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A Comparative Study on the Effectiveness of Mindfulness Therapy, Cognitive Rehabilitation Exercises, and Pharmacotherapy in Reducing Non-Motor Symptoms in Parkinson's Patients

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Abstract

Background & Objectives: This study aimed to examine the comparative effectiveness of mindfulness therapy, cognitive rehabilitation exercises, and drug therapy in addressing non-motor symptoms among patients with Parkinson's disease (PD).

Materials & Methods: This applied research, employing an experimental design, utilized a single-factor model with two levels and three groups analyzed through a mixed-method approach. The study population included Parkinson's patients in Shiraz, and the sample was selected purposively based on Cohen's (1986) experimental research sample size table, comprising 18 participants per group including mindfulness, pharmacotherapy (Escitalopram) as control and cognitive rehabilitation, totaling 54 participants. Instruments used for the assessment and diagnosis of disorders, as conducted by a clinical specialist, included the Unified PD Rating Scale (UPDRS), SCID-5-CV, MMSE (to screen for dementia), and the Non-Motor Symptoms Scale for Parkinson's Patients (NMSS).

Results: The findings confirmed the effectiveness of mindfulness therapy and cognitive rehabilitation in mitigating non-motor symptoms, including cardiovascular issues, sleep disturbances, fatigue, mood and cognitive impairments, perceptual problems and hallucinations, attention and memory deficits, and dysfunctions in the digestive, urinary, and sexual systems, along with other miscellaneous conditions ($P < 0.05$).

Conclusion: Based on the findings, it is recommended that Parkinson's care centers implement mindfulness therapy and cognitive rehabilitation exercises to enhance the aforementioned components, thereby contributing to the overall well-being of PD patients.

Keywords: Mindfulness, Cognitive rehabilitation, Parkinson, Elderly, Non-Motor symptoms.

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Introduction

Parkinson's disease (PD) is a chronic and progressive neurological disorder characterized by clinical features such as tremors, rigidity, bradykinesia, postural instability, cognitive and autonomic dysfunction, and sleep disturbances (1). Diagnosing PD in its early stages is challenging due to the lack of specific diagnostic tests, such as blood tests or brain imaging. The disease results from the degeneration of both dopaminergic

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and non-dopaminergic neurons, along with disruptions in neurotransmitter systems (2). The loss of dopamine-producing brain cells leads to the emergence of symptoms such as delayed movement initiation and increased muscle tone, which contribute to motor control disorders. Consequently, patients experience resting tremors, gait disturbances, postural instability, and balance issues in daily life. As the disease progresses, additional challenges such as initiating movements and maintaining rhythmic walking patterns exacerbate these complications (3, 4).

However, PD symptoms are not confined to motor issues and patients also experience non-motor symptoms that become more apparent as the chronic disease advances (5). Non-motor symptoms—such as depression, anxiety, sleep disorders, memory and cognitive impairments, stress, fear, and social withdrawal—are also prevalent (6). These non-motor symptoms significantly diminish the patient's quality of life and psychosocial functioning. Unfortunately, non-motor symptoms are often overlooked, with over 50% of them remaining undiagnosed in clinical practice (7).

Non-motor symptoms can manifest at any stage of the disease, occurring in 21% of patients at the time of diagnosis and rising to 90% after seven years (7). Moreover, an extensive international study revealed that fewer than 2% of patients reported no non-motor symptoms (8). These symptoms encompass cognitive deficits, psychiatric disturbances, autonomic dysfunction, gastrointestinal issues, sleep disturbances, fatigue, sensory impairments, and olfactory dysfunction. Certain symptoms, such as constipation, rapid eye movement (REM) behavior disorder, depression, and olfactory impairments, may precede motor symptoms by years.

The individual afflicted with PD typically demonstrates social withdrawal, reduced cognitive flexibility, and a diminished ability to cope with challenges. Many patients seem to experience significant emotional constraints. Determining the extent to which these behavioral inconsistencies are caused by the disease's organic progression versus the patient's cognitive reactions to these changes remains difficult (9). Non-motor symptoms, combined with functional impairments and disease progression, are critical determinants of quality of life for both patients and their family caregivers. These challenges often necessitate long-term caregiving, typically provided by family members, which imposes significant physical, emotional, and psychosocial burdens on caregivers (10).

Given these complexities, it is essential to adopt a therapeutic approach that comprehensively addresses the disease. Combining mental training programs with clinical symptom assessment may prove beneficial for both patients and their caregivers (11).

Cognitive rehabilitation involves a structured set of therapeutic activities aimed at enhancing cognitive functions, based on a thorough evaluation of mental and behavioral disorders (12, 13). Over the past few decades, cognitive rehabilitation has been widely used to support patients with brain injuries (14). For instance, a study comparing a therapeutic package tailored to psychological factors related to PD and Memory Specificity Training (MEST) found that MEST, as a multidimensional intervention, effectively improved patients' mood (9). Non-pharmacological interventions, including cognitive rehabilitation, have been developed as personalized medicine strategies to address cognitive and functional impairments associated with PD (15, 16).

Luo et al. (17) found that cognitive behavioral therapy (CBT) effectively treated certain non-motor symptoms in Parkinson's patients, although it was less effective for fatigue and quality of life. Cognitive rehabilitation is a promising therapy for addressing cognitive impairments in PD, with several studies confirming its efficacy. Additionally, research has observed subtle cognitive improvements in Parkinson's patients following cognitive rehabilitation, suggesting

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neuroplasticity induced by cognitive exercises in the context of a degenerative disease (18). A long-term study evaluating the effects of cognitive rehabilitation on cognition, function, and brain activity reported sustained improvements even 18 months after treatment (18).

Another therapy explored in this research is mindfulness-based therapy, which emerged in psychotherapy in the late 1970s, particularly in conjunction with meditation. It has been used alongside bibliotherapy, as an adjunct to psychotherapy, or independently as a form of short-term psychotherapy. These innovative therapies emphasize two critical aspects of mindfulness: present-moment awareness and acceptance, often referred to as the "Third Wave" of behavioral therapy (19).

Mindfulness enables individuals to perceive events as less disruptive by focusing on the present moment (20). A meta-analysis by Lin et al. (21) revealed that mindfulness therapies and meditation significantly improved Unified PD Rating Scale (UPDRS) scores and cognitive function. However, no significant differences were observed between mindfulness therapies and controls regarding walking speed in the PD Questionnaire (PDQ-39). Pickut et al. (22) investigated neurobehavioral changes associated with mindfulness-based interventions (MBIs) in Parkinson's patients. Their findings indicated significant improvements, including reduced UPDRS scores, increased PDQ-39 scores, and enhanced mindfulness levels as measured by a five-dimensional mindfulness questionnaire.

Although alternative and complementary therapies are increasingly used for chronic conditions like PD, the behavioral effects of mindfulness training remain underreported, highlighting the need for further research. In light of the aforementioned considerations, this study aims to examine whether mindfulness therapy, cognitive rehabilitation, and pharmacotherapy differ in their effectiveness in alleviating non-motor symptoms.

Materials and Methods

The present study employed a quasi-experimental design with a pre-test/post-test framework and a three-month follow-up. The first experimental group received pharmacotherapy (Escitalopram) combined with mindfulness therapy, the second experimental group underwent cognitive rehabilitation alongside pharmacotherapy (Escitalopram), and the control group received single pharmacotherapy (Escitalopram). Given its nature, this study is classified as quantitative research. Regarding its objective, it qualifies as applied research. The study's design diagram is presented in Table 1, with additional procedural details outlined in Flowchart 1.

Population, Sample, and Sampling Procedure

The sample size in the present study consisted of 54 patients diagnosed with PD who were referred to the Neurology Unit of Imam Reza Clinic in Shiraz in 2023. Based on Cohen's Effect Size table (d=0.88), the participants were equally divided into three groups of 18 persons each. The samples were selected through purposive sampling among PD patients. For the selection process, first, the neurologists referred the patients to the therapist, who explained the study and its objectives to them. Those who agreed to participate were then referred to a clinical specialist for diagnostic interviews and clinical evaluation.

Table 1. Research Design Diagram Table

Type of assignment	Groups	Pre-Test	Independent Variable	Post-Test	Follow up
R	X_1	T_1	X_1	T_2	T_3
R	X_2	T_1	X_2	T_2	T_3
R	Control	T_1		T_2	T_3

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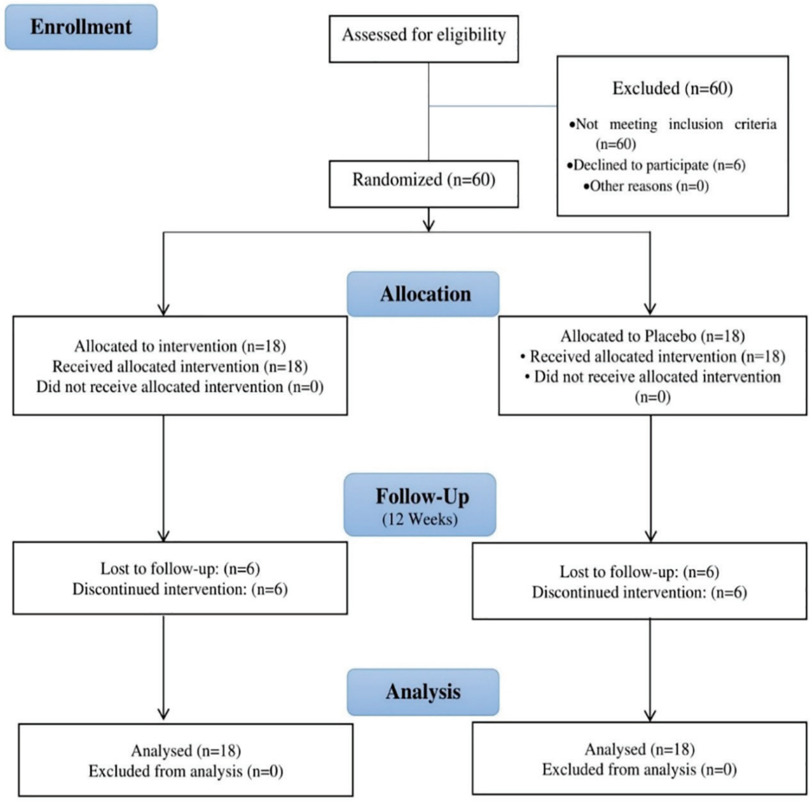

Flowchart 1. Consort Flow Diagram

Research Instrument

The Mindfulness Therapy Protocol (23), which was applied in this study for PD, was a 7-week group intervention that was largely skill-based and psychoeducational. Weekly sessions lasted 2 to 2.5 hours, and comprised extensive in-session practice of formal mindfulness training techniques (body scan, sitting meditation, mindful yoga, and walking meditation) and discussions about the challenges participants faced in integrating mindfulness into their daily lives. In the body scan, participants bring attention to each part of their bodies, from head to toe, recognizing the thoughts or sensations associated with each body part before moving attention to the adjacent regions. In sitting meditation, participants are instructed to adopt an alert and relaxed body posture, bring their attention to the sensations of breathing, and return their attention to the breath when it wanders. Mindful stretching and Hatha yoga consist of gentle stretching and strengthening exercises, with moment-to-moment awareness of the sensations that arise as participants position their bodies into the described postures. Similarly, walking meditation is conducted with awareness of the sensations of body movement and the thoughts, feelings, and images that arise as one walks at a slow pace.

The Cognitive rehabilitation protocol (18) was a 7-week group intervention that was used in this research. Cognitive rehabilitation is a neuropsychological treatment for cognitive impairment based on theoretical models of restoration, compensation, and optimization of cognitive functions targeting specific cognitive skills. During the training, participants perform repetitive cognitive exercises that vary depending on the cognitive domain being trained and the difficulty of the task. “Restoration” of a cognitive function is based on exercising the specific domain with the goal of reaching a preserved level.

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Pharmacotherapy was also used for all three groups (mindfulness, cognitive rehabilitation, and control). This is a type of treatment in which prescription drugs are used by specialist doctors to control and reduce disease symptoms. These drugs, known as psychotropic medications, are used in the field of mental health and in the treatment of psychiatric disorders, and are classified based on their clinical use (24).

The UPDRS was used to homogenize the groups with respect to motor symptoms and diagnosis. This scale comprises four sections: 1. Non-motor aspects of experiences of daily living, 2. Motor aspects of experiences of daily living, 3. Motor examination, and 4. Motor complications (25).

Mini Mental State Examination Test for Exclude Dementia

The Mini-Mental State Examination (MMSE) developed by Folstein et al. (26) consists of 11 questions designed to transform dementia from a qualitative attribute to a quantitative measurement (orientation memory, attention and focus, language and cognitive abilities, and visual-spatial ability). Dementia, one of the most common neurological diseases and a significant health risk for elderly individuals, imposes a substantial burden on patients, their families, and society. This condition leads to severe functional impairment, loss of independence, and increased dependence on others. Furthermore, it results in increased anxiety, depression, and significant expenditure of time and resources for patient care.

The MMSE comprises four subscales: orientation memory (16 points), attention and focus (5 points), language and cognitive abilities (8 points), and visual-spatial ability (1 point). This individual assessment should be administered within 5 to 10 minutes by the examiner. The total possible score is 30, with scores below 25 indicating possible brain damage or mild dementia, and scores below 20 suggesting definite cognitive impairment or severe dementia. Using the ROC (receiver operating characteristic) curve, a score of 22 was established as the cut-off point, yielding 90% sensitivity. The cut-off scores are 18 for men and 17 for women. In Iran, this test's validity and reliability were examined by Ansari et al. (27).

Non-Motor Symptoms Scale for Parkinson's Diseases

This scale was employed to assess and measure non-motor symptoms in patients with PD. The Non-Motor Symptoms Questionnaire contains 30 items across 9 components: (1) cardiovascular including collapse, (2) sleep/fatigue, (3) mood/cognition, (4) perceptual problems/hallucinations, (5) attention/memory, (6) digestive system, (7) urinary system, (8) sexual function, and (9) miscellaneous cases (Table 2). All symptoms were evaluated over the past month. Each symptom is assessed on two dimensions: a) Intensity: 0=None, 1=mild: symptoms present but causing little disturbance or functional impairment, 2=moderate: causing some disturbance or functional impairment, 3=severe: causing major disturbance or functional impairment, and b) frequency: 1=rarely (less than once a week), 2=sometimes (once a week), 3=often (several times a week), 4=very often (daily or all the time). Yes/No answers were excluded from the final calculation of intensity × frequency. The Persian version of this questionnaire was validated by Eghlidos et al. (28), who conducted a cross-sectional study on patients with PD. Following cross-cultural adaptation, the acceptability, validity, accuracy, and reliability of the Persian version were thoroughly assessed.

Results

The participants' demographic information is presented in Table 3. It is important to note that these demographic characteristics were considered as confounding variables in the analysis.

Based on the results presented in Table 3 and subsequent analyses, significant relationships were found between patients' age, education,

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Table 2. Components and Items Related to Each Component of Non-motor Symptoms Scale for Patients with Parkinson's

Domain	Domain Title	Number of Items
1	Cardiovascular domain including collapse	2
2	Sleep/fatigue	4
3	Mood/cognition	6
4	Perceptual problems/hallucinations	3
5	Attention/memory	3
6	Digestive system	3
7	Urinary system	3
8	Sexual function	2
9	Miscellaneous cases	4

Table 3. Demographic information of research groups

Confounding Variable		Mindfulness Group		Cognitive Rehabilitation Group		Control Group	
		Abundance	Percent	Abundance	Percent	Abundance	Percent
Sex	Men	8	44.44	9	50	7	38.88
	Women	10	55.55	9	50	11	61.11
Age	30-40	2	11.11	1	5.55	0	0
	40-50	5	27.77	7	38.88	8	44.44
	50-60	11	61.11	10	55.55	10	55.55
Education	Illiterate	0	0	0	0	0	0
	Less than a diploma	9	50	7	38.88	11	61.11
	Diploma	6	3.33	8	44.44	5	27.77
	Bachelor's degree	2	11.11	3	16.66	1	5.55
	Masters and above	1	5.55	0	0	1	5.55
Duration of illness	4-6	8	44.44	9	50	10	55.55
	6-8	11	61.11	9	50	8	44.44
Total		18	33.33	18	33.33	18	33.33

and duration of illness variables and the test results. These findings strongly suggest that age, education, and duration of illness are confounding variables that have influenced the relationship between gender and test results.

To address this, we initially employed the classification method to control for the confounding effects of age, education, and disease duration. Specifically, chi-square test was conducted to examine the relationship between these factors at various levels of the confounding variables.

It is noteworthy that educational attainment may serve as a preventive factor or delay the onset of the disease, as higher levels of education are associated with increased brain activity and neuroplastic properties similar to those developed through cognitive rehabilitation. Regarding disease onset, it typically manifests due to genetic factors between the ages of fifty and sixty, with early-onset cases being extremely rare. There exists a variant called juvenile parkinsonism that affects children, though its prevalence is negligible.

Table 4 presents the descriptive statistics (Mean and Standard Deviation) for non-motor symptom scores in the experimental groups (mindfulness therapy and cognitive rehabilitation) and the control group across pre-test, post-test, and follow-up phases.

As the results indicate, mean scores for both the mindfulness therapy and cognitive rehabilitation groups showed significant decreases from pre-test to post-test across all micro-components.

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Table 4. Mean and SD for Non-Motor Symptoms Components Based on Different Assessment Stages in the Groups

Dependent Variable		Mindfulness Therapy Group			Cognitive Rehabilitation			Control Group		
		Pre-test	Post-test	Fallow-up	Pre-test	Post-test	Fallow-up	Pre-test	Post-test	Fallow-up
Cardiovascular	Mean	06.6	44.3	61.4	6.17	3.33	4.17	6.33	3.67	4.61
	Standard deviation	15.2	79.1	03.2	2.33	1.68	2.18	2.27	1.81	2.33
Sleep/fatigue	Mean	17.22	83.14	83.16	23.28	15.61	18.17	23.22	17.67	19.72
	Standard deviation	00.7	80.5	6.21	5.47	4.67	5.32	5.50	5.48	5.62
Mood/ cognition	Mean	72.28	00.20	22.33	2	16.39	19.56	29.39	19.89	23.11
	Standard deviation	62.9	37.8	9.11	11.18	8.66	9.29	10.84	7.99	8.36
Perceptual problems/ hallucinations	Mean	89.8	06.5	6.61	9.61	5.61	7.06	9.22	6.33	7.61
	Standard deviation	48.3	69.2	24.3	4.23	3.27	3.59	3.98	3.12	3.63
Attention/ memory	Mean	83.13	67.7	67.9	14.83	8.17	10.33	13.78	9.78	11.61
	Standard deviation	95.5	88.3	45.4	6.27	4.00	4.42	6.16	5.35	5.83
Digestive system	Mean	72.17	44.10	83.12	13.24	10.28	12.28	13.74	10.78	13.11
	Standard deviation	39.6	59.4	06.5	7.11	5.30	5.81	7.01	5.09	5.52
Urinary system	Mean	39.12	83.10	00.12	13.06	11.78	13.33	12.78	11.61	13.28
	Standard deviation	41.4	64.4	81.4	4.56	4.47	4.55	5.06	5.71	5.97
Sexual function	Mean	61.16	89.9	22.12	16.56	10.22	11.94	16.00	12.72	15.00
	Standard deviation	69.13	00.4	62.4	5.78	4.32	4.23	4.87	4.51	4.20
Miscellaneous cases	Mean	00.26	78.18	94.20	25.28	17.56	19.89	24.11	19.61	21.39
	Standard deviation	59.9	44.8	85.8	8.38	7.79	7.66	9.87	8.29	8.46
Total	Mean	39.152	94.100	06.118	153.11	98.94	116.72	152.06	112.06	129.44
	Standard deviation	59.43	36.33	36.37	39.22	28.19	31.32	36.79	33.10	34.56

Based on the results presented in the table, these findings suggest that mindfulness therapy and cognitive rehabilitation were effective in reducing non-motor symptoms.

Based on the results in Table 5 and considering that the significance level obtained for each study variable exceeds 0.05, the null hypothesis was retained. This indicates that the data distribution across the three groups is normal, thus warranting the use of parametric tests. To evaluate the effectiveness of mindfulness therapy and cognitive rehabilitation on non-motor component scores across pre-test, post-test, and follow-up phases, a mixed-design MANCOVA or multivariate analysis of covariance (with both within-subjects and between-subjects factors) was conducted. Prior to examining the significance of mean differences in non-motor symptoms among the three groups across the three therapy stages, assumptions of homoscedasticity and sphericity were tested. These results are presented in Tables 6 and 7.

The results demonstrate that the assumption of homogeneity of variance has been met ($p<0.05$). Additionally, the variance of differences between all group combinations (sphericity)

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Table 5. Shapiro-Wilk test results on therapy outcomes of various approaches

Group	Variables	Non motor symptoms		
	Stage	Pre-test	Post test	Fallow up
Mindfulness therapy	Z	0.945	0.959	0.961
	sig	0.356	0.581	0.621
Cognitive Rehabilitation	Z	0.948	0.955	0.966
	sig	0.494	0.511	0.721
Control	Z	0.933	0.923	0.935
	sig	0.218	0.146	0.240

Table 6. Levene's Test F to Check homoscedasticity in Groups for Non-Motor Symptoms Components

Dependent variables	Df1	Df2	Indicator	Step		
				Pre-test	Post-test	Fallow-up
Cardiovascular	**2**	51	Statistics F	0.03	0.14	0.22
			P	0.97	0.87	0.80
Sleep/fatigue	**2**	51	Statistics F	0.69	0.51	0.15
			P	0.51	0.61	0.86
Mood/ cognition	**2**	51	Statistics F	0.30	0.10	0.28
			P	0.74	0.91	0.76
Perceptual problems/ hallucinations	**2**	51	Statistics F	0.42	1.36	0.36
			P	0.66	0.27	0.70
Attention/ memory	**2**	51	Statistics F	0.01	0.83	0.59
			P	0.99	0.44	0.56
Digestive system		51	Statistics F	0.09	0.23	0.31
			P	0.92	0.80	0.73
Urinary system	**2**	51	Statistics F	0.10	1.75	1.88
			P	0.90	0.18	0.16
Sexual function	**2**	51	Statistics F	1.02	0.08	0.14
			P	0.37	0.92	0.87
Miscellaneous cases	**2**	51	Statistics F	0.30	0.06	0.18
			P	0.74	0.95	0.84

Df1: Degree of Freedom1, Df2: Degree of Freedom2

must be equivalent. To assess this assumption, we conducted Mauchly's Test of Sphericity, with the results presented in Table 7.

The results reveal that the sphericity assumption has not been met ($p < 0.05$). Consequently, the Greenhouse-Geisser correction was applied to ensure more accurate estimates in hypothesis testing (Hooman, 1991), and the within-groups ANOVA was computed with this sphericity adjustment.

The results presented in Table 8 indicate that, with respect to the within-group factor, the calculated F-value is significant at the 0.05 level when examining the effect of stages (pre-test, post-test, and follow-up) on non-motor symptom components ($p < 0.05$). These findings suggest that both interventions (mindfulness therapy and cognitive rehabilitation) significantly impacted non-motor symptom components when compared to the control group. Furthermore, the significant decrease in non-motor symptom scores observed during the follow-up stage relative to pre-test scores demonstrates that the reduction in symptoms persisted beyond the intervention period. This sustained improvement suggests the long-term effectiveness of both interventions (mindfulness therapy and cognitive rehabilitation) in managing non-motor symptoms. These differences are illustrated in Chart 1.

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Table 7. Mauchly's Sphericity Test to Check homoscedasticity for Non-Motor Symptoms Components

Variable	DF	Index	Epsilon
Cardiovascular	2	Mauchly's W	0.85
		P	0.15
Sleep/fatigue	2	Mauchly's W	0.81
		P	0.005
Mood/cognition	2	Mauchly's W	0.38
		P	0.001
Perceptual problems/ hallucinations	2	Mauchly's W	0.77
		P	0.001
Attention/memory	2	Mauchly's W	0.37
		P	0.001
Digestive system	2	Mauchly's W	0.46
		P	0.001
Urinary system	2	Mauchly's W	0.64
		P	0.001
Sexual function	2	Mauchly's W	0.47
		P	0.001
Miscellaneous cases	2	Mauchly's W	0.36
		P	0.001

DF: Degree of Freedom

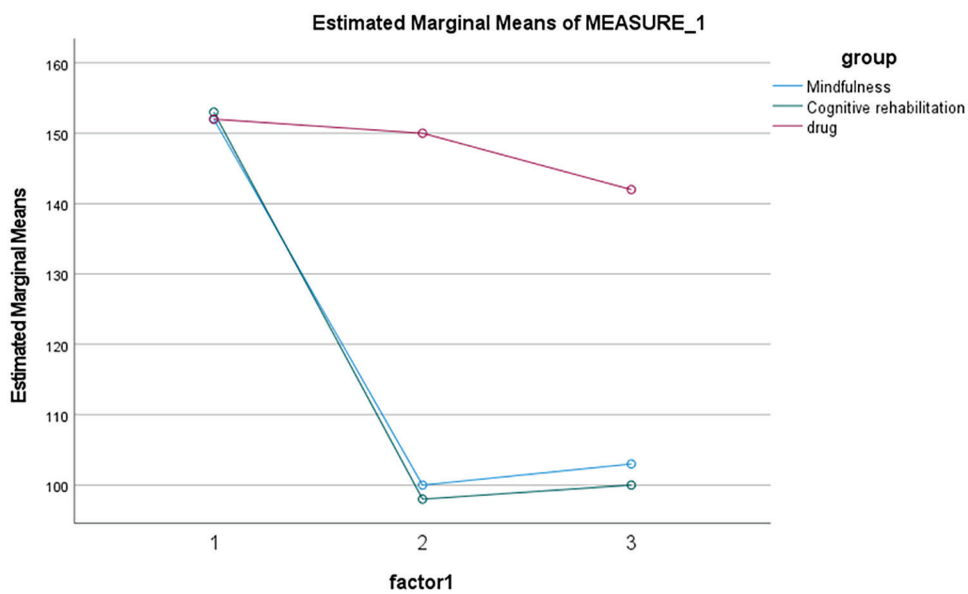

Chart 1. Estimated Marginal Means Graph for the Scores of Non-Motor Symptoms in 3 Groups of Mindfulness Therapy, Cognitive Rehabilitation, and Control at Pre-test, Post-test, and Follow up

Discussion and Conclusion

Mindfulness-based therapy has emerged as a promising therapeutic approach for managing chronic diseases, particularly PD. This discussion examines mindfulness treatment outcomes in relation to gender, age, and educational level as confounding variables. Mindfulness encompasses practices of awareness, present-moment consciousness, and nonjudgmental acceptance, which have been shown to reduce anxiety, depression, and stress symptoms associated with PD. This therapeutic approach additionally enhances quality of life, emotional regulation, and life satisfaction.

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Table 8. Mixed Models ANOVA for the Scores of Non-Motor Symptoms Components by Greenhouse-Geisser Test or within-groups and between-groups factors has been presented in Table 6.

Variable	Statistical factors/indexes	SS	DF	MS	F	Sig	Eta Coefficient
Cardiovascular	Within-groups	31.202	1.73	116.71	181.25	0.001	0.68
	Test interaction	43.1	3.47	0.41	0.64	0.025	0.61
	Between-groups	68.2	2	1.34	0.11	0.004	0.49
Sleep/fatigue	Within-groups	37.1321	1.86	787.80	276.90	0.001	0.64
	Test interaction	59.28	3.35	8.52	3.00	0.030	0.35
	Between-groups	93.137	2	68.96	0.74	0.028	0.48
Mood/ cognition	Within-groups	79.2733	1.23	2217.02	174.56	0.001	0.77
	Test interaction	84.32	2.47	13.32	1.05	0.039	0.46
	Between-groups	75.275	2	137.88	0.56	0.022	0.57
Perceptual problems/ hallucinations	Within-groups	59.349	1.62	215.20	220.01	0.001	0.71
	Test interaction	37.7	3.25	2.27	2.32	0.046	0.53
	Between-groups	15.21	2	10.57	0.30	0.012	0.64
Attention/ memory	Within-groups	44.873	1.23	711.98	247.02	0.001	0.63
	Test interaction	56.43	2.45	17.75	6.16	0.002	0.45
	Between-groups	11.48	2	24.06	0.31	0.012	0.38
Digestive system	Within-groups	75.1272	2	636.38	255.25	0.001	0.63
	Test interaction	95.4	2.59	1.91	0.50	0.019	0.56
	Between-groups	90.11	2	5.95	0.61	0.002	0.49
Urinary system	Within-groups	83.70	1.47	48.26	16.88	0.001	0.35
	Test interaction	88.3	2.93	1.32	1.46	0.018	0.27
	Between-groups	79.29	2	14.89	1.22	0.008	0.21
Sexual function	Within-groups	78.813	1.31	622.11	151.65	0.001	0.74
	Test interaction	22.93	2.62	35.63	8.69	0.001	0.25
	Between-groups	00.100	2	50.00	1.79	0.030	0.19
Miscellaneous cases	Within-groups	72.1181	1.22	971.37	175.25	0.001	0.67
	Test interaction	40.62	2.43	25.64	4.63	0.009	0.36
	Between-groups	16.30	2	15.08	1.07	0.003	0.29

SS: Sum of Squares, DF: Degree of Freedom, MS: Mean Square, F: Frequency, Sig: significance

Research indicates gender-specific responses to mindfulness therapy. Women may derive greater benefits from mindfulness techniques due to heightened stress levels stemming from social roles and cultural expectations. Conversely, men may exhibit greater resistance to emotional engagement, potentially diminishing treatment effectiveness. Age represents another significant factor, as older individuals often confront challenges such as diminished independence and physical limitations. For this demographic, mindfulness exercises can serve as valuable tools for improving quality of life and addressing emotional and physical challenges. Educational attainment may influence outcomes, with higher-educated individuals potentially demonstrating better comprehension of mindfulness techniques and greater likelihood of program participation. Conversely, those with lower educational levels may encounter greater difficulties in implementing these techniques.

Given that these variables can affect treatment effectiveness both independently and in combination, a multifactorial model is necessary for understanding these interactions. Individual treatment plans may require specific adjustments based on patients' gender, age, and educational level. The psychological construct of mindfulness has garnered significant attention recently. While most research has focused on

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clinical trials evaluating mindfulness-based interventions' efficacy, yielding promising results for treating psychological and physical symptoms, future research should explore the underlying mechanisms of mindfulness-based interventions. Kabat-Zinn's (1994) widely cited definition describes mindfulness as "paying attention in a specific way: purposefully, in the present moment, and nonjudgmentally." This definition encompasses three core components: intention, attention, and attitude. These components function as interrelated aspects of a simultaneous cycle rather than discrete processes. Mindfulness operates as a moment-to-moment process (5). As Kabat-Zinn notes, intentions guide practice and provide context for specific exercises. He further reflects that while initially believing meditation practice alone would drive change and growth, experience revealed the necessity of personal concepts and ideas, which themselves are dynamic and evolving. In conclusion, the findings indicate that mindfulness therapy and cognitive rehabilitation represent the most effective treatment approaches when accounting for variations in educational level, age, and disease duration among PD patients.

Taking into consideration the decreasing scores of the experimental groups in the post-test and follow-up stages, and their significant difference from the medication (control) group across all components of non-motor symptoms, it can be concluded that non-pharmacological therapies are strongly recommended as alternative and effective treatments alongside psychedelic drugs.

Patients with PD tend to become more isolated compared to their pre-disease life due to functional impairments and withdrawal from their previous daily activities. This isolation may accelerate the onset and progression of non-motor symptoms. Therefore, therapies that support cognitive rehabilitation are crucial for PD patients. Furthermore, cognitive rehabilitation exercises, which function as engaging games while enhancing patients' cognitive function, introduce an entertaining element to their daily routines, making therapeutic participation more natural and appealing.

The third wave of behavioral therapies, such as mindfulness, can help prevent symptom overestimation by fostering intentionality and non-judgmental present-moment awareness. Moreover, the group-based nature of these therapies provides an additional therapeutic benefit, as interaction with peers can help normalize negative emotions and mitigate feelings of isolation and social withdrawal.

Mindfulness training, as taught by qualified and experienced teachers, may offer a more participatory medicine, empowering the individual by engagement to learn how to strengthen internal resources to help cope with chronic disease. Mindfulness training may help to restore some degree of self-determination in the experience of living with PD. This is in line with person-centered research that employs scientific methods that are holistic, integrated, and transdisciplinary (29).

If mindfulness training is taught by skillful and experienced teachers, it can present a more participatory medication which empowers the patients by engaging to learn how to reinforce their inner resources to help deal with chronic disease. Some degree of self-determination may be reinstated in the experience of coping with PD through mindfulness training. This is in accordance with the person-centered approach that utilizes scientific methods which are holistic, integrated, and transdisciplinary (3).

Study Limitations

These therapies are limited to non-dementia patients, which presents challenges in participant recruitment and selection. Additionally, the target population primarily comprises older adults who may be reluctant to participate in research studies. However, the involvement of active PD associations has facilitated sample recruitment and enabled the provision of focused non-pharmacological therapeutic services.

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Human and Animal Rights

This research adhered to principles of confidentiality. All participants provided informed consent prior to completing the questionnaires.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Consideration

The study was conducted in accordance with the Declaration of Helsinki. Participants were informed of their right to withdraw at any time. All participant information was kept confidential, with coding systems used in place of names. Informed consent was obtained from all participants prior to study commencement.

Code of Ethics

This research was approved by the Research Vice-Chancellor of Islamic Azad University, Bushehr branch (ethics code: IR.BPUMS.REC.1402.079) and registered with Iran's International Clinical Trial Registration Center, a WHO-approved institution (registration number: IRCT20240727062560N1).

Authors' Contribution

Mohammad Hossein Arab, PhD candidate in psychology, drafted the manuscript and conducted psychological interventions. Moloud Keykhosravani supervised the research process and managed data analysis. Hossein Baghooli, as the primary consultant professor and clinical psychologist, supervised psychological interventions. Vahid Reza Ostovan, as the secondary consultant and neurologist, oversaw medical interventions throughout the project.

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