Original Article

The Efficacy of Augment of D-Cycloserine and Cognitive-behavioral Therapy on Adolescent with one Type of Anxiety Disorders: A Double-blind Randomized Controlled Trial

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Abstract

Background: This study was designed to investigating the effect of combining D-cycloserine (DCS) and cognitive-behavioral therapy (CBT) on adolescent with at least one type of anxiety disorders. **Materials and Methods:** The present study was conducted as a double-blind randomized controlled trial on 36 adolescent with anxiety disorders. Patients were assessed in two groups. In addition to 4 sessions of weekly CBT in both groups; case group, received a 50-mg DCS capsules, control group, received Placebo daily for a month. Patients received DCS capsules or placebo 1 h before sessions of CBT. Age, sex, kind of anxiety disorders "screen for child anxiety related disorders (SCARED)" and "cognitive abilities test (CATS)" scores were evaluated and compared between groups. **Results:** The mean age of the studied patients (29 females (80.6%) and 7 males (19.4%)) was 14.1 ± 1.8 years. The most frequent anxiety disorder among the study population was generalized social disorder (GAD) (77.7%). Age, sex and the frequency of anxiety disorders were not statistically significant between the study groups ($P > 0.05$). The mean score of "SCARED" and "CATS" at before starting the treatment, after treatment and three month after the treatment were not statistically significant between groups ($P > 0.05$). Also, decrease in values of "SCARED" and "CATS" during the evaluation time periods was not statistically significant between groups ($P > 0.05$). **Conclusions:** Findings of this study showed that there has been no difference in symptoms improvement in adolescent with anxiety disorder who received treatment protocol including 4 sessions of CBT, weekly, together with 50 mgs of DCS compared to the patients of the control group.

Keywords: *Anxiety disorder, CATS, cognitive-behavioral therapy, D-cycloserine, SCARED*

Introduction

Anxiety disorders are among the chronic and common diseases in Psychiatry. Common anxiety disorders among the population include social anxiety disorder (SAD), specific phobias (SP), posttraumatic stress disorder, obsessive-compulsive disorder (OCD), panic disorder (PD) and agoraphobia in such a way that a significant percent of the population of today's industrial world suffer from these disorders.[1,2] And personal and economic burden associated with these disorders is very high.[1]

Anxiety disorders are among the most common psychiatric disorders in children and adolescents in epidemiological studies, reported to occur about 5.7 to 17.7% in foregoing age groups: 2.6 to 15.4% assigned to generalized anxiety disorder (GAD), 5 to 22% assigned to SAD and 5% assigned to SP.[3-5] If anxiety symptoms be considered under diagnostic threshold, 70% of the children of school age suffer from anxiety.[5] Educational performance, patients themselves or others developing the disease, being ridiculed by others, making mistakes and physical appearance can be considered to be the most common causes of anxiety in patients of these ages.[5] Childhood anxiety disorders are so debilitating. Thus, they cause an obvious decrease in home and school performance, reducing the contact with peers and self-confidence.[4-6] These disorders affect adulthood performance and mostly cause depression, drug abuse, suicide, tendency to be alone and the need for hospitalization.[7]

It's seen, in longitudinal studies, that childhood anxiety disorders are chronic and stable[7,8] and in girls, they are to be more

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common after adolescence.[9] Furthermore, there is a high simultaneity between anxiety and conduct disorders causing health care systems to face a lot of problems.[4]

Studies have shown the advantages of drug therapy and CBT in anxiety disorders in which selective serotonin reuptake inhibitors (SSRIs) have been widely investigated.[10] Moreover, some efforts have been made in the past to improve the response to treatment with the combination of CBT and drug therapy (for instance, Antidepressants or Benzodiazepines) which have had disappointing results,[11,12] in recent years, pursuant to the results of the studies showing some of the main pathways and neurotransmitters controlling fear, a fresh strategy has emerged to be applied to use the combination of drug therapy and CBT.[13] D-cycloserine (DCS) is a drug used to treat chronic tuberculosis in human beings. It is also used for patients with Schizophrenia,[14-16] social behavior[17] in Autism and cognitive performance in Alzheimer's disease.[18,19] Despite some preliminary results in the treatment of each of these patients with Schizophrenia or Alzheimer's disease, evidences have been disappointing finally. Various studies have revealed that D-cycloserine, when prescribed for animals as a single dose before or immediately after conditional fear, can facilitate the extinction of conditional fear.[20-24] Other studies conducted on laboratory animals[25,26] have shown the effects of this drug on anxiety disorders, results of which, in recent years, have led to some programs in DCS-usage applied for patients with anxiety disorders. In their early attempts, Ressler *et al*.[27] investigated the effect of prescribing DCS before treatment sessions in patients with specific fear of height disorder compared to placebo and showed that symptoms of fear of height in DCS-receptor group during a week and 3 month after treatment decreased more than in the control group. Moreover, no certain side effect has been reported in these patients. In another study, patients with social phobia were under treatment with CBT coupled with DCS (50-mg) and were compared to placebo-receptor patients. Social anxiety level has been investigated at the beginning of the study, after treatment and 1 month after the last session, as well. The symptoms of social phobia disorder have decreased in the case group more than in placebo-receptor group. The difference, however, has continued to increase with the passage of time. Other human studies on adults have shown that CBT with 50 mgs of DCS capsules before CBT sessions in patients with social phobia[28,29] and panic disorder[30] to affect the primary consequences. Similarly in their study, Hofmann *et al*. have supported DCS to be prescribed with CBT in patients with anxiety disorders.[28] In some other nonclinical studies,[31] no difference has been observed between the case and control groups in regard to the effect of DCS on the process of anxiety disorders.

Given that a few number of studies have been conducted on investigating the effect of combining the DCS and CBT on the decrease in symptoms of anxiety disorders and that these studies merely focus on some subgroups of these disorders and no similar study has been carried out in this respect in Iran, and on the other hand, due to lack of motivation and inability of the families of the adolescents with anxiety disorders to pay the CBT expenses and insurance companies not paying the CBT expenses, more studies are necessary to be conducted on investigating the combination of drug therapy and CBT in anxiety disorders to lower the treatment expenses and to save time. Therefore, the present study was designed to assess the effect of combining the DCS and CBT on patients with one type of anxiety disorders.

Materials and Methods

The present study was conducted as a double-blind randomized controlled trial on 36 adolescents with anxiety disorders referring to anxiety clinic in an 8-month period (from September, 2011 to May, 2012). The patients in this study include 12- to 20-year-old adolescents, mainly diagnosed by ADIS[4,5] to have anxiety disorders, needing therapeutic interventions and receiving anti-anxiety treatment according to the child sub-specialist psychiatrist. Lack of any background pertaining to serious or physical problems, mood disorders, psychosis or delusional disorders and drug dependency, lack of any changes in anti-anxiety drugs or any changes in their doses during 4 weeks before the study, lack of learning disorders based on mental check-up, lack of any background associated with seizure and severe depression coupled with the thoughts of suicide and having the IQ equal or higher than 80 (it was measured applying Raven Test and by an independent psychiatrist) are of inclusion criteria. In addition, the patients absent for more than one session and those whose parents or themselves did not intend to continue the treatment were excluded from the study. The present study was investigated and approved in Isfahan University of Medical Sciences and after the parents of participating patients were explained about and informed of the aims of the study, written informed consent was obtained from them all.

Patients meeting the inclusion criteria were selected in a simple non-random manner and in the order of referring to the clinic and were randomly divided into two 18-member groups of case and control by the random-maker software "Random Allocation". The case group included 18 patients who, in addition to CBT, received a 50-mg D-cycloserine pill daily for a month (low dose of mg D-cycloserine was chose, because, previous study,[27] found no difference between the effects of 50 or 500 mg of D-cycloserine, and another study[28] demonstrated positive therapeutic effects for D-cycloserine augmentation of cognitive behavioral treatment employed the drug at only a 50-mg dose). On the other hand, the control group included 18 patients who, in addition to CBT, received Placebo pill daily for a month. In Isfahan University of Medical Sciences, Faculty

of Pharmacy, 250-mg D-cycloserine pills were changed into 50-mg ones and also placebo pills were made with the same size and shape as the main drug and were distributed to the researchers.

Age, sex and anxiety disorders (GAD, SAD, SP, PD and OCD) were variables to be observed in this study. Moreover, the symptoms of anxiety disorders were investigated using the standard questionnaire "SCARED"[32] and automatic thoughts in children and adolescents were studied by the standard questionnaire "CATS".[33] "SCARED" is a multifaceted standard questionnaire applied for investigating the symptoms of anxiety disorders in 9 groups, including 66 questions (from 0 = Almost Never to 4 = Almost Always). Furthermore, "CATS" is a self-assessment standard questionnaire assessing the thoughts in children and adolescents during the recent weeks. It is designed in four areas (four subscales of cognitive content) such as physical threat, social threat, personal failure and hostility, each of which including 10 questions (from 0 to 4).

Before treatment, demographic data of the patients, frequency of anxiety disorders and symptoms of anxiety disorders, based on "SCARED" questionnaire, and results of the investigation of the automatic thoughts of children and adolescents during the recent week, based on "CATS" questionnaire were collected. Then, the patients in two groups were under the treatment protocol including 4 sessions (90 min) of CBT weekly. Also, 4 sessions (90 min) of CBT were held for the patients' parents in groups. Patients, in addition, based on their treatment, group received DCS capsules or placebo daily for a month. After one-month period of treatment and 3 months after treatment completion, "SCARED" and "CATS" questionnaires were filled in again in both groups. All of the processes of studied variables assessment and CBT were carried out by a psychiatrist not informed of assigning patients to treatment groups.

Data collected were analyzed by statistical software "SPSS-20". Quantitative variables as Mean ± SD and qualitative ones as number (percent) are presented. Sex and the frequency of anxiety disorders in study groups were assessed applying Pearson Chi-square test. Furthermore, Independent sample T-test was used to investigate the age, "SCARED" and "CATS" rates in groups during the study time periods. The process of changes in "SCARED" and "CATS" during the evaluation time periods was compared between groups using repeated measurements of ANOVA. The level of significance in all cases is considered to be less than 0.05.

Results

Based on the inclusion criteria, in this study, totally 40 patients were observed and analyzed, 36 of them fell into two 18-member groups of case and control. Four patients (2 of whom because of not meeting the inclusion criteria and 2 due to not consenting to participate in the study) were excluded from the study [Figure 1]. In addition, two patients of the control group and one patient of the case group have been absent in CBT sessions, each for one session. These patients completed the treatment protocol and attended the final analysis after the complementary session was assigned in which they participated.

The mean age of the studied patients (29 females (80.6%) and 7 males (19.4%)) was 14.1 ± 1.8 years. The most frequent anxiety disorder among the study population was GAD with the frequency of 28 cases (77.7%) and the least frequent ones were SAD and PD with the frequency of 7 cases (11%). The other disorders in all studied patients include Social *P* with the frequency of 22 (61.1%), SP with the frequency of 16 (45%) and OCD with the frequency of 11 (30.5%). In Table 1, age, sex and frequency of anxiety

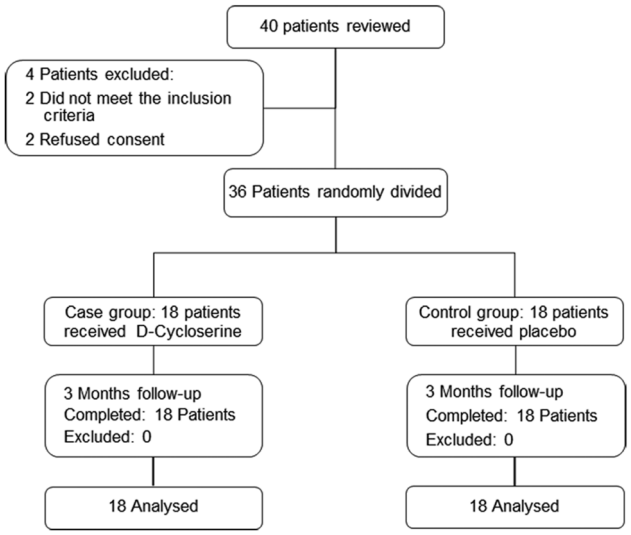

Figure 1: Patients who entered the study, were divided into the study groups, followed up and analyzed

Table 1: Comparison of baseline characteristics in 36 adolescents with anxiety disorders

	Case group	Control group	*P*
Age (year)	14.6±2.1	13.5±1.5	0.08*
Sex			
Male	4 (22.2)	3 (16.7)	1[I]
Female	14 (77.8)	15 (83.3)	
Separation anxiety disorder	1 (5.6)	6 (33.3)	0.08[I]
Specific phobias	10 (55.6)	6 (33.3)	0.31[II]
Social phobia	10 (55.6)	12 (66.7)	0.49[II]
Obsessive-compulsive disorder	4 (22.2)	7 (38.9)	0.28[II]
Generalized anxiety disorder	13 (72.2)	15 (83.3)	0.69[I]
Panic disorder	4 (22.2)	3 (16.7)	1[I]

Data are mean±1SD and number (%), Case group: 18 patients received cognitive-behavioral therapy with D-Cycloserine, Control group: 18 patients received exposure therapy with placebo, *P* v*alu*es calculated by*independent sample *T*-test, [I]Fisher's exact test and [II]Chi-Square test

disorders have been compared between the study groups, based on the results of which there has been no statistically significant difference between the case and control group in respect to these variables ($P > 0.05$).

The results of the comparison of the mean score of "SCARED" and "CATS" between the case and control groups at the beginning of the study, early after termination of treatment and 3 months after treatment are presented in Table 2. As it's seen, during all of the study time periods, the mean score of "SCARED" in control group has been higher than in the case group. However, there has been no statistically significant difference between two groups ($P > 0.05$). Also, no significant difference in the mean score of "CATS" during the study time periods has been observed ($P > 0.05$). The results of repeated measurements of ANOVA test in investigating the process of decrease in values of "SCARED" [Figure 2] and "CATS" [Figure 3] during the evaluation time periods revealed that there was no statistically significant difference in decreasing process of these variables in both groups of case and control ($P > 0.05$). Moreover, during none of study time periods, there was a significant differences in the mean score of "SCARED" and "CATS" between the study groups based on the type of anxiety disorder. There were no side effects in both of the studied groups' patients.

Discussion

The present study was conducted with the aim of investigating the effect of DCS coupled with CBT on adolescents with anxiety disorders. Our results revealed that the mean score of "SCARED" has been higher in the control group than in the case group. However, the difference is not statistically significant. The mean score of "CATS", also, was not significantly different between groups during any of the study time periods. These results show that adding 50 mgs of DCS to the CBT protocol of the patients has led to no significant difference in the result of the treatment in DCS-receptor patients compared to placebo-receptor ones. Furthermore, the mean score of "SCARED" and "CATS" during the study time periods in the study groups, based on the anxiety disorder types, showed no statistically significant difference. However, considering the frequency distribution of the anxiety disorder type in the study patients, despite the insignificance of this difference, the statistical power in showing the difference between groups may be low due to low frequency of these disorders among the study groups. In addition, in some patients, there are several anxiety disorders, making it difficult to differentiate drug effects based on the type of anxiety disorder.

In a systematic review study in 2010, Ganasen *et al*.[33] showed that prescribing DCS before CBT sessions would

Table 2: Comparison of SCARED and CATS in 36 adolescents with anxiety disorders

	Case group	Control group	*P*
SCARED Score			
Baseline	105.2±33.4	107.8±44.5	0.71
End of treatment	72.1±34.7	84.1±34.7	0.35
3 months after treatment	48±31.6	57.1±33.6	0.39
CATS Score			
Baseline	51.3±23	56.3±28.4	0.58
End of treatment	35.3±27.2	42.6±28.3	0.23
3 months after treatment	19.8±12.5	26.3±15.1	0.21

Data are Mean±1SD, Case group: 18 patients received cognitive-behavioral therapy with D-Cycloserine, Control group: 18 patients received exposure therapy with placebo. *P* values calculated by independent sample *T*-test

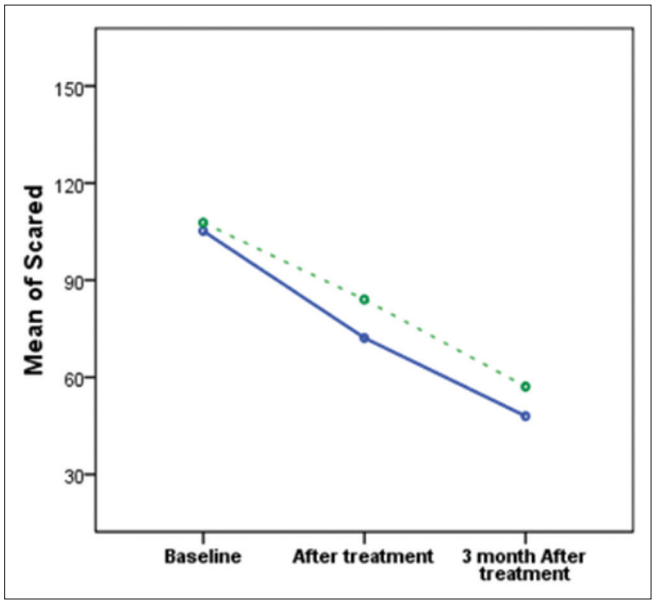

Figure 2: Comparison of means of SCARED Scores between study groups during 4 months study period. In both groups after the study means of scared were decreased compared to before study and differences between groups was not statistically significant (*P* = 0.49)

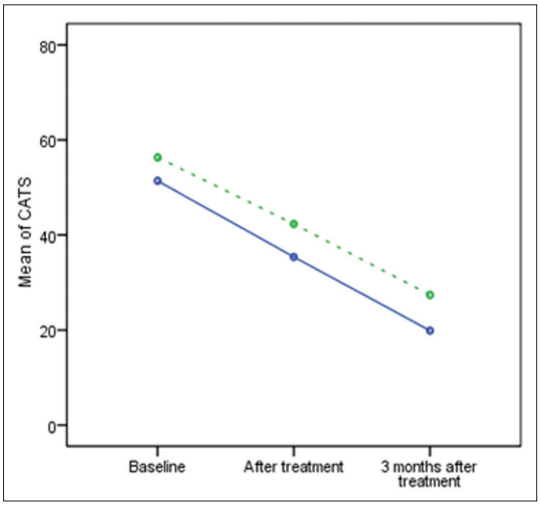

Figure 3: Comparison of means of CATS scores between study groups during 4 months study period. In both groups after the study means of CATS were decreased compared to before study and differences between groups was not statistically significant (*P* value = 0.33)

be more effective than CBT alone, investigating the studies conducted on patients with anxiety disorders (PD, OCD, SAD and SP). In a meta-analysis study[34] investigating the other studies, it has been revealed that DCS reduces the fear in animals and human beings in CBT sessions of anxiety disorders. DCS effectiveness has been reported to be dependent on dose, time and length of usage period, as well. In a review article[13] it is suggested that using acute dosing of DCS in anxiety disorders (SP and SAD) can be far more effective and that a treatment plan with acute dosing would be much better than one with chronic dosing. However, the treatment plan in the present study including 50 mgs of DCS in patients with anxiety disorders coupled with 4 sessions of CBT, weekly, showed no difference in obtained results between the study groups.

SAD is among the common anxiety disorders in adolescents. The recent treatment including the combination of CBT and drug therapy is to decrease the symptoms of this disorder.[35,36] In a Randomized Double-blind Placebo-controlled study, Hofmann *et al*.[13] have investigated the effect of DCS on 27 patients with SAD and revealed that anxiety disorder has been observed in DCS-receptor group to be in a significantly lesser extent than in the control group. Furthermore, in a study in the United States, 50 mgs of DCS together with CBT in patients with SAD decreased the symptoms of SAD in DCS-receptor group more than in the control group.[28] In the present study, there were 10 patients with SAD in the case group and 12 patients with the same disorder in the control group. However, no significant difference (improvement) was observed in patients' condition between two groups after the treatment protocol was completed. These results are different those studies mentioned before. The differences in results probably is due to difference in treatment protocol or perhaps because patients in foregoing studies have been merely with SAD, while, in the present study, in addition to SAD, some other anxiety disorders have been observed in patients.

Storch *et al*.[36] have investigated the effect of DCS on 24 adults with the OCD. They held 12 sessions of CBT, weekly for all patients. Four hours before each session of which the patients of the case group received 250-mg DCS capsules, while the patients of the control group received placebo. Based on the result of their study, there has been no significant difference in respect to the variables between groups. Moreover, in another study, Storch *et al*.[37] prescribed 25- and 50-mg DCS capsules for 30 adolescents with OCD, based on their weights and 1 h before CBT. The results of their study, also, showed no significant difference between two groups. In another study, Wilhelm *et al*.[38] evaluated the effect of 100 mgs of DCS, an hour before each session of CBT (10 sessions) and revealed that there was a significant improvement in DCS-receptor group, in comparison to the control group. The present study is conducted on patients with various types of anxiety disorders in which there are 4 patients with OCD in the case group and 7 patients with the same disorder in the control group. No significant improvement in patients' condition were observed between two groups after prescribing 50 mgs of DCS, an hour before CBT sessions (4 sessions) and during one month of treatment. These results have been similar to those of Storch *et al*.[36] and Storch (2010) *et al*.[37] studies and different from those of Wilhelm *et al*.'s.[38] However, treatment protocols of all of these studies have been different from one another. In addition, a fewer number of studied patients in the present study have been with OCD compared with those in above-stated ones.

Similar to the results of previous studies on the patients with anxiety disorder[27,28] and to those of other conducted studies on the patients with Alzheimer's disease,[39] no specific side effects were observed among the patients of DCS-receptor group in this study. This similarity shows that there is not any significant difference in different doses of DCS between the case and placebo group in respect to the occurrence of side effects.

Based on the type of anxiety disorder in study groups, the low number of samples can be considered as one of the limitation of the present study, indicating that this small number of samples would not be sufficient to show the difference between groups based on the type of the anxiety disorder. In the present study, however, the number of samples was calculated based on the study aim, which is to investigate the effect of DCS on improving the symptoms of patients with anxiety disorders, which can investigate the effect of DCS on patients with simultaneously several anxiety disorders. Therefore, future studies are recommended to be designed according to the frequency distribution of types of anxiety disorders or on patients developing a specific anxiety disorder with specific sample size.

Conclusion

As a whole, the results of the present study revealed that there has been no difference in symptoms improvement in adolescent patients with anxiety disorder who received treatment protocol including 4 sessions of CBT, weekly, together with 50 mgs of DCS, compared to the patients of the control group. However, considering the difference in the results of various studies with different treatment protocols, conducting more studies in this respect seems to be necessary.

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Conflicts of interest

There are no conflicts of interest.

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