Original Article

Comparing the Effectiveness of Modular Cognitive-Behavioral Therapy, Pharmacotherapy (Paroxetine), and Their Combination in Intolerance of Uncertainty and Meta-Worry among Female University Students with Generalized Anxiety Disorder

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Abstract

Background: This study aimed to compare the effectiveness of pharmacotherapy and modular cognitive-behavioral therapy, as well as their combination, in intolerance of uncertainty and meta-worry among female university students with generalized anxiety disorder.

Objectives: Paying attention to psychological, cognitive-behavioral and biological dimensions in patients with generalization anxiety disorder causes continuity of therapeutic effects.

Methods: The present study was a semi-experimental research. The statistical population comprised all female students of the Islamic Azad University of Mashhad, of which 60 people were selected by a convenience sampling method and were randomly assigned to three experimental groups and one control group. All groups were initially pretested; afterward, the first experimental group received modular cognitive-behavioral therapy during ten 90-minute sessions; the second experimental group received pharmacotherapy and one daily dose of paroxetine; and the third experimental group received combination therapy; however, the control group was placed on the waiting list. At the end of the treatment period and three months thereafter, the participants were given a post-test and a follow-up test. The required data were collected through questionnaires, namely Freeston Intolerance of Uncertainty Scale and Wells Anxious Thoughts Inventory. The data were analyzed in SPSS-24 software using the repeated measures analysis of variance.

Results: The results demonstrated that all three therapeutic approaches compared to the control group were effective in reducing intolerance of uncertainty and meta-worry. However, the combination therapy was significantly superior to any of the two treatment approaches alone ($P<0.05$).

Conclusion: Considering the biological and psychological underpinnings of generalized anxiety disorder, the combination of psychological and drug therapies seems to be a more effective approach to improving anxiety states.

Keywords: Combination therapy, Generalized anxiety, Intolerance of uncertainty, Meta-worry, Modular cognitive-behavioral therapy, Pharmacotherapy

1. Background

Anxiety disorders have a great negative impact on a wide range of dimensions of human existence and can lead to intolerance of uncertainty and meta-worry. In the last two decades, the interest in developing effective treatment methods has increased, and several methods and techniques have been used to reduce and eliminate anxiety symptoms. Therefore, it is important to identify and compare the effective methods for the treatment of anxiety and psychological states in generalized anxiety disorder (such as intolerance of uncertainty and meta-worry). (1).

In general, anxiety is the most common psychiatric disorder among adolescents, while this rate is between 12% and 20% among university students. This statistic indicates the importance of treating anxiety in students. People with generalized anxiety disorder have problems in various areas of life (2). A high percentage of patients with generalized anxiety disorder suffer from another disorder (3). The severity of the symptoms of people with comorbidities is to the extent that it leads to a serious disruption in the process of their life activities (4, 5).Research has shown that anxiety disorders have a negative effect on a wide range of factors, including academic and social performance (6,7).

Generalized anxiety disorder is the culmination of chronic anxiety disorder characterized by excessive and uncontrollable worry (8). One of the main characteristics of generalized anxiety disorder is the constant presence of uncontrollable anxiety, anger, and worry observed in a person for 6 months and on most days. Generalized anxiety disorder is associated with symptoms such as restlessness, aggression, muscle contraction, fatigue, sleep disturbances, difficulty in concentration (9) vague concerns about the absence of specific objects, stimuli, or situations (10), motor tension, autonomous hyper-arousal, feelings of fear and anxiety, excessive worry, and hyper-vigilance (11).

Cognitive patterns of generalized anxiety disorder indicate the existence of defects and deficiencies in information analysis as well as distortions in the

cognitive processes of information processing (12). The cognitive-behavioral approach considers generalized anxiety disorder to be the result of incorrect initial interpretations (13). The third cognitive model proposed by Salkovskis (14) focuses on identifying and modifying negative evaluations of intervening thoughts, correcting the attitudes related to a sense of responsibility, preventing neutralization resulting from evaluations affected by a sense of responsibility, and increasing exposure to reduce anxiety, and reducing avoidance behaviors. In the last cognitive formulation for this disorder, it is assumed that cognitive processes that are harmful to evaluation, including risk perception and personal responsibility assessment, will lead to neutralizing anxiety behaviors following the occurrence of thoughts (15).

A review of the research literature suggests that one of the variables associated with anxiety (16). in people with a generalized anxiety disorder is meta-worry, distress tolerance, and ambiguity tolerance. Unfortunately, the chronic nature of the disease, the absence of proper prognosis and definitive treatment, and the individual's involvement in adolescence and youth issues cause numerous mental problems in these people, and the inability to control distress, ambiguity, meta-worry, depression, and stress are common (17). Considering the results of several studies (18), the effectiveness of these factors in the prevalence and acceleration of anxiety has been investigated and confirmed.

In addition to the association of this construct with meta-worry, distress tolerance, and ambiguity tolerance, the distress resulting from uncertainty is significantly correlated with anxiety arousal and depression along with the lack of pleasure (19). A review of the research literature indicates that one of the variables associated with anxiety and worry in these people is intolerance of uncertainty (16). In the intolerance of uncertainty model related to worry, intolerance of uncertainty plays an important role in creating and perpetuating excessive worry in these people. Intolerance of uncertainty can be defined as a type of cognitive bias that affects how one perceives, interprets, and responds to ambiguous situations at the cognitive, emotional, and behavioral levels. People who are intolerant of uncertainty believe that uncertainty is stressful and annoying, uncertainty about the future is unfair, and negative events are unexpected and should be avoided; moreover, uncertainty interferes with a person's ability to act and behave. Further, people with a low tolerance of uncertainty experience a lot of stress in ambiguous situations. These individuals perceive more situations vaguely and, as they find it difficult to tolerate this ambiguity, they experience high and persistent emotional arousal and anxiety (20). Research background demonstrates that behavioral problems of people with generalized anxiety disorder

cause problems in their daily lives and put a lot of stress on the family environment of these people. In addition to the association of this construct with meta-worry, the distress resulting from uncertainty is significantly correlated with anxiety arousal and depression, along with the lack of pleasure. From a fatalistic point of view, uncertainty is always caused by the lack or inefficiency of knowledge, which is related to one's internal factors and cannot be controlled (19). As a result, this lack of control will create disorders in adolescents and young people, and the disorder should be prevented by teaching them the necessary skills (21).

Argue that the concerns of people affected by meta-worry cover a wide range of issues, and their thinking style is characterized by extreme and uncontrollable anxiety. The concern of these people is pathological. Wells and (22) distinguish between adaptive and maladaptive worries and believe that the adaptive type helps to solve problems (leading to problem-focused behavior), while the maladaptive type has a recurring range of negative outcomes, and the individual continues the use of coping solutions until internal goals are achieved. From the viewpoint of (23), anxiety is intrusive but controllable and is a coping approach that can become the center of one's worries. Anxiety includes catastrophizing and its mental control is difficult; however, the process itself can be a source of worry. People with anxiety disorders often report that they have been anxious most of their lives. Meta-worry exacerbates anxiety symptoms in people with a generalized anxiety disorder (24, 25) concluded in a study that among anxiety disorders, generalized anxiety disorder takes the greatest influence from meta-worry.

In introducing and proposing treatment programs for generalized anxiety disorder, findings have indicated that this disorder, often characterized by depression and lower mood and performance than in early years, may lead to other anxiety disorders over time and negative performance in various aspects of life in adulthood if not treated properly (26). Therefore, to have a healthy society, it is necessary to help prevent (27) and treat generalized anxiety disorder. In this regard, various therapeutic strategies, such as individual therapy (28), behavioral therapy (29), cognitive-behavioral therapy (30), family therapy (31), pharmacotherapy (32), and group therapy, or a combination of these strategies (33), have been used. However, while on the one hand, all these strategies have sometimes been useful only clinically and in the short-term, other factors, such as comorbid anxiety symptoms (29), behavioral disorders (30), lack of appropriate social skills, and the sensitivity of adolescents and youths to changes in treatment methods (34), have caused the most effective treatment for generalized anxiety disorder remains in doubt. Nevertheless, the results of some studies conducted on generalized anxiety disorder indicate the

minimum expected results (35). The results of some studies have reported little success in examining the improvement of adolescents and young people treated with cognitive-behavioral therapy alone or pharmacotherapy alone. However, the success of each of these methods alone has been observed in normal conditions and without other problems at older ages (29, 35). Post-treatment assessments have reported a 43-47% improvement. However, this amount of improvement can be considered a result of compatibility with treatment plans (29). It can be concluded that one of the reasons for the ineffectiveness of cognitive-behavioral therapy or pharmacotherapy alone is the inflexibility of these methods (36). Hence, the effective internal and external moderating factors and individualizing the interventions have been considered (37). Chorpita's cognitive-behavioral model was presented to respond to these challenges, in which the person's problem is identified by providing a practical model of the problem and then effective internal and external moderating factors and interventions are tailored to the individual's problem through individualizing. Although Chorpita has provided a positive history for this approach, there is no consistent support for the effectiveness of this method alone for generalized anxiety disorder (29).

In the last two decades, numerous methods and techniques have been employed to reduce and eliminate anxiety (38). Due to the cognitive nature of anxiety, cognitive therapy-based approaches have shown good results in this area. In a study, Gratz demonstrated that modular cognitive-behavioral therapy was effective in anxiety symptoms and emotion regulation in anxious patients (39). Ordaz and Becker described the effectiveness of this method in anxiety to be successful. Some recent studies have reported the effectiveness of this method in generalized anxiety (40-43). Although the cost of generalized anxiety disorder is not exactly clear due to functional impairment, most clinicians and researchers in this field agree that the disorder imposes high costs on society. Therefore, it seems necessary to study and compare effective treatments for generalized anxiety disorder. Chorpita has provided a model based on cognitive-behavioral therapy that has been approved in numerous experimental studies for decreasing anxiety (44). This important cognitive-behavioral approach is modular therapy, which was developed by Eisen and Silverman for children with generalized anxiety disorder, and Durand also prescribed school avoidance for children suffering from anxiety. This model has been used for children with anxiety disorders, and follow-ups have indicated the effectiveness of this approach for adolescents and youths (45, 46). The modular cognitive-behavioral therapy program comprises self-monitoring therapeutic techniques, social skills training,

cognitive restructuring, rewards, reinforcement strategies, maintenance and reinforcement of strengths, prevention, and attention to time. Research shows that this treatment is effective in reducing the symptoms of generalized anxiety disorder (44). In their research, Toozandehjani investigated the effectiveness of modular cognitive-behavioral therapy and quality of life skills in intolerance of uncertainty, symptoms of generalized anxiety disorder, and motivational beliefs of students with test anxiety (47). The results exhibited that these two therapies have been effective in the intolerance of uncertainty, symptoms of generalized anxiety disorder, and motivational beliefs of students; however, the treatments were not significantly different. Moreover, in their study, Ramezani approved the effectiveness of modular cognitive-behavioral therapy in generalized anxiety disorder symptoms and intolerance of uncertainty among female students (48). Doustkam demonstrated the effectiveness of modular cognitive-behavioral therapy in facial interpretation and the fear of negative evaluation in paranoid students (49). Toozandehjani and Abhar Zanjani also indicated the effectiveness of this treatment in the clinical symptoms and self-control of psychosomatic patients with skin sensitivity (50).

In addition to modular cognitive-behavioral therapy, other therapies, including pharmacotherapy, have a significant impact on anxiety symptoms in generalized anxiety disorder. These drugs include monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, antidepressants, and beta-blockers. Paroxetine and other selective serotonin reuptake inhibitors have been confirmed as one of the effective drugs for the treatment of a wide range of anxiety disorders, such as generalized anxiety disorder and panic disorder (51). The research results obtained by Sadock suggested that paroxetine was 55% effective in patients with anxiety disorders (52).

In a study, Irons and Lad compared the effectiveness of modular cognitive-behavioral therapy and dialectical therapy in the intolerance of uncertainty and generalized anxiety disorder symptoms in students with test anxiety (53). According to the results, the two therapies have been effective in the research variables; nevertheless, the treatments did not differ significantly from each other.

In a study, Denise and Ben-Porath investigated the effectiveness of modular cognitive-behavioral therapy, compared to pharmacotherapy, in the symptoms of generalized anxiety disorder and academic adjustment of students with attention deficit hyperactivity disorder (32). The results suggested that both treatments were significantly effective in reducing the symptoms of generalized anxiety disorder and increasing the academic adjustment of students. The results of a study by Abolqasemi about anxiety disorders indicated the

higher effectiveness of combination therapy in the follow-up phase (54). Further, in another research, Mehryar showed a more significant effect of combination therapy in the follow-up phase in patients with anxiety (55). Although all three approaches of modular therapy, pharmacotherapy, and their combination are used in the treatment, it is important to repeat and compare the effectiveness of each of these intervention methods. By conducting this research, if the previous results are confirmed, additional evidence will be provided and, in case of not being confirmed, new windows will be opened for research. To the best of our knowledge, no research has been conducted so far in Iran to compare the effectiveness of these three treatment approaches among university students.

2. Objectives

Therefore, with regard to the need to conduct a detailed study and address the details of the phenomenon in question, the present study aimed to answer the question of whether pharmacotherapy, modular cognitive-behavioral therapy, and their combination had different effects in the intolerance of uncertainty and meta-worry of female university students with generalized anxiety disorder. Hence, the research hypotheses are as follows: "The effectiveness of combination therapy and modular cognitive-behavioral therapy in the intolerance of uncertainty and meta-worry varies among female university students with generalized anxiety disorder; the effectiveness of combination therapy and pharmacotherapy in the intolerance of uncertainty and meta-worry varies among female university students with generalized anxiety disorder; the effectiveness of modular cognitive-behavioral therapy and pharmacotherapy in the intolerance of uncertainty and meta-worry varies among female university students with generalized anxiety disorder."

3. Methods

Research method

The present semi-experimental research was conducted based on a pretest-posttest and follow-up control group design. The target population of this study encompassed all female students studying in Mashhad universities, Iran, in 2017-2018 who showed symptoms of generalized anxiety disorder. The statistical sample included 60 of these students who were selected through convenience sampling and were randomly divided into three experimental groups (n=15) and one control group (n=15). The inclusion criteria were being diagnosed with a generalized anxiety disorder (based on the clinical interview for DSM-5), having a score of generalized anxiety disorder questionnaire higher than the cut-off

score of 10, living in Mashhad, being willing to participate in the research, not suffering from other psychological disorders, being between 18 and 24 years old, and lacking any physical illness. On the other hand, the exclusion criteria included having any of the clinical disorders, major depression, and substance abuse problem, being under psychological or pharmacological treatment at the same time as the study, having a debilitating physical illness that makes it difficult to participate in the group, and being absent for more than two sessions in treatment. Before starting the study, the subjects were informed about the research purpose and were assured about the confidentiality of information. They were also informed of the possibility of study withdrawal at any research stage. Thus, informed consent, voluntary participation in the research, the right to withdraw from the study, the safety of the intervention, willingness to answer questions, and presenting the results if desired were among the ethical criteria of the research. Further, after the end of the research period, training the skills based on the modular approach was performed during ten sessions for the control group through weekly assignments and regular exercises.

Research tools
Generalized Anxiety Disorder Scale-7

This 7-item questionnaire is designed specifically to measure generalized anxiety disorder by Spitzer (56). The replies are rated on a 4-point Likert scale of 0=never, 1=several days, 2=more than half of the days, and 3=almost every day. The reliability coefficients of this scale have been satisfactory, ranging from 0.74 to 0.88. Cronbach's alpha in different studies has been in the range of 0.84 to 0.92 (57).

Wells Anxious Thoughts Inventory

This scale, developed by Wells , is a 22-item measurement tool (with 21 items in Iranian culture) and assesses meta-worry (7 items), social anxiety (8 items), and health anxiety (6 items) (58). The responses to each subtest, are scored on a 4-point Likert scale (59). Taherifar validated this scale in Iran and reported the internal consistency of meta-worry, social anxiety, and health anxiety to be 0.81, 0.85, and 0.74, respectively (60). Further, the reliability of the Wells Anxious Thoughts Inventory was obtained to be 0.92 by the test-retest method and 0.89 by the split-half method (25).

Intolerance of Uncertainty Scale

This 27-item scale was developed by Freeston to assess individuals' emotional, cognitive, and behavioral responses to uncertain situations. The replies to this questionnaire are rated on a 5-point Likert scale ranging from 1=not at all to 5=very high. The internal consistency of this test has been reported to be 0.91. Moreover, it has a significant correlation with the Penn

State Worry Questionnaire (r=0.63) and Dimensions of Worry Questionnaire (r=0.57) also reported the internal consistency of this scale to be 0.93 (61, 62).

Research implementation method

Initially, the code of ethics was obtained from the Islamic Azad University, Neyshabur Branch, Neyshabur, Iran (ID IR.IAU.NEYSHABUR.REC.1399.004). Afterward, a sample of 60 people (out of the 93 initial clients) was selected using the convenience sampling method from female students who referred to the counseling and psychology center of the Islamic Azad University from October to December 2017-2018 and had generalized anxiety disorder symptoms (obtaining scores above

average in the General Anxiety Disorder Questionnaire) and met the inclusion criteria. The subjects were then randomly assigned into three experimental groups and one control group and were pretested. At the end of the treatment period, with an interval of one week, the questionnaires were again completed by all four groups. Additionally, three months after the end of the treatment period, the subjects were given a follow-up test. To observe the ethical principles in the field of education, at the end of the work, the control group also received modular cognitive-behavioral skills training. This treatment was performed by a clinical psychologist with a doctorate degree. Table 1 presents the summary of the intervention sessions.

Table 1. Structure of modular cognitive-behavioral therapy sessions (Chorpita model) pharmacotherapy, and combination therapy

Session 1: Welcoming; introducing members to each other; establishing communication; explaining the goals and rules of the group, including not being absent, being timely present, and doing the assignments; stating the principle of confidentiality and mutual respect; practicing fear thermometer with students; building a collective fear ladder; summing up and fun ending.
Session 2: Reviewing the previous session; training on the nature of anxiety; preparing the members for exposure exercises; training on the three components of anxiety (physiological, cognitive, and behavioral emotions); distributing emotion sheets; encouraging the members to talk about anxiety and possible consequences; explaining the importance of exposure exercise; summing up; giving assignments and fun ending.
Session 3 (meeting with family): Meeting with other family members and reassuring and encouraging them; providing explanations about the active and fruitful role of parents; explaining the nature of anxiety; providing a booklet on the principles of success and a booklet on anxiety; summing up and concluding the session.
Session 4: Reviewing the previous session; providing explanations about the new stage (exposure); selecting easy items from the fear ladder and exposure practice; resting and re-practicing exposure; summing up and giving feedback on behaviors and feelings; providing assignments and fun ending (at the end of the session, the topics were reviewed and summarized).
Sessions 5 to 7: Reviewing the previous sessions; selecting the higher items from the fear ladder, exposure, and practice; summing up and giving feedback on behaviors and feelings; providing assignments and fun ending (at the end of the session, the topics were reviewed and summarized).
Session 8: Reviewing the previous session; explaining how thoughts affected emotion; teaching about identifying the thought from emotion; training the negative thought correction technique; practicing, teaching cognitive restructuring, and explaining catastrophic thinking; finding cases of catastrophic thinking with Socratic questioning; recording catastrophic thoughts; providing assignments; summing-up and fun ending (at the end of the session, the topics were reviewed and summarized).
Session 9 (work with family members): Explaining the differential reinforcement skill, the effect of rewards, extinction, extinction burst, and active disregard and its important factors; practicing skills; explaining how to create a reward program and reinforcers; preparing a list of rewards; preparing a table of reinforcers; preparing a list of desirable behaviors; practicing reward techniques; students' presence in the session and providing explanations about changes in family relationships; practicing skills with the student; summing-up and fun ending.
Session 10: Reviewing the previous session; reviewing the progress of treatment; re-examining the initial situation and evaluating the learned skills; reviewing the benefits of the learned skills; family presence in the session; explaining the important role of student and family in the progress of treatment; explaining the concepts of slips and deviations and recurrence of the disease; re-emphasizing the need to continue practicing at home; emphasizing the implementation of the list of rewards; announcing the end of treatment sessions and noting that it is possible to meet again if desired.
Note: Due to research limitations, this treatment was performed on a group basis and as mentioned earlier, modular therapy provided a practical model of the client's problem and effective internal and external moderating factors and regularly dealt with these factors to identify the underlying problem of the individual and coordinate itself with the individual's problem by individualizing the interventions. Therefore, for more individualization in this study, we first tried to homogenize the sample group as much as possible. Moreover, during the treatment sessions, individual sessions were held between the sessions for some members of the group.
Pharmacotherapy: Each participant in the pharmacotherapy group received one dose of paroxetine daily and seven doses per week. According to the psychiatrist, to prevent side effects, three to four days in the first week of taking the drug, the subjects took half a dose of paroxetine a night. Moreover, during the entire course of treatment, a contact number was provided to the participants to be in touch and inform in case of possible side effects. Except for drowsiness in the first few nights of taking the drug, no specific side effects were reported.
Modular cognitive-behavioral therapy combined with pharmacotherapy: In combination therapy, modular cognitive-behavioral therapy (according to the instruction mentioned above) was performed simultaneously with pharmacotherapy (including one daily dose of paroxetine).

Data analysis methods

In addition to descriptive statistics indicators, inferential statistics indicators, such as factorial repeated measures analysis of variance, were used for data analysis. Using post-hoc tests, the significant effect of the approaches was compared with each other. The analyses were performed in SPSS-22 software.

Statistical findings

The mean and standard deviation related to the

variable of generalized anxiety to determine the samples are presented in Table 2.

Based on the results of Table 2, it can be said that the highest scores of generalized anxiety were in the combination therapy, the pharmacotherapy, and the modular cognitive-behavioral therapy groups in descending order.

As can be seen in Table 3, the amount of ambiguity tolerance in the experimental groups increased, in comparison to the control group, and

Table 2. Mean and standard deviation of anxiety scores to determine sample individuals

Variable	Groups	Mean	Standard deviation
Generalized anxiety disorder	Control group	46.73	3.712
	Experimental group 1	47	5.126
	Experimental group 2	47.67	4.336
	Experimental group 3	48.2	3.839

Table 3. Mean and standard deviation of pretest, posttest, and follow-up test of ambiguity tolerance, and meta-worry

Variable	Group	Pretest		Posttest		Follow-up test	
		M	SD	M	SD	M	SD
Ambiguity tolerance	Control group	15.13	2.61	15.33	1.91	15	2.13
	Experimental group 1	15.33	2.60	18.66	1.17	18.26	1.38
	Experimental group 2	15.4	3.06	18.93	1.38	18.66	1.54
	Experimental group 3	15.80	3.05	19.53	0.74	19.46	0.915
Meta-worry	Control group	13.33	2.43	12.93	2.21	12.80	2.17
	Experimental group 1	13.93	2.65	10.93	2.60	10.80	2.48
	Experimental group 2	13.13	2.41	9	2.72	9.46	2.13
	Experimental group 3	13.73	2.43	9.4	2.09	8.33	2.55

Table 4. Summary of the results of Mauchly's sphericity test

Therapy	Variable	Mauchly's sphericity test	Chi-square statistic	Degree of freedom	Significance level	Greenhouse-Geisser test	Epsilon Huynh-Feldt test	Lower domain estimation
Modular cognitive-behavioral therapy	Meta-worry	0.487	19.414	2	0.001	0.661	0.706	0.500
	Ambiguity tolerance	0.304	32.144	2	0.001	0.590	0.622	0.500
	Distress tolerance	0.071	71.400	2	0.001	0.518	0.540	0.500
Pharmacotherapy	Meta-worry	0.647	11.737	2	0.003	0.739	0.799	0.500
	Ambiguity tolerance	0.490	19.286	2	0.001	0.662	0.707	0.500
	Distress tolerance	0.154	50.424	2	0.001	0.542	0.567	0.500
Combination therapy	Meta-worry	0.671	10.773	2	0.005	0.752	0.814	0.500
	Ambiguity tolerance	0.205	42.844	2	0.001	0.557	0.584	0.500
	Distress tolerance	0.343	28.923	2	0.001	0.603	0.638	0.500

this was greater in the combination therapy group. To check the necessity of performing ANOVA with repeated measures, Mauchly's sphericity test was used. The results of this test are tabulated in Table 4. Moreover, the amount of meta-worry in the experimental groups decreased, compared to the control group, and this was greater in the combination therapy group.

Considering that the significance level in the above test in modular cognitive-behavioral therapy is less than 0.05 for the variables of meta-worry and ambiguity tolerance, by selecting the epsilon of the correction rate in each case for repeated measures analysis of variance, Greenhouse- Geyser test statistic has been applied.

The first research hypothesis stated that "the effectiveness of combination therapy and modular cognitive-behavioral therapy in distress tolerance, ambiguity tolerance, and meta-worry varies among female students with a generalized anxiety disorder".

Based on the results of variance analysis with repeated measures, this hypothesis was confirmed (Table 5).

Although both types of treatment (combination therapy and modular cognitive-behavioral therapy) were effective in improving the condition of the

subjects (P<0.05), the group-related significance level was lower than 0.05 in the variable of meta-worry. Therefore, the effect of combination therapy and modular cognitive-behavioral therapy was different on these two variables. The impact of these two therapies on ambiguity tolerance and distress tolerance was not significantly different. However, the amount of meta-worry in the posttest and follow-up test in the combination therapy group was much lower than that in the modular cognitive-behavioral therapy group. Hence, the effectiveness of these two treatments in the above variables was different.

The second research hypothesis indicated that "the effectiveness of combination therapy and pharmacotherapy in meta-worry, distress tolerance, and ambiguity tolerance varies among female students with a generalized anxiety disorder". The effectiveness of these two treatments in the above variables was not different (Table 6).

Although both types of treatment (combination therapy and pharmacotherapy) have been effective in improving the condition of the subjects (P<0.05), the effect of these two therapies on ambiguity tolerance, distress tolerance, and meta-worry is not significantly different. Therefore, the effectiveness of these two treatments in the above variables was not different.

Table 5. Repeated measures analysis of variance to compare the pretest, posttest, and follow-up test in the treatment groups

Scale	Source of effect	Sum of squares	Degree of freedom	Mean square	F	Significance	Eta squared
Meta-worry	Group	78.400	1	78.400	5.645	0.025	0.168
	Error	388.889	28	13.889			
Ambiguity tolerance	Group	7.511	1	7.511	0.417	0.524	0.015
	Error	504.311	28	18.011			
Distress tolerance	Group	71.111	1	71.111	0.764	0.390	0.027
	Error	2606.044	28	93.073			

Table 6. Repeated measures analysis of variance to compare the pretest, posttest, and follow-up test in the treatment groups

Scale	Source of effect	Sum of squares	Degree of freedom	Mean square	F	Significance	Eta squared
Meta-worry	Group	2.500	1	2.500	0.202	0.656	0.007
	Error	345.822	28	12.351			
Ambiguity tolerance	Group	4.4444	1	4.444	0.275	0.604	0.010
	Error	451.778	28	16.135			
Distress tolerance	Group	67.600	1	67.600	0.724	0.402	0.025
	Error	2614.133	28	93.362			

Table 7. Repeated measures analysis of variance to compare the pretest, posttest, and follow-up test in the treatment groups

Scale	Source of effect	Sum of squares	Degree of freedom	Mean square	F	Significance	Eta squared
Meta-worry	Group	900/52.900	1	52.900	3.295	0.080	0.105
	Error	556/449.556	28	16.056			
Ambiguity tolerance	Group	0.400	1	0.400	0.025	0.876	0.001
	Error	867/449.867	28	16.067			
Distress tolerance	Group	0.044	1	0.044	0.001	0.983	0.001
	Error	911/2595.911	28	92.711			

The third research hypothesis suggested that "the effectiveness of modular cognitive-behavioral therapy and pharmacotherapy in distress tolerance, ambiguity tolerance, and meta-cognition varies among female students with a generalized anxiety disorder". The effectiveness of these two treatments in the above variables was not different (Table 7).

Although both types of treatment (modular cognitive-behavioral therapy and pharmacotherapy) were effective in improving the condition of the subjects (P<0.05), the impact of these two therapies on ambiguity tolerance, distress tolerance, and meta-worry was not significantly different. Therefore, the effectiveness of these two treatments in the above variables was not different.

5. Discussion

The findings demonstrated that all three treatments were effective in significantly reducing the symptoms of a generalized anxiety disorder (distress tolerance, ambiguity tolerance, and meta-worry) in the posttest and follow-up test. Nonetheless, comparing the treatments with each other in post-treatment and follow-up evaluation, especially in the follow-up period, showed that the combination therapy was statistically superior to modular cognitive-behavioral therapy and pharmacotherapy in significantly reducing the severity of intolerance of uncertainty and meta-worry.

These findings are consistent with the results of other similar studies (19, 21, 44, 46, 48, 63) indicating the effectiveness of modular cognitive-behavioral therapy in the intolerance of uncertainty and meta-worry. Moreover, the findings of this

research are in line with those of other studies suggesting the effectiveness of pharmacotherapy in the intolerance of uncertainty and meta-worry in patients with generalized anxiety disorder (51).

Although these three therapeutic approaches seem somewhat different, they suggest that manipulating the client's acquired behavior, along with modifying the distortions and changes in cognitive processes and biological changes underlying anxiety symptoms, may lead to more positive outcomes in comparison with the use of each method alone (64). Based on the model by Mineka and Zinbarg genetic and natural factors, the history of conditioning, the history of sociocultural learning, the experience of direct traumatic conditioning and replacement, the perception of uncontrollability, the unpredictability of stressful events, and conditional stimulus characteristics of individuals are considered effective vulnerability factors in the occurrence of anxiety symptoms (distress tolerance, ambiguity tolerance, and meta-worry) (65).

According to Shapiro, humans have an innate physiological system and link information processing to mental health (66). Psychological damage occurs when the information processing system stops. Harmful information (such as meta-worry and intolerance of uncertainty) is stored as stagnant, unresolved, and fixed at the moment the traumatic event occurs. Everyday stimuli evoke the negative feelings and beliefs that lie in these traumatic memories, causing the person to react mentally, emotionally, and behaviorally in a way that is consistent with the injury and increasing the severity of his anxiety symptoms.

Combination therapy helps people learn the ability to regulate their misbehavior and improve

their mental health by controlling the biochemical changes underlying the anxiety symptoms (paroxetine). They would also learn modular skills for emotional self-regulation, emotion control, and rumination on the other. These skills include changing faulty thinking processes and cognitive reconstruction of emotional responses, breaking the cycle of negative inner experiences, exposure to anxiety-producing situations, relaxation, situational awareness, cognitive reconstruction, hierarchical regulation of anxiety, and inhibition of the sympathetic and muscular nervous system through the taurine network in sleep (67, 68).

The contemporary learning approach states that the factors that occur after conditioning affect the quality and severity of conditioned anxiety. In combination therapy, both physical and psychological dimensions of the client are taken into account and in fact, the combination of antidepressants (paroxetine) and cognitive-behavioral therapy has advantages over each separately for the treatment of generalized anxiety disorder symptoms (distress tolerance, ambiguity tolerance, and meta-worry). Therefore, the higher significant effect of combination therapy can be logically explained in the variable of meta-worry, which is the main basis of anxiety.

In explaining this finding, it can be mentioned that combination therapy has reduced the symptoms of a generalized anxiety disorder (distress tolerance, ambiguity tolerance, and meta-worry) in clients by reversing and modifying the client's incorrect cognitive and emotional processes, changing traumatic memories and disturbing information, simultaneously changing emotions, thoughts, and feelings (32), disrupting the cycle of negative internal experiences, focusing on people's cognition, preventing negative mood, and focusing on correcting negative thinking patterns on the one hand, and using paroxetine to increase serotonin levels and thus enhancing the motivation and mood of clients on the other (51).

Given the fact that in this study, the effect of paroxetine on reducing and improving anxiety mood in patients with symptoms of generalized anxiety disorder was proved, and the superiority of combination therapy was confirmed, it may be said that paroxetine does not have a specific anti-anxiety effect and is mainly effective in decreasing the symptoms of generalized anxiety disorder by reducing the clinical side effects and manifestations of this disorder. That is to say, paroxetine provides the necessary ground for the effectiveness of other treatments and does not improve the anxiety symptoms of clients in the long run (51). Therefore, it can be concluded that this research, probably due to the short duration of paroxetine treatment, has not been able to properly evaluate its effectiveness. On the other hand, the effects of paroxetine remain stable only as long as it is continued, while the effects

of psychological therapies are much more stable than pharmacotherapy alone. According to the results of most studies conducted so far, serotonergic drugs have antidepressant effects. Modular cognitive-behavioral therapy also improves anxiety symptoms, and therefore, the combination of pharmacotherapy and modular cognitive-behavioral therapy is superior to any of the treatments alone (53).

Overall, the findings of most studies suggest that both paroxetine and modular cognitive-behavioral therapy are more effective in anxiety symptoms. It is possible that anxious thoughts persist and that the cognitive aspects and attributional style are at least to some extent the causes of the recurrence of anxious thoughts in clients who have been treated with medication. The recurrence of anxiety symptoms when stopping the drug might be due to other factors, such as physiological factors and cognitive attributions. Hence, cognitive-behavioral methods are essential for studying and changing beliefs, unhealthy attitudes, and attributional style, as well as compensating for the shortcomings of paroxetine treatment alone (9). As a result, increasing the effectiveness of combination therapy compared to any of the treatments alone can be justified.

On the other hand, it can be concluded that this research, probably due to the short period of treatment with paroxetine and modular cognitive-behavioral therapy, has not been able to properly evaluate their effectiveness. Further, the effects of paroxetine remain stable only as long as it is continued; however, the effects of psychological therapies are much more stable than pharmacotherapy alone and require attention to different psychological dimensions of clients (53). It is possible that because of the short duration of this research, many of the techniques and skills of modular cognitive-behavioral therapy have not been considered and used. On the other hand, the rapid effect of paroxetine on the anxiety symptoms of clients has caused the effectiveness of these two treatments not to differ. Therefore, the non-superiority of these two therapies over each other can be justified (32).

In general, the results of the present study indicated that modular cognitive-behavioral therapy could be as effective as pharmacotherapy in anxiety symptoms. Moreover, it has fewer side effects compared to pharmacotherapy. In addition to the effectiveness of psychological and pharmacological treatments, psychological therapies have longer-term effects than pharmacotherapy. Its simplicity, low cost, and short duration are the other advantages that facilitate the treatment process and allow for the development of treatment, which is of great importance to both the therapist and the client. On the other hand, combination therapy (modular cognitive-behavioral therapy together with

pharmacotherapy) is more effective in reducing the clinical symptoms of generalized anxiety disorder relative to any of the treatments alone (53).

6. Conclusion

In the end, it should be noted that the impossibility of random selection of subjects, lack of control over other factors affecting generalized anxiety disorder, time constraints on technique implementation and training, lack of an independent assessor, and lack of mutual awareness of the researcher were among the limitations of this study. Therefore, it is recommended that the training courses be extended, the interaction and combination of the above training be considered in other fields, psychotherapy with the effect of placebo be used in the control group, projects with a complete lack of mutual awareness be carried out, independent assessors be used, programs for stress coping training and effective communication skills be provided to these people, and a booklet on therapy skills of the modular approach and coping with anxiety and stress be developed for these people.

Ethical Considerations

Before starting the study, the participants were assured of the confidentiality of their information, and they were informed of the right to withdraw from the study at any stage. Therefore, informed consent, voluntary participation in the research, the right to leave the study, the safety of the intervention, and answering the questions and presenting the results if desired were among the ethical criteria of the research. Besides, after the end of the research period, training the skills based on the modular approach was performed during ten sessions in the control group through weekly assignments and regular exercises.

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Conflicts of interest

The authors of the article declared no conflict of interest.

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