression Scale and the Beck Anxiety Inventory to collect data on the study groups, therefore, their scales and the sample group were different from those of the present research (32).

In a study conducted by Grossman et al. (2010), patients with MS, who participated in eight 2.5-hour sessions of mindfulness-based intervention (MBI) training, experienced a significant improvement in the severity of depression and anxiety, quality of life, and fatigue. The therapeutic impact persisted over a 6-month follow-up period (33). Another research by Carletto et al. (2016) on 88 patients suffering from MS demonstrated the efficacy of MBI on quality of life, depression, anxiety, fatigue, and interpersonal relationship among patients with MS and their caregivers up to 6 months after the intervention (37). The findings of the above studies are in line with those of our investigation in depression and anxiety variables. Emotional disorders like depression and anxiety are associated with enhanced regional activation within the ventrolateral prefrontal cortex (PFC) in patients with MS (38). Mindfulness-based exercises like meditation reduce the activity of lateral PFC (39).

Kolahkaj et al. (2015) conducted a research on 48 patients with MS. The patients were randomly allocated into 2 groups: the control and the intervention groups. The intervention group took part in an 8-week mindfulness-based stress reduction (MBSR) training. They used depression, anxiety and stress scales (DASS-21) for data collection and reported that MBSR significantly alleviated depression, anxiety, and stress in patients with MS up to 1 month post intervention. The findings of this study correspond with those of the current research. However, the treatment and the sample size of the research were different from those of the present study (40).

In fact, mindfulness is able to teach people how to focus on their experiences and accept them as they are

Table 2. The Demographic Characteristics of Patients in MiCBT and TAU Groups[a]

Variables	Conditions	Groups		P Value
		MiCBT	**TAU**	
Marital status	Single	8 (34.8)	9 (37.5)	0.846[b]
	Married	15 (65.2)	15 (62.5)	
Education	Diploma	11 (47.8)	13 (54.2)	0.544[c]
	Associate degree	3 (13)	2 (8.3)	
	Bachelor	7 (30.4)	9 (37.5)	
	Master of Science	2 (8.7)	0	
Family history	Yes	6 (26.1)	7 (29.2)	0.813[b]
	No	17 (73.9)	17 (70.8)	
Age		36.78 ± 6.12	36 ± 7.08	0.688[d]
Age at onset		29.39 ± 5.68	29.38 ± 6.43)	0.993[d]
Disease duration		7.39 ± 3.51)	6.71 ± 3.19	0.489[d]

Abbreviations: MiCBT, mindfulness integrated cognitive behavior therapy; TAU, treatment as usual.
[a] Values are expressed as No (%) or mean ± SD.
[b] Chi-square test.
[c] Fisher's exact test.
[d] Independent-samples t test.

Table 3. The Mean Scores of Depression, Anxiety, and Stress in the Pre- and Posttest for Each Group[a]

Variables	Pretest		Posttest		F	P Value	Observed Power
	MiCBT	**TAU**	**MiCBT**	**TAU**			
Depression	16.96 ± 7.1	14.58 ± 10.93	6.17 ± 5.7	11.92 ± 10	42.16	< 0.001[b]	1.000
Anxiety	13.2 ± 7.25	11.08 ± 7.9	6.09 ± 5.2	10.08 ± 7.58	20.63	< 0.001[b]	0.993
Stress	22.09 ± 6.07	20 ± 8.46	10.87 ± 6.3	19.67 ± 8.87	73.01	< 0.001[b]	1.000

Abbreviations: MiCBT, mindfulness integrated cognitive behavior therapy; TAU, treatment as usual
[a] Values are expressed as No (%) or mean ± SD.
[b] $P < 0.05$.

without any prejudgment. They can, as a result, subdue their habitual responses and manage them effectively (41). Hence, mindfulness skills training can help reduce depression, anxiety, and stress in several ways: First, it teaches the skills necessary for people to see their mental states as transient not reality. As a result, people learn how to face the positive and negative content of their thoughts and emotions, which leads to not being drowned to the past and future thoughts. By living in the moment, individuals can guard against depression, anxiety, and stress. Mindfulness therapies like MiCBT can also facilitate these strategies through acceptance of internal experiences and nonjudgmental awareness to them (42). Such enhanced awareness can set the grounds for better management of emotional states by preventing the patients from being trapped in mental rumination. Second, mindful breathing serves to teach people how to live in the present, drifting apart from

internal troublesome experiences, and thoughts. This exercise helps patients stop the cycle of rumination (43), gradually strengthening a sense of self-control and the ability to tolerate and accept unpleasant experiences to better cope with what they go through. Moreover, sustained monitoring of the breath is neuroanatomically related to the midline frontal cortex, basal ganglia, anterior prefrontal cortex, and anterior right parietal cortex and can bring about improvement in both the executive control network and the alertness network (29). Nonetheless, the frontal and prefrontal regions dysfunction is observed in patients experiencing depression (44). Third, in the MiCBT training, body scanning intends to elevate the introspective awareness and acceptance in everyday situations. In fact, it seems that those individuals who are skilled in the recognition of the early body sensations and accept them as they happen, tend to be more sophisticated in

regulating emotions, which usually manifest themselves in the form of thoughts and sensations. In addition, the reorganization of brain pathways (neuroplasticity) in somatosensory pathways, which takes place during the formal practice of body scan techniques, facilitates the transfer of introspective skills in daily life (29). As a result, individuals can manage their emotions better in everyday situations. Fourth, the interpersonal skills training in MiCBT training promotes interpersonal relationships and appropriate concentration on other people (36). Experts believe that depression is relieved when individuals reduce their extreme focus on themselves (45). A recent study also suggested that interpersonal skills and assertiveness training could reduce depression, anxiety, and stress (46).

Several limitations of this investigation need to be mentioned. The primary limitation was the gender of the study sample. They were all female patients with MS, which may affect the generalizability of the results. The second limitation was the lack of a follow- up period due to time limitation. The other limitation was the lack of theoretical background for the study because of novelty of the intervention. Thus, it is recommended that future studies assess the effect of MiCBT on both male and female patients with MS over follow-up periods. Advantages of this study included involving a control group, focusing on psychological symptoms simultaneously giving their high comorbidity rate, and administrating MiCBT as a treatment procedure whose efficacy had not been explored on patients with MS and stress.

This study demonstrated that MiCBT effectively contributes to lower depression, anxiety, and stress in patients with MS. Therefore, considering the advantages and disadvantages, MiCBT can be adopted as a complementary therapy for patients with MS as well as a regular program in MS societies.

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Footnotes

Authors' Contribution: Study concept and design: Shima Bahrani and Fatemeh Zargar; data collection: Gholamali Yousefipour and Shima Bahrani; analysis and Interpretation of data: Hossein Akbari and Shima Bahrani; final revision and editing the manuscript: Fatemeh Zargar;

study supervision: Fatemeh Zargar and Gholamali Yousefipour

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