Original Article

The effectiveness of group intervention focused on intolerance of uncertainty on psychological distress and quality of life in multiple sclerosis patients

Hani Rahimi, Mohammadreza Pirmoradi, Fahimeh Fathali Lavasani, Hojjatollah Farahani[1]

Abstract:

AIM AND BACKGROUND: Multiple sclerosis (MS) is a long-course incurable disease as well as an unknown prognosis causing patients to experience a variety of psychological outcomes. Meanwhile, inability to control the disease-related uncertainty leads to the use of maladaptive coping strategies, causing more psychological distress. This study investigated the effectiveness of intervention focused on the intolerance of uncertainty on psychological distress and quality of life in MS patients.

MATERIALS AND METHODS: This research adopted a true experimental design. All phases of the study were conducted online due to the COVID-19 pandemic during 2021 in Tehran. The statistical population of the study was purposefully selected from among MS patients and was randomly assigned to three groups of 20: IU intervention and two control groups (cognitive behavioral therapy (CBT) and treatment as usual (TAU) groups). The study included pre-test, post-test, and follow-up stages. The outcome measures of the study included the Depression Anxiety Stress Scale (DASS-21) as well as Multiple Sclerosis Quality of Life-54 (MSQoL-54). Mixed analysis of variance was used to analyze the data.

RESULTS: The results showed that IU intervention compared to CBT, is more effective on psychological distress (depression $P = 0.006$, anxiety $P = 0.01$, and stress $P = 0.01$) and quality of life ($P = 0.001$) in MS patients. Nonetheless, IU-focused intervention is more effective than TAU on psychological distress (depression $P = 0.0001$, anxiety $P = 0.0001$, stress $P = 0.0001$) as well as quality of life ($P = 0.0001$) in these patients.

CONCLUSIONS: IU-based intervention can reduce psychological distress and improve quality of life of MS patients. Accepting uncertainty can reduce the anxiety and stress of MS patients which can increase the quality of life of these patients.

Keywords:

Cognitive behavioral therapy, intolerance, multiple sclerosis, psychological distress, quality of life, uncertainty

Department of Clinical Psychology, School of Behavioral Sciences and Mental Health (Tehran Institute of Psychiatry), Iran University of Medical Sciences, Tehran, Iran, [1]Department of Psychology, Tarbiat Modares University, Tehran, Iran

Address for correspondence:
Dr. Mohammadreza Pirmoradi, PhD in Clinical Psychology, Assistant Professor, Department of Clinical Psychology, School of Behavioral Sciences and Mental Health (Tehran Institute of Psychiatry), Iran University of Medical Sciences, and Tehran, Iran.
E-mail: Pirmoradi.mr@iums.ac.ir

Introduction

Multiple sclerosis (MS) is a myelogenous disease of the central nervous system in which the myelin sheath of the central nervous system, such as the brain, optic nerve, and spinal cord, is damaged.[1] The spread of this disease is growing increasingly in the youth,[2] and in recent studies, the incidence of MS has been estimated to increase from 0.05 to 2.85 per 100,000 people and its prevalence from 0.69 to 26.92 per 100,000 people.[3] MS is known as the "thousand faces" disease because it affects the central nervous system and therefore, it increases the probability of psychological

symptoms.[4–5] Among these psychological symptoms are psychological distress[6] and decreased quality of life.[7] Psychological distress has been suggested as the most important event or the second risk factor for MS.[8] Psychological distress is a term describing the general psychopathology of an individual with a set of symptoms of perceived depression, anxiety, and stress.[9] Research has shown that 50% of people with MS have experienced depressive disorder at least once.[10,11]

On the other hand, anxiety symptoms in these patients such as depression reduce their general health and lead to a decline in well-being and quality of life.[12] Quality of life is a multidimensional concept encompassing physical, mental and social health. This component is increasingly considered as an important indicator of the effectiveness of health interventions in the field of health policymaking.[13] In this regard, the results of previous studies have shown that patients with MS have significantly lower quality of life compared to healthy people in the community as well as patients with other chronic diseases such as epilepsy, diabetes, rheumatoid arthritis and inflammatory bowel disease.[14]

Due to the complex and chronic nature of MS, drug treatment alone cannot solve all of the patient's problems, and in addition to medications, the use of psychological therapies can be effective to accelerate the treatment process, prevent recurrence, and increase the duration of treatment. One of the oldest therapies in this field is cognitive behavioral therapy (CBT), which has been shown by several studies to be effective in MS patients.[15-20] Moreover, people with chronic diseases such as MS experience uncertainty due to lack of knowledge about the status of the disease and the length of their treatment,[21] and in fact, living with uncertainty is a part of the daily experience of MS patients.[22] According to research, the core of psychological distress in MS patients is their inability to tolerate uncertainty.[23] This disability leads to behaviors that aim to increase control, such as avoiding anxious situations and mental rumination in relation to the source of stress. These strategies ultimately lead to increased anxiety and depression.[24-25] Therefore, by targeting intolerance of uncertainty (IU) as the focus of MS psychotherapy, we can take a step towards an integrated approach for these patients. This integrated approach allows clinical specialists to create single interventions for multiple problems in these patients.[26]

IU-focused intervention is designed by considering some basic principles of CBT as well as acceptance and commitment therapy. This treatment focuses on recognizing the controllable and uncontrollable aspects of MS, setting personal goals for accepting the disease regardless of uncertainty, as well as mindfulness exercises, and finding ways to live alongside personal

values despite uncertainty about the future.[26] The results of Molton *et al*.'s[27] study showed that interventions focusing on the inability to tolerate uncertainty led to a decrease in IU and increased acceptance of symptoms in patients with MS, but had little effect on patients' anxiety. Other studies have confirmed the effectiveness of IU-based intervention in other groups, such as breast cancer patients[28] and generalized anxiety disorder (GAD) patients.[29,30]

Due to the unpredictable nature of MS and the importance of inability to tolerate uncertainty in these patients,[23] the aim of this study was to evaluate the effectiveness of intervention focused on inability to tolerate uncertainty on psychological distress and quality of life in patients with multiple sclerosis.

Materials and Methods

Study design and setting
This study was a true experimental research including three phases of pre-test, post-test and a three-month follow-up with equivalent control groups. The research design involved three groups assigned to one experimental group and two control groups through simple random sampling procedure. Due to the COVID-19 pandemic and the inclusion of MS patients in the list of high-risk groups for this disease, the phases of this study, including the intervention, pre- and post-tests as well as follow-up, were performed online. The present study was conducted in Tehran, Iran in 2021.

Study participants and sampling
In order to conduct the study, after the approval of the MS Association of Iran, the invitation to participate in the research was placed as an advertising poster in the Association's telegram channel. As it is suggested in the literature,[31] in experimental studies and group therapy, the number of participants in each group should not be less than 15. Thus, considering the inclusion criteria, 60 patients who volunteered to participate in the study were purposefully selected and randomly assigned to three groups of 20: intervention (IU) and two control groups (CBT and treatment as usual (TAU)).

Inclusion criteria included definite diagnosis of MS by a neurologist, the age range of 18–55 years, having a minimum education of diploma, having a medical record in the MS Association, obtaining a score between 0 and 5 on the Expanded Disability Status Scale (EDSS) and having the necessary facilities for online participation in different phases of the research (laptops or smart phones). Exclusion criteria included Diagnostic and Statistical Manual of Mental Disorders (DSM) (5th edition) diagnosis of psychotic or bipolar disorder, DSM-5 diagnosis of drug use disorder, and the presence of a physical illness

that prevented them from attending treatment sessions, recurrence of the disease, hospitalization of the patient during the intervention, involvement in a serious life crisis during the intervention period according to the patient's report and also the absence of more than three sessions in treatment sessions. Based on the exclusion criteria, 11 patients were excluded during the study (IU: 4; CBT: 3; TAU: 4). The CONSORT diagram is provided in Figure 1.

The online formats of the research questionnaires were prepared via Google Forms and were sent to patients in all three phases (before and after the intervention and 3-month follow-up phases) through Telegram or WhatsApp applications. Skype was also used to perform intervention sessions. In order to prevent the researcher's bias, the intervention sessions of inability to tolerate uncertainty were conducted by the first author while CBT sessions were conducted by a clinical psychologist, both of whom were PhD candidates in clinical psychology.

IU-focused intervention was based on the protocol of Molton *et al*.,[27] performed in 12 sessions of two hours duration on a weekly basis. Descriptions of the sessions are given in Table 1.

CBT was based on the protocol of Van den Akker *et al*.,[21] performed in 12 sessions of two hours duration on a weekly basis. Descriptions of the sessions are given in Table 2.

Data collection tools
The Depression anxiety stress scale (DASS-21)
This questionnaire was first introduced by Lovibond in 1995.[31] This questionnaire has 21 questions from which 7 were used to measure each of the symptoms of depression, anxiety and stress.[32] In the study by Sinclair *et al*., the reliability of internal consistency of this questionnaire for depression, anxiety and stress was reported to be 0.91, 0.80 and 0.84, respectively.[32,33] In research by Manafi and Dehshiri, the reliability of this questionnaire using Cronbach's alpha coefficient for depression, anxiety and stress amounted to 0.81, 0.82 and 0.78, respectively.[34]

Multiple sclerosis quality of life questionnaire (MSQoL-54)
This questionnaire was designed by Vickery in 1995 and consists of 54 items that fall into 12 scales. These 12 scales are divided into two general dimensions: physical health and mental health.[35] Vickery reported the internal consistency reliability coefficients of the 12 scales of this questionnaire between 0.75 and 0.96.[36] Borhani and Ghaem also reported the internal consistency reliability of the scales of this questionnaire between 0.65 and 0.94 and the total reliability of the questionnaire using Cronbach's alpha coefficient as 0.96.[37]

Ethical consideration
This study was registered at the Iranian Registry of Clinical Trials with the code of IRCT20210414050967N2, and approved by the Ethics Committee of Iran University of Medical Cciences, approval no. IR.IUMS. REC.1399.1073. The ethical considerations of the present study included the completion of the informed consent form by the research participants, the confidentiality of the recorded information, and giving the right for participants to participate in or withdraw from the study.
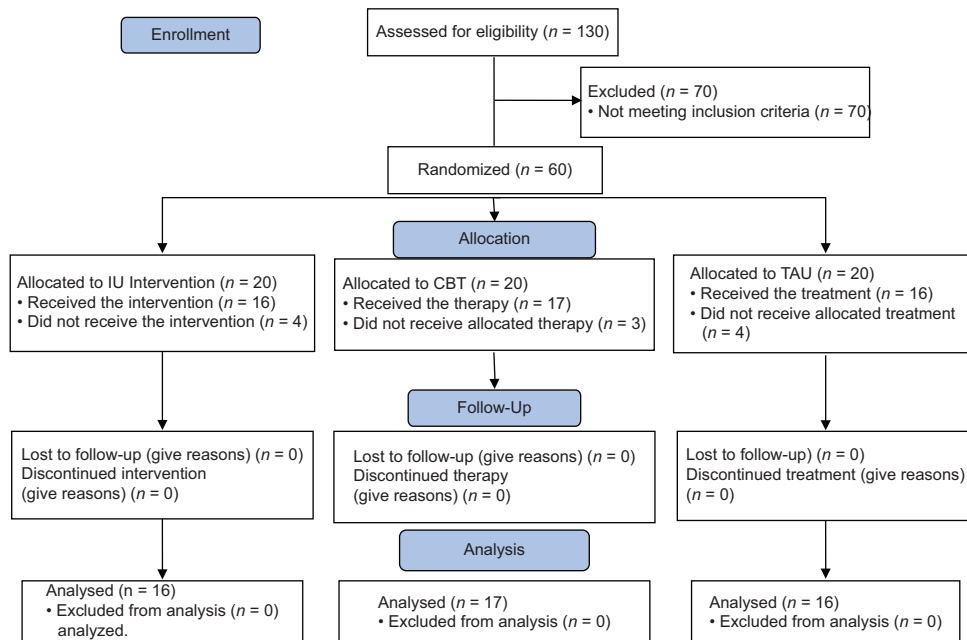

Figure 1: CONSORT flowchart

Table 1: Summary of IU intervention sessions

IU Sessions Schedule	Content of the Sessions
Sessions 1-2	Introduction; description of session rules, introducing the IU treatment and its main components; introducing "uncertainty" and its resulting anxiety; introducing coping continuum (from over-control to avoidant behaviors).
Sessions 3-5	Teaching the differences between thoughts and emotions; introducing mindfulness meditation as a tool for non-judgmental awareness of thoughts and reactions related to uncertainty; teaching attention biases due to stress caused by uncertainty.
Sessions 6-7	Familiarity with controllable and uncontrollable aspects of MS; familiarity with two overly common control strategies (rumination and catastrophizing) as individual efforts to reduce uncertainty; introducing some management methods to control excessive control strategies.
Sessions 8-9	Introducing "acceptance" and its role in MS; acceptance to integrate MS as one aspect among the various aspects of individual life, not as the only aspect of life; the relationship between tolerance of uncertainty and acceptance of MS; the use of acceptance to feel comfortable while having incomplete awareness of what will happen in the future.
Sessions 10-11	Awareness of life values; teaching the differences between value, purpose and choice; awareness of the role of certainty-seeking in taking one's energy and moving away from life values; discussing personal values and pursuing them despite the existence of MS.
Session 12	Reviewing the skills and techniques taught during the intervention; discussing the strategies to maintain these skills; planning for relapse prevention (how to deal with uncertainty in situations where concerns arising from lack of full awareness come back to the patient).

Table 2: Summary of CBT sessions

CBT Sessions Schedule	Content of the Sessions
Sessions 1-2	Introduction; trying to get to know each other; getting acquainted with group therapy and the importance of participation in all training sessions and the importance of doing homework; introducing CBT and its effectiveness in chronic diseases, especially MS; explaining thinking, feeling, the relationship between emotions and thoughts and behavior, and the important role of thoughts; cognitive behavioral formulation and setting functional and objective goals for participating patients.
Sessions 3-4	Analyzing the new identity after the diagnosis of MS; discussing changes in the areas of work, family, friends, etc.; identifying cognitive distortions associated with MS; challenging cognitive distortions associated with the disease; and cognitive reconstruction of these beliefs.
Sessions 5-6	Identifying cognitive distortions related to common symptoms of MS; cognitive reconstruction of dysfunctional thoughts related to symptoms; explaining the consequences of continuous focus on symptoms, practicing to reduce attention to symptoms through reversal attention techniques.
Sessions 7-8	Regulating sleep pattern: explaining the importance of sleep hygiene and a regular sleep/wake cycle; training sleep hygiene and behavioral instructions to improve the sleep/wake cycle; regulating patients' physical activity according to their baseline physical activity; teaching patients to regulate their exercise program by systematically increasing regular physical activity to achieve predefined goals.
Sessions 9-10	Organizing social activities: empowering patients to develop social activities by teaching communication skills and discussing barriers to communicating with others and how to deal with it; correcting unrealistic expectations of others and the environment; teaching how to express your personal limitations and boundaries to important people in your life.
Sessions 11-12	Regulating mental activities: encouraging and supporting patients to increase mental activities such as reading or working with a computer; teaching them how to deal with possible cognitive impairments such as memory or concentration problems; reviewing skills and techniques taught during the treatment; discussing strategies for maintaining these skills; and planning for relapse prevention.

Data analysis

Since the present research design is true experimental with heterogeneous groups, with pre-test, post-test and follow-up, the best statistical method for data analysis is the mixed-design analysis of variance (ANOVA) (factor analysis with repeated measures).

Results

After the exclusion of 11 participants, 49 participants with an age range of 23–42 years and an average age of 30.79 ± 5.06 years took part in the study. Regarding their educational degree, 18 had a diploma (36.7%), 26 had a bachelor's degree (53.1%) and 5 had a master's degree (10.2%). Twenty-two participants were male (44.9%) and 27 were female (55.1%). Table 3 shows the descriptive indicators of the quality-of-life (QoL) scores, depression, anxiety and stress in three assessment phases for the groups.

The Chi-squared values obtained in all variables of the study, except stress, are significant at the level of $P \leq 0.05$, and due to the heterogeneity of the matrix, the corrected coefficients should be used; hence, Geisser coefficients were employed in the present study. In the stress variable, sphericity coefficients are used.

As shown in Table 4, considering that the amount of ETA squares in the experimental group in all research variables (QoL, depression, anxiety and stress) is more than 0.14, according to the general rule of ETA squares, it can be held that the results of this study indicate the high effectiveness of the intervention programs focused on the inability to tolerate uncertainty.

Table 5 shows the results of the mixed ANOVA test for quality of life, depression, anxiety and stress. As can be observed, the effect of measurement time on quality of life, depression, anxiety and stress scores is significant. With these conditions, it can be stated that regardless of the studied groups, there is a significant difference between the mean scores of QoL, depression, anxiety and stress in pre-test, post-test and follow-up. Furthermore, F values are significant in evaluating the effect of experimental intervention on all variables at the level of $P \leq 0.05$, pointing to a significant difference between groups.

Moreover, two-way comparisons of intragroup and intergroup differences were investigated using the Bonferroni test. Intragroup comparisons show that in the research variables, the mean of post-test and follow-up test in the experimental group is significantly higher than that of the pre-test group. Also, the difference between post-test and follow-up test scores is not significant. Intergroup comparisons show that there is a significant difference between post-test and follow-up scores in the intervention group focused on IU with both control groups [Table 6].

Discussion

The aim of this study was to evaluate the effectiveness of IU-focused intervention on psychological distress and quality of life in MS patients. The results of the analysis of research data revealed that this intervention had a significant effect on reducing psychological distress and increasing the quality of life in MS patients and this effect continued at follow-up. The results of the study are in line with those of Molton *et al.*,[27] Beheshti *et al.*,[29] Hebert and Dugas,[29] Ghielen *et al.*,[38] Shareh and Asgharkhah,[39] Mills and Allen,[40] as well as Simpson *et al.*[41]

The choice of IU intervention is based on the fact that uncertainty tolerance is a fundamental element in promoting mental well-being outcomes such as reducing psychological distress and increasing quality of life.[23,26] In many ways, choosing to tolerate uncertainty as a goal is not common in classical interventions. Classical therapies often prioritize psychological distress (e.g., anxiety) and identify structures that may contribute to the problem, such as behavioral activation and

Table 3: Descriptive indicators of the quality of life, depression, anxiety and stress scores by group and test

Variable	Assessment phase	SD±Mean		
		IU	CBT	TAU
Quality of Life	Pre-test	38.12±8.99	40.05±8.02	38.62±8.30
	Post-test	68.18±6.41	58.52±8.57	39.18±8.30
	Follow-up	65.81±5.62	55.47±7.13	41.31±6.59
Depression	Pre-test	10.25±2.23	10.64±2.37	10.12±1.78
	Post-test	6.00±1.41	7.76±1.95	10.25±2.20
	Follow-up	6.50±1.31	8.11±1.96	10.00±1.96
Anxiety	Pre-test	11.50±2.09	11.12±1.96	11.31±2.15
	Post-test	7.06±1.52	8.43±1.54	10.56±1.50
	Follow-up	7.52±1.43	8.93±1.80	10.56±2.73
Stress	Pre-test	10.50±2.16	9.94±2.56	10.43±1.75
	Post-test	6.12±1.62	7.58±2.00	10.43±1.63
	Follow-up	6.37±1.54	7.82±2.32	11.18±1.90

Table 4: Investigation of homogeneity of variances and variance-covariance matrix

Variables	Box's M Test			Mauchly's Test		
	M	F	P	Mauchly	χ^2	P
Quality of Life	14.07	1.06	0.38	0.57	24.91	0.0001
Depression	22.80	1.71	0.06	0.57	25.12	0.0001
Anxiety	19.52	1.46	0.12	0.83	7.77	0.02
Stress	10.51	0.79	0.65	0.91	3.87	0.14

Table 5: Mixed analysis of variance test for quality of life, depression, anxiety and stress

Variable	Sum of Squares	Df	Mean Squares	F	Level of Significance	Effect Size	Statistical Power
Quality of Life							
Time	8192.19	1.40	5837.65	225.62	0.0001	0.83	1.00
Experimental v.	7753.89	2	3876.94	29.49	0.0001	0.59	1.00
Time* Experimental v.	4110.28	2.80	1464.46	56.60	0.0001	0.71	1.00
Depression							
Time	164.07	1.40	117.14	106.61	0.0001	0.69	1.00
Experimental v.	155.04	2	77.52	7.75	0.001	0.25	0.93
Time* Experimental V.	91.56	2.80	32.68	29.74	0.0001	0.56	1.00
Anxiety							
Time	202.93	1.86	108.94	40.81	0.0001	0.47	1.00
Experimental v.	118.43	2	59.21	10.01	0.0001	0.30	0.97
Time* Experimental V.	69.98	3.72	18.78	7.03	0.0001	0.23	0.99
Stress							
Time	139.55	2.00	69.77	71.5	0.0001	0.60	1.00
Experimental v.	236.57	2	118.28	12.04	0.0001	0.34	0.99
Time* Experimental V.	116.12	4	29.03	29.79	0.0001	0.56	1.00

Table 6: Bonferroni test (pair-wise comparison between IU group and control groups)

Variables	Comparisons	The difference between IU and control group 1 (CBT)		The difference between IU and control group 2 (TAU)	
		Mean differences	Sig	Mean differences	Sig
Quality of Life	Post-test differences	9.65	0.001	29.00	0.0001
	Follow-up differences	10.34	0.0001	24.50	0.0001
Depression	Post-test differences	−1.76	0.006	−4.25	0.0001
	Follow-up differences	−1.61	0.01	−3.50	0.0001
Anxiety	Post-test differences	−1.37	0.01	−3.50	0.0001
	Follow-up differences	−1.63	0.007	−3.31	0.0001
Stress	Post-test differences	−1.46	0.01	−4.31	0.0001
	Follow-up differences	−1.44	0.02	−4.81	0.0001

cognitive assessments.[16] For example, in the traditional CBT model, anxiety is a key target, and other positive effects (including less IU) may occur incidentally during the intervention. In comparison, in the IU-focused intervention, it directly and openly targeted uncertainty and the discussion about uncertainty and the resulting stress was the core of the intervention. Although this intervention also had an effect on anxiety, it was not the main focus.

Moreover, as IU is the core of MS and cannot be considered as a result of depression or anxiety caused by the disease,[23] this intervention can be promoted as a universal, effective, integrated treatment exclusively for MS, like the Unified Protocol (UP) for the treatment of mood disorders, developed universally and exclusively for mood disorders.[25] The advantage of an integrated approach is that it allows specialists to achieve a single intervention for multiple patient problems rather than mastering different interventions. Because MS has many psychological consequences such as fatigue, depression, anxiety, mental retardation, etc., this integrated approach can be effective.

The results of the present study are consistent with those in the study by Molton *et al.*[27] illustrating that IU-focused intervention can be effective on psychological distress and QoL of patients with MS. Moreover, in line with the results of the present study, the intervention of Hebert and Dugas was performed based on behavioral experiments.[30] In their study, behavioral experiments were used to change beliefs associated with uncertainty. This cognitive behavioral approach was effective in reducing the GAD rate in this sample and supported the idea that GAD symptoms can be reduced by targeting IU alone. Although the present intervention focused more on radical acceptance of uncertainty and cognitive fault strategies (rather than behavioral treatment to challenge beliefs about uncertainty) and more on uncertainty related to a medical condition, the primary goal of both interventions was similar: increased tolerance of uncertainty that leads to increased acceptance of MS; even this effectiveness is greater than its effect on IU.[27]

One of the main elements of this study was to address uncertainty-related cognitions and perhaps more importantly, to promote the view that one can live well despite uncertainties and their related cognitions. In this regard, in accordance with the principles of treatment based on acceptance and commitment, this theme is supported by the idea that an unpleasant scenario (for example, the presence of uncertainty) does not need to be controlled or resolved in life, but the goal is to be able to coexist in its presence and to focus on living according to our values.[7] We believe that the reluctance to live with uncertainty is a barrier to acceptance in many MS patients. In general, according to acceptance-based therapies, the ability to "accept MS" means accepting its challenges, one of which is certainly living with the unpredictable ghost of functional loss.[37]

On the other hand, another aspect of the current intervention was mindfulness and its related techniques. In these sessions, clients learned to recognize the differences between their feelings and thoughts and to take a non-judgmental approach to their feelings and thoughts through mindfulness techniques. Various studies have shown the effectiveness of mindfulness therapies on psychological distress and quality of life in MS patients.[37–40] Mohamadirizi *et al.*[42] found that mindfulness-based interventions can increase secure attachment in MS patients and contribute to their mental health. Some studies have also shown that increasing MS patients' awareness of the disease process and its challenges improves their QoL.[42] The results of this study are consistent with those of Mohamadirizi *et al.*[42] Perhaps in explaining the findings, it can be claimed that since the IU intervention uses mindfulness techniques associated with increased immunity in these patients, it is expected that it increases uncertainty tolerance in these patients. Also, since relaxation techniques are used in this treatment, it would lead to decreased psychological distress in these patients. This finding is in line with the research by Soheili *et al.*,[43] that showed the effect of relaxation on anxiety and depression in MS patients.

Alternatively, in this treatment, patients became aware of the controllable and uncontrollable aspects of MS and learned to replace the attempt to control the uncontrollable condition (the course or prognosis of the disease) by accepting the uncontrollable aspects. In this regard, clients were trained to identify and reduce mental control strategies such as catastrophizing and mental rumination. By reducing these strategies, the tolerance of uncertainty in these clients increased, which in turn resulted in decreased psychological distress and improved QoL.

Another element in IU intervention which is directly related to QoL is the emphasis on the role of values.[26] Clients in this treatment have learned to distinguish between values, goals, and decisions, and realized that their efforts to overcome uncertainty would keep them away from their values in their life.

Limitations and recommendations

One of the limitations of this study was the lack of classification of people at the stage of diagnosis of MS. Since the time elapsed from the diagnosis of the disease can affect the performance of individuals, it is better to examine the diagnosis stage of the disease as a moderating variable in future research. Also, another limitation of the study was the short period of the follow-up stage which should be considered while generalizing the findings.

Conclusions

The results of the present study showed that IU intervention had a significant effect on reducing psychological distress and increasing the quality of life of MS patients. MS is a chronic disease and these patients need lifelong self-care and treatment, as in other chronic diseases[44]; thus, IU intervention, incorporating health-promoting behaviors and enhancing some dimensions of lifestyle behaviors, can add more to their general health as well as psychological health. Given the fact that psychological distress and quality of life are two essential components of psychological and general health in MS patients, their improvement through IU intervention will enhance these patients' general, mental, and psychological health. Employing IU intervention can be effective as a complementary treatment along with drug therapy to reduce the psychological problems of MS patients; thus, MS associations and health policymakers can consider incorporating IU intervention in improving MS patients' physical and mental health. Further studies with different IU design and implementation are required to target various aspects of patients with MS.

Acknowledgements

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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