Cognitive Behavioral Sex Therapy: An Emerging Treatment Option for Nonorganic Erectile Dysfunction in Young Men: A Feasibility Pilot Study

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ABSTRACT

Introduction: An increasing number of young men have been found to develop nonorganic erectile dysfunction (NOED) in recent years. The NOED has been shown to respond better to cognitive behavior sex therapy (CBST) in a few past studies.

Aim: The present research aims to establish the efficacy of CBST as a promising treatment option in young men suffering from NOED by administering a feasibility pilot trial.

Methods: 28 young men (M = 31 years) out of a total of 39 men (7 excluded, 4 quit treatment) diagnosed with NOED from sexual health clinics in Pakistan were recruited to receive CBST treatment (n = 13) on average twice a week for a period of 50 minutes per session for a period of 4, 6, 8, and 12 weeks for the mild, mild to moderate, moderate, and severe forms of NOED, respectively, and sildenafil citrate group (n = 15) receiving sildenafil citrate 50 mg on demand. The trial design was sequential random assignment clinical trial.

Main Outcome Measures: International Index of Erectile Functioning-5 and Depression Anxiety Stress Scale-21 were used before treatment, after treatment, and in follow-up as the main outcome measures.

Results: The repeated measures analysis of covariance established a nonsignificant difference between CBST and sildenafil citrate 50 mg in NOED scores improvement, NOED severity reduction, and reduction in depression scores at posttreatment assessment. There were significant differences among different CBST modalities in improving NOED scores, reduction in NOED severity, and depression scores. There was significant difference in CBST and sildenafil citrate 50 mg in anxiety reduction at posttreatment assessment. The covariates age, age groups, and NOED duration did not significantly impact the treatment outcome for both treatment groups except age which impacted the interaction of treatment and anxiety scores.

Conclusion: The CBST is an emerging and promising treatment choice in younger men suffering from NOED.

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Key Words: Non Organic Erectile Dysfunction; Erectile Dysfunction; Sildenafil Citrate; Cognitive Behavior Sex Therapy; Sex Therapy; Men Health

INTRODUCTION

An increasing number of men are complaining of erection-related problems in Pakistan.1,2 In recent years, the ratio of men experiencing erectile dysfunction (ED) in younger age (below 40 years) has been increased significantly.3 More young men (30%) are now complaining of ED that need a comprehensive approach to the treatment as reported by previous studies.4 Several of these studies had been conducted in Western countries, and very little data exist about the prevalence and other correlates of ED in young men in non-Western parts of the world, yet these studies point that ED is a quite common condition in young age.5,6 It has been learnt that one in every 4 men who sought help for ED in Italy was under the age of 40 years.6 The number of men younger than 40 years who seek help for ED has increased since 2011. In Pakistan, the study by Khanzada et al2 reported the prevalence of nonorganic erectile dysfunction
Sexual Medicine.12 The nonorganic or psychogenic ED can be differentiated from organic ED if the onset of the problem is sudden, if there are good nocturnal erections, and if ED occurs only in some situations or contexts. The classification of ED is supported to be in categories of organic, nonorganic, or idio-pathic instead of organic or psychogenic.13

Among the persons suffering from ED, a significant proportion suffers from primarily nonorganic or psychogenic ED. A nonorganic or psychogenic ED is the persistent inability to achieve or sustain an erection sufficient for the completion of sexual activity due to nonorganic or psychological factors. This definition of ED has been endorsed by the Fourth International Consultation on Sexual Medicine of International Society of Sexual Medicine.12 The nonorganic or psychogenic ED can be differentiated from organic ED if the onset of the problem is sudden, if there are good nocturnal erections, and if ED occurs only in some situations or contexts. The classification of ED is supported to be in categories of organic, nonorganic, or idiopathic instead of organic or psychogenic.13

It has been reported that psychological factors contribute significantly in the development of NOED in younger age. Generally, young men need sexual imagination and fantasy to get good-quality erections. So, any psychological disturbance can interfere with their ability to achieve an erection even if the physical structures are intact.14 The psychological factors include, lack of sex education,1 psychiatric disorders,4,15 family pressures and postmarital relationship conflicts,5,4,15 insecure childhood attachment, and guilt over early sexual experiences.16 Generally, the psychological factors do not show any kind of biomarkers in the sufferers of ED.17 Psychological factors often include symptoms of mild anxiety or depression as a comorbid condition.13,18 Often, the strongly comorbid conditions of ED and premature ejaculation (PE) are associated with increased incidence of anxiety and depression in men experiencing both conditions.3,19–22

The relationship between ED and PE is not yet clear and is complex.23 The ED itself is the strongest risk factor for developing PE in men and vice versa.24 The men with ED often need intense penile stimulation to get aroused, which may lead to PE,25 whereas the PE leads to early detumescence which exacerbates the condition of ED.26 Moreover, the severity level of ED increases the chances of developing PE. The severe cases of ED increase the risk of PE by 52.4% compared with the mild cases of ED which may increase the risk of PE by only 29.5%.27 The greater scores on IIEF-5 are associated with decreased occurrence of PE in men.28

Similarly, studies showing the link between ED and depression are mixed in opinion. Some studies report that depressive illness leads to the development of ED, whereas some other studies report that ED leads to the development of depression.29 The ED may increase the risk of developing depression by 8.7–43.1% as compared to those who do not have ED.29,30 On the other hand, there are some antidepressant drugs belonging to the selective serotonin reuptake inhibitor (SSRI) class which are known to increase the risk of developing ED. One of these drugs is paroxetine.31 Although, the empirical studies involving the use of citalopram did not find a causal link between citalopram use and development of ED, the patients’ subjective reports indicated a possible link between citalopram and ED.32 The other drugs of the SSRI class are not known to increase the risk of developing ED.4 The mechanism of SSRI leading to the development of ED is not yet clear. One possible explanation is the downregulating role of SSRI through the human hypothalamic-pituitary-testes axis in men with depression, thereby depression leading to ED.33 Another possible role is that of the neurotransmitter serotonin. Serotonin is associated with both depression and PE.34 Hence, a possible link between ED and PE and the development of depression are comprehensible.

Another psychological condition associated with ED is anxiety. Anxiety creates stress and inhibits the normal sexual response leading to ED. This mechanism is often mediated by cognitive factors and leads a man to experience performance anxiety.35 The cognitive factors include maladaptive attitudes, dysfunctional beliefs, and negative automatic thoughts with overemphasis on obtaining erection. This excessive concern leads to anticipation of sexual failure and decrease in erectile functioning.36,37 The classic macho attitude comprising of maladaptive sexual beliefs such as “men are always ready for sex”; “men have to satisfy their partners at any cost”; and “men should maintain an erection until the end of sexual activity” play a significant role in this cognitive formulation of erectile difficulty.37

Several studies in the past indicated a possible psychological approach toward the management of ED in younger men. The prominence of these approaches comes from the integration of the classic sex therapy with modern cognitive behavior therapy terming it as cognitive behavior sex therapy (CBST). The CBST has found to be an effective treatment strategy for ED of psychological or nonorganic nature.38–43

The CBST takes into consideration such cognitive and behavioral factors related to sexual activity within a sexual relationship.38,39 Although CBST does not address the neurovascular mechanisms involved in an erectile response, it helps to address the psychological correlates and concomitants associated with ED.38,39 The CBST involves several components including psychosexual education to the patient, the identification of the
problem in context of patient, sexual role play exercises, strategies to reduce performance anxiety, sexual attitudes restructuring, sexual activity–related Socratic dialog and sexual communication skills building, and so on.38–40,44 Recently, mindfulness-based techniques in conjunction with cognitive behavior therapy have also been found useful in the treatment of ED because of situational or psychological causes. These studies demonstrate the efficacy of either individual or group form of mindfulness in making men learn to focus their attention on present moment and other nonjudgmental exercises useful in the amelioration of symptoms of NOED.45–49

Traditionally, the men with ED had been treated with the classic phosphodiesterase type-5 inhibitors (PDE5i), the sildenafil citrate (SC).50–52 SC is a selective inhibitor of phosphodiesterase type-5 and increases the activity of cyclic guanosine monophosphate.50 The treatment outcomes with SC in individuals with ED are mixed.

In one such study, 52% of the participants benefitted from the daily administration of PDE5i, but they did not resolve the ED completely.53 The participants did report an improvement in erectile function but did not report improvement in intercourse satisfaction. The pharmacological agents do not provide a full recovery in cases of NOED.38 It is estimated that 30–40% of patients do not respond to SC.54 Those who respond to PDE5i do so only intermittently.50 This is the area where PDE5i such as SC fails to address the issue, especially if it is related to psychological or relationship factors.35 The CBST has been shown to be a promising therapeutic approach for such individuals.38,39 Recently, CBST was found to be a potential long-term treatment of choice for ED in Pakistani men.41

The present research was conducted with a purpose to assess the efficacy of CBST and compare the efficacy of CBST with the efficacy of traditional treatment with SC (PDE5i) in young men diagnosed with NOED. The study specifically aimed to find out the differences in NOED scores on IIEF-5, severity of NOED, and associated depression and anxiety scores at 3 time points in the 2 intervention groups. Furthermore, it was assumed that different NOED severity levels would be benefitted by different number of sessions of CBST.

MATERIALS AND METHODS

Research Design

A randomized, sequential clinical trial design was used in this research. The participants either received CBST or the SC. The responses were measured at 3 time points namely before treatment, just after the treatment, and at follow-up.

Participants

A total of 39 men who presented at sexual health clinics in the South Punjab state of Pakistan were referred to the principal investigator for treatment of ED. A small number of participants could only be recruited because of the cultural sensitivity of the sexual health issue in Pakistan. 32 of those men were screened eligible to participate in the study. They were sequentially allocated to the CBST group (n = 16) and SC group (n = 16). There were 3 and 1 drop out in the CBST and SC group, respectively. 13 and 15 participants completed their participation in CBST and SC groups, respectively, and were included in the final analysis. The participants’ age ranged from 21 to 39 years (M = 31 years for both treatment groups). The participants had ED symptoms lasting from 6 months to beyond 3 years. They were categorized as suffering from mild, mild to moderate, moderate, and severe NOED based on their IIEF-5 scores of 17–21, 12–16, 8–11, and 5–7, respectively. The participants were selected using the following inclusion and exclusion criteria.

Inclusion Criteria

The patients of ED without the history of prior treatment; medical, hormonal, neurological, or psychiatric illness; substance abuse including recreational substances; obesity; or on cardiovascular and psychiatric medications were included in the sample. The patients in the age group of 18–39 years who were in a heterosexual relationship for at least 6 months were included in the sample.

Exclusion Criteria

The patients of ED with a history of prior treatment; medical, hormonal, neurological, or psychiatric illness; substance abuse including recreational substances; obesity; or on cardiovascular and psychiatric medications were excluded from the sample. The patients older than 18 years or older than 40 years were excluded from the sample. The patients aged or older than 40 years were excluded from the sample because they had organic etiology in most cases.4,14 The men in nonheterosexual relationships were excluded from the sample because of the cultural and religious sensitivity attached with the nonheterosexual orientation in Pakistan.

Measures

Demographic Information Questionnaire/Informed Consent Form

A demographic information questionnaire and an informed consent form (ICF) containing information related to age of the patient and duration of the ED were developed by the principal investigator. All the participants were required to fill up the ICF before taking part in the study.

International Index of Erectile Functioning-5

IIEF-5 is a brief standardized self-administered scale developed to assess the presence and severity level of ED in men. IIEF was developed by Rosen in 1999 as a brief version to aid in the diagnosis of ED.55 IIEF is a likert-type scale which has 5 items.
Each item contains 5-point response categories. The total score is the sum of all the responses from 1 to 5 on all 5 items. The minimum score on the scale is 5, and maximum score can be 25. The scale helps to categorize ED into no ED (22–25), mild ED (17–21), mild to moderate ED (12–16), moderate ED (8–11), and severe ED (5–7) based on the symptoms suffered in the last 6 months. The standardized Urdu version was used to diagnose the patients with the condition which has the Cronbach Alpha reliability of 0.88.56

Depression, Anxiety, and Stress Scale-21

The Depression, Anxiety, and Stress Scale-21 (DASS-21) is a brief self-report set of items designed to measure depression, anxiety, and stress in general population developed by Lovibond S.H. and Lovibond P.F. in 1995.57 The scale has 21 items. Each subset has 7 items to assess the constructs of depression, anxiety, and stress. The DASS-21 is a 4-point likert scale, and the items ask respondents to view themselves in the past 6 months and give response to each item on a scale of zero to 3 where zero represents no occurrence and 3 represents always occurs. Each domain has its own predetermined cutoff scores. The standardized Urdu version was available to be used with the local population. The Cronbach alpha reliability of Urdu version of the scale is 0.84 for the depression subscale, 0.82 for the anxiety subscale, and 0.87 for the stress subscale.56

Procedure

The participants were purposively sampled from the sexual health clinics in the South Punjab state of Pakistan. The participants were selected on the basis of inclusion and exclusion criteria. All the participants filled the essential ICF before enrolling for the study. Then, all the participants were sequentially and randomly assigned to either treatment condition by the principal investigator. The participants in the first treatment group received CBST while the participants in the second treatment group received SC 50 mg on demand 1 hour before the desired sexual intercourse with the partner. The decision to administer SC on demand was made because of cost and availability of the drug in Pakistani market. Only transitory headaches were reported by the participants in the SC group. The CBST was administered individually to the men with NOED twice a week by the principal investigator/psychologist for a period of 50 minutes on each session for a period of 4, 6, 8, and 12 weeks for mild, mild to moderate, moderate, and severe NOED, respectively. This NOED severity dependent element of CBST was chosen to see the efficacy of CBST sessions for each severity level of NOED. The decision of CBST administration twice a week by the principal investigator was made with a view to keep men engaged in therapy and to properly monitor the effects of CBST. The absence rate of men in the therapy sessions was negligible. All the homework assignments were practiced by the men with their partners 2-3 times a week. The therapist monitored and reviewed these assignments. The men occasionally experienced difficulty in practicing present moment mindfulness at home. Some other men reported it hard to refrain from sexual intercourse while practicing the stop-start technique. The contents of the CBST are outlined in Table 1. These contents have been adapted by the similar studies conducted earlier.58,59 The participants were followed up after 4, 6, 8, and 12 weeks for CBST treatment based on their NOED severity before treatment and after 12 weeks for the SC group. The 2 scales, IIEF-5 and DASS-21, were administered at the follow-up visit.

Statistical Analysis

The data were analyzed by using the Statistical Package for Social Sciences, version 25 (SAS Institute, Cary, NC). Only the participants who completed the study were entered into the analysis. The analysis of dropout participants was not conducted as their size was too small to be meaningful. The analysis was presented in the form of descriptive statistics including mean and standard deviation of NOED scores, NOED severity, depression, and anxiety scores across 3 time points. The demographic variables have been reported in the form of frequencies. The mixed repeated measures analysis of covariance was performed to statistically analyze the impact of treatment on NOED scores, NOED severity, depression, and anxiety scores across 3 time points. These analyses produced within-subject results and between-subjects results. The NOED scores, NOED severity, depression, and anxiety scores across 3 time points, were treated as within-subject factors while forms of treatment was treated as between-subject factors. The pairwise interaction of within-subject and between-subject factors was presented in the form of graphs separately for NOED scores, NOED severity, depression, and anxiety scores. The age, age groups, and NOED duration were entered as covariates. There were 2 age groups: one from 18 to 29 years and the other from 30 to 39 years. There were 3 levels of NOED duration, ranging from minimum 6 months to 3+ years. In these analyses, an effect was significant at the 95% confidence interval. The partial eta square ($\eta^2_p$) was used as a medium of effect size. The 0.02, 0.09, and 0.25 were considered small, medium, and large effect sizes, respectively.59

Ethics Statement

The study was approved by the Departmental Research Ethics Committee of the Department of Psychology at the International Islamic University, Pakistan, number DREC/IIU-PHDPSY/2017/8203. The WHO Universal Trial Number is U1111-1244-3834, and the trial was registered with the US trial registry at ClinicalTrials.gov with number NCT04179747. The study period was from January 2018 to July 2018. The informed consent was obtained from all the participants before enrolling them.

RESULTS

Baseline Characteristics of Participants

The Baseline Characteristics of the participants and descriptive statistics of the treatment variables have been outlined in Table 2
### Table 1. Components of cognitive behavior sex therapy, on individual basis (based on cognitive model of erection by Nobre and Gouveia 2000)^62

| Session       | Components (individual therapy)                                                                 |
|---------------|-----------------------------------------------------------------------------------------------|
| First week    | Case formulation in the context of unique psychosexual history                                 |
|               | Psychosexual education (lectures by the therapist, instructional videos, books in local language) |
|               | Exploration of sexual myths                                                                  |
|               | Penetration is forbidden till the therapist advises otherwise                                 |
| Second week   | Reconstruction of sexual attitudes, socratic dialog                                             |
| Third week    | Exploration of automatic thoughts and catastrophization (performance demand and failure anticipation), socratic dialog |
| Fourth week   | Relaxation exercises (mindful breathing) and mindfulness (nonjudgmental, present moment focus approach), to help the client control negative stress (the clients are encouraged to practice these exercises at home and record in log book till the end) |
|               | Homework assignment: spending nonsexual pleasant time with partner (sharing past good times, saying good things to partner) |
| Fifth week    | Learning sexual communication and love skills (spending time together, emotional expression, love talk, surprise gifts) |
|               | Homework assignment: exploration of personal and partner’s bodies (pay attention to emotions and thoughts in a nonsexual manner) |
| Sixth week    | Review of relaxation exercises and mindfulness                                               |
|               | Homework assignment: sensate focus i;                                                        |
|               | The client is instructed to play with his partner. He is instructed to involve his partner in mutual caressing to each other bodies except the genital area and breasts. He is further instructed to communicate his sexual thoughts and feelings. If the client and his partner reach a high level of sexual arousal, they may have an orgasm, but separately. The client is further instructed to communicate and discuss about this new sexual experience with his partner. |
| Seventh week  | Review of love and sexual communication skills                                                 |
|               | Homework assignment: sensate focus ii;                                                        |
|               | The client is instructed to give and receive stimulation of the whole body, including genital areas and breast, but not up to the orgasm, giving indications to each other. If the client and his partner reach a high level of sexual arousal, they may have an orgasm, but separately. The client is further instructed to communicate and discuss about this new sexual experience with his partner. |
| Eighth week   | Review of sensate focus i and ii                                                               |
|               | Homework assignment: stop and start technique;                                                |
|               | The client asks his partner to stimulate his penis until it achieves an erection, then she stops stimulating until the penis becomes flaccid; repeat this exercise 3 times. Here, both partners can achieve orgasm but not through sexual intercourse. This exercise demonstrates that it is not necessary that a man constantly maintains the erection once reached (cognitive restructuring of a myth). |
| Nineth week   | Homework Assignment: Stop and Start Technique with a lubricant;                               |
|               | The client asks his partner to stimulate his penis with a lubricant until it achieves an erection, then she stops stimulating until the penis becomes flaccid; repeat the exercise 3 times. Here, both partners can achieve orgasm but separately. This exercise demonstrates that erection may decline, but that can be achieved again and creates a sensation of warmth and dampness (similar to vaginal walls inside). The client learns to enjoy sexual sensations together instead to go for sexual intercourse instantaneously. |
| Tenth week    | Review of stop and start technique                                                             |
|               | Homework assignment: undemanding sexual intercourse                                           |
|               | When the client learns to get erection, his partner inserts the erect penis into her vagina, slowly progressing to climax by making few ample movements. The client’s partner detaches herself from him before ejaculation. The client eventually learns that penetration is not necessary for sexual satisfaction in every encounter, releasing the pressure to get an erection off the mind of client. |
| Eleventh week | Review of home assignments and discussion about hot issues                                     |
|               | Sexual penetration is permitted now onward.                                                    |
| Twelth week   | Termination of therapy, review of therapy goals and outcomes                                  |
|               | Posttreatment assessment                                                                      |

Note: These components were merged and covered in less number of sessions for moderate and mild cases of nonorganic erectile dysfunction (NOED). No component of therapy was omitted for moderate and mild cases of NOED.
and 3 respectively. A total of 28 participants completed the study and were included in the final analysis. 13 of them received CBST treatment while 15 received SC. The minimum age of participants for the CBST and SC groups was 21 and 24 years, respectively, whereas the maximum age was 39 years for both treatment groups. There were almost equal number of participants belonging to the age group of 18–29 years (38% vs 47%) and age group of 30–39 years (61% vs 53%) in the CBST and SC groups, respectively. There were 8%, 54%, and 38% vs 33%, 47%, and 20% of the participants in the CBST and SC groups, respectively, whose NOED duration was 6 months–1 year, 1–3 years, and beyond 3 years.

Repeated Measures Analysis of Covariance

Table 4 shows the within-subject and between-subjects results as computed by repeated measures analysis of covariance where age, age groups, and NOED duration were entered as covariates.

### Within-Subject Results

There was a statistically significant within-subject interaction effect of treatment with NOED scores ($F(2, 40) = 2.95$, $P < .05$, $\eta^2 = 0.37$) when controlling for age, age groups, and NOED duration.

### Between-Subjects Results

There were statistically significant between-subject interaction effects of treatment groups with NOED scores, NOED severity, and depression scores ($F(4, 20) = 4.69$, $P < .05$, $\eta^2 = 0.48$; $F(4, 20) = 4.45$, $P < .05$, $\eta^2 = 0.47$; and $F(4, 20) = 3.36$, $P < .05$, $\eta^2 = 0.40$, respectively) when controlling for age, age groups, and NOED duration. Only, the covariate of age was found to statistically impact anxiety and treatment groups interaction ($F(1, 20) = 7.05$, $P < .05$, $\eta^2 = 0.26$).

### Graphical Pairwise Comparisons

The pairwise comparisons of the interaction effects of treatment with NOED scores, NOED severity, depression, and anxiety scores across 3 time points have been presented by visual graphs in Figures 1–4.

### Within-Subject Pairwise Comparisons

The within-subject pairwise comparisons show significant increase in NOED scores and significant decrease in NOED severity, depression, and anxiety scores after treatment and during follow-up when compared to before treatment as represented by Figures 1–4. There was no significant change in NOED scores, NOED severity, depression, and anxiety scores at follow-up as compared with those after treatment.

### Between-Subject Pairwise Comparisons

Figure 1 shows the comparisons of treatments in improving NOED scores on IIEF-5. The 4wCBST treatment is significantly different from the other modalities of CBST and SC. All other modalities of CBST and SC significantly increased NOED scores after treatment.

Figure 2 shows the comparisons of treatments in reducing NOED severity. The 4wCBST treatment was significantly less efficient in reducing NOED severity than 8wCBSF, 12wCBST, and SC. The 12wCBST significantly reduced NOED severity compared with 6wCBST.

Figure 3 shows the comparison of treatments in reducing depression scores. The 6wCBST treatment was significantly less efficient in reducing depression scores than other modalities of CBST and SC.

Figure 4 shows the comparison of treatments in anxiety scores. The 8wCBST and 12wCBST significantly reduced anxiety scores after treatment compared with other treatments.

### Table 2. Frequency of demographic variables

| Demographic variables | Frequency | Percent (%) |
|-----------------------|-----------|-------------|
| Age (years)           |           |             |
| Minimum               | CBST 21   | SC 24       |
| Maximum               | CBST 39   | SC 39       |
| Age groups (years)    |           |             |
| 18–29                 | CBST 5    | SC 7        |
| 30–39                 | CBST 8    | SC 8        |
| Total                 | CBST 13   | SC 15       |
| NOED duration         |           |             |
| 6 months–1 year       | CBST 1    | SC 5        |
| 1–3 years             | CBST 7    | SC 7        |
| Beyond 3 years        | CBST 5    | SC 3        |
| Total                 | CBST 13   | SC 15       |

CBST = cognitive behavior sex therapy; NOED = nonorganic erectile dysfunction; SC = sildenafl citrate.
In the present study, there was no significant difference between both the treatment conditions in bringing change in NOED scores across the 3 time points. The SC was not significantly different from the new pilot treatment approach, CBST. Both, the CBST and SC brought about significant differences in NOED scores after treatment and during follow-up compared with before treatment. This finding is important and confirms the recent past study of cognitive behavior therapy effectiveness conducted with Pakistani men for the amelioration of ED.\textsuperscript{40,41} These improvements were significantly different after treatment and during follow-up compared with before treatment but were not significantly different during follow-up compared

Table 3. Descriptive statistics

| Variables                          | Treatment | Mean | Standard deviation | N  |
|-----------------------------------|-----------|------|--------------------|----|
| NOED scores, before treatment     | 4wCBST    | 21.00| 0.00               | 2  |
|                                   | 6wCBST    | 14.00| 1.89               | 6  |
|                                   | 8wCBST    | 10.00| 1.41               | 4  |
|                                   | 12wCBST   | 6.00 | .                  | 1  |
|                                   | SC        | 12.13| 3.96               | 15 |
|                                   | Total     | 12.64| 4.17               | 28 |
| NOED scores, after treatment      | 4wCBST    | 20.50| .70               | 2  |
|                                   | 6wCBST    | 15.83| 2.13               | 6  |
|                                   | 8wCBST    | 13.75| .95                | 4  |
|                                   | 12wCBST   | 9.00 | .                  | 1  |
|                                   | SC        | 13.66| 2.99               | 15 |
|                                   | Total     | 14.46| 3.20               | 28 |
| NOED scores, follow-up            | 4wCBST    | 20.00| 0.00               | 2  |
|                                   | 6wCBST    | 16.33| 2.33               | 6  |
|                                   | 8wCBST    | 13.50| 1.00               | 4  |
|                                   | 12wCBST   | 10.00| .                  | 1  |
|                                   | SC        | 13.86| 2.64               | 15 |
|                                   | Total     | 14.64| 2.97               | 28 |
| NOED severity, before treatment   | 4wCBST    | 1.00 | 0.00               | 2  |
|                                   | 6wCBST    | 2.00 | 0.00               | 6  |
|                                   | 8wCBST    | 3.00 | 0.00               | 4  |
|                                   | 12wCBST   | 4.00 | .                  | 1  |
|                                   | SC        | 2.46 | 0.83               | 15 |
|                                   | Total     | 2.39 | 0.83               | 28 |
| NOED severity, after treatment    | 4wCBST    | 1.00 | 0.00               | 2  |
|                                   | 6wCBST    | 1.66 | 0.51               | 6  |
|                                   | 8wCBST    | 2.00 | 0.00               | 4  |
|                                   | 12wCBST   | 3.00 | .                  | 1  |
|                                   | SC        | 2.06 | 0.59               | 15 |
|                                   | Total     | 1.92 | 0.60               | 28 |
| NOED severity, follow-up          | 4wCBST    | 1.00 | 0.00               | 2  |
|                                   | 6wCBST    | 1.66 | 0.51               | 6  |
|                                   | 8wCBST    | 2.00 | 0.00               | 4  |
|                                   | 12wCBST   | 3.00 | .                  | 1  |
|                                   | SC        | 2.00 | 0.53               | 15 |
|                                   | Total     | 1.89 | 0.56               | 28 |
| Depression, before treatment      | 4wCBST    | 9.00 | 1.41               | 2  |
|                                   | 6wCBST    | 3.33 | 2.42               | 6  |
|                                   | 8wCBST    | 8.00 | 1.63               | 4  |
|                                   | 12wCBST   | 10.00| .                  | 1  |
|                                   | SC        | 6.13 | 2.06               | 15 |
|                                   | Total     | 6.14 | 2.66               | 28 |

(continued)

Table 3. Continued

| Variables                          | Treatment | Mean | Standard deviation | N  |
|-----------------------------------|-----------|------|--------------------|----|
| Depression, after treatment        | 4wCBST    | 7.00 | 1.41               | 2  |
|                                   | 6wCBST    | 3.33 | 2.42               | 6  |
|                                   | 8wCBST    | 6.00 | 1.63               | 4  |
|                                   | 12wCBST   | 8.00 | .                  | 1  |
|                                   | SC        | 5.60 | 1.54               | 15 |
|                                   | Total     | 5.35 | 2.04               | 28 |
| Depression, follow-up              | 4wCBST    | 6.00 | 2.82               | 2  |
|                                   | 6wCBST    | 3.66 | 1.50               | 6  |
|                                   | 8wCBST    | 5.00 | 1.15               | 4  |
|                                   | 12wCBST   | 6.00 | .                  | 1  |
|                                   | SC        | 5.20 | 1.47               | 15 |
|                                   | Total     | 4.92 | 1.58               | 28 |
| Anxiety, before treatment          | 4wCBST    | 3.00 | 1.41               | 2  |
|                                   | 6wCBST    | 3.66 | 1.96               | 6  |
|                                   | 8wCBST    | 4.00 | 1.63               | 4  |
|                                   | 12wCBST   | 8.00 | .                  | 1  |
|                                   | SC        | 5.60 | 2.16               | 15 |
|                                   | Total     | 4.85 | 2.20               | 28 |
| Anxiety, after treatment           | 4wCBST    | 3.00 | 1.41               | 2  |
|                                   | 6wCBST    | 2.33 | 2.33               | 6  |
|                                   | 8wCBST    | 3.00 | 2.00               | 4  |
|                                   | 12wCBST   | 6.00 | .                  | 1  |
|                                   | SC        | 4.93 | 1.83               | 15 |
|                                   | Total     | 4.00 | 2.17               | 28 |
| Anxiety, follow-up                 | 4wCBST    | 3.00 | 1.41               | 2  |
|                                   | 6wCBST    | 2.33 | 1.50               | 6  |
|                                   | 8wCBST    | 2.00 | 1.63               | 4  |
|                                   | 12wCBST   | 6.00 | .                  | 1  |
|                                   | SC        | 5.20 | 1.97               | 15 |
|                                   | Total     | 4.00 | 2.24               | 28 |
| Age (years)                        | CBST      | 31.38| 6.69               | 13 |
|                                   | SC        | 31.20| 5.07               | 15 |

CBST = cognitive behavior sex therapy; NOED = nonorganic erectile dysfunction; SC = sildenafil citrate.

DISCUSSION

In the present study, there was no significant difference between both the treatment conditions in bringing change in NOED scores across the 3 time points. The SC was not significantly different from the new pilot treatment approach, CBST. Both, the CBST and SC brought about significant differences in NOED scores after treatment and during follow-up compared with before treatment. This finding is important and confirms the recent past study of cognitive behavior therapy effectiveness conducted with Pakistani men for the amelioration of ED.\textsuperscript{40,41} These improvements were significantly different after treatment and during follow-up compared with before treatment but were not significantly different during follow-up compared
Table 4. Within-subject and between-subjects effects

| Effects                        | df(error df) | F     | Sig. | Partial Eta² |
|-------------------------------|--------------|-------|------|--------------|
| NOED score*Treatment          | 8 (40)       | 2.95  | 0.01 | 0.37         |
| NOED Score*Treatment          | 4 (20)       | 4.69  | 0.00 | 0.48         |
| NOED Severity*Treatment       | 4 (20)       | 4.45  | 0.01 | 0.47         |
| Depression*Treatment          | 4 (20)       | 3.36  | 0.02 | 0.40         |
| Anxiety*Age                   | 1 (20)       | 7.05  | 0.01 | 0.26         |

NOED = nonorganic erectile dysfunction.

The participants showed stability in NOED scores recorded at follow-up. Those improvements did not change over time when assessed at follow-up. The no further improvement at follow-up may be attributed to a short duration between posttreatment and follow-up assessments. The covariates age, age groups, and duration of NOED did not appear to affect treatment outcome across all time points.

There were significant differences in both treatment conditions in bringing improvement in NOED scores and reduction in NOED severity and depression scores. Despite significant differences, generally both treatment conditions, CBST and SC, were effective in improving NOED scores and reducing NOED severity and depression scores. This is in confirmation with an earlier study by McCabe and Althof.9 The differences were among the different modalities of CBST viz 4w, 6w, 8w, and 12wCBST. However, there was statistically significant difference in both treatment conditions in reducing anxiety scores. The CBST was more effective in reducing anxiety scores than SC because of its emphasis on replacing maladaptive cognitions.39

The medicinal properties of SC provide a boost in erectile functioning and rigidity but did not bring amelioration of anxiety among men taking SC. The CBST is considered an effective treatment approach not only for improving erectile functioning but also for addressing anxiety-producing thoughts and emotions, thereby bringing a positive improvement in anxiety scores.40,41

The effective role of CBST in treating NOED establishes it as an evidence-based treatment approach among Pakistani men. The Pakistani men are different from Western men in their thoughts and beliefs. Such differences are accounted for by different set of values and socialization as received by their culture. The gender roles make the sexual role different for Pakistani men from their Western counterparts. But the effectiveness of CBST proves that Western CBST techniques are both culture fair and effective and can be used with men of other cultures too as documented by similar studies.40,41 In Pakistani culture, psychosexual education, debunking of sexual myths, and restructuring of sexual beliefs and standards are the major components of change because these components address the indigenous sexual issues different from Western men. Moreover, the sensate focus and stop-start exercises were an important component of CBST in addition to providing psychosexual education and teaching adaptive sexual attitudes, although some men reported difficulty in refraining from sexual intercourse during practicing of the stop-start technique. Despite these occasional difficulties, the CBST is a promising treatment approach especially in cultures like Pakistan where sexuality education is scarce and myths related to sexual activity are widespread.1

The current finding about the effective role of CBST in ameliorating symptoms of NOED stresses the role of biopsychosocial approach while viewing the ED. It shows that nonmedical factors also play an important role in the development and maintenance of ED. Previously, with the advent of PDE5i, the SC was considered the drug of choice for the treatment of erectile dysfunction.
difficulties in men. The CBST can be administered in combination with other therapeutic treatments such as SC.38–41

In a number of studies, age has been found associated with prevalence and severity of ED. Age has been reported as an independent risk factor for ED diagnosis or treatment.60 The results of this study point toward mixed results. The age was only found to be a factor in anxiety scores among different treatments. This could be attributed to the fact that age exerts a significant influence on treatment or diagnosis in men who are older than 40 years. The age groups did not appear to be a factor in treatment effects across different treatments.

The duration of NOED did not influence the effects of treatment across all time points. In a previous study, the men with a longer duration of the disorder were more likely to seek treatment. However, they were not satisfied with the treatment outcome when the treatment was administration of PDE5i.61 No other study with influence of duration on psychotherapeutic outcome of ED exists. This study finds no interaction effect of NOED duration on NOED scores, severity, depression, and anxiety scores.

Limitations
The study has certain limitations:

1. The study lacks in the administration of detailed use of investigative techniques to rule out the organic etiology of ED.

2. The frequency of sexual intercourse as a measure of avoidance was not assessed across 3 time points in both treatment groups.

3. The study did not involve the assessment of the sexual enjoyment and pleasure as the outcome in both treatment conditions.

4. The pilot study had low number of participants in each NOED severity category so the effect of number of sessions on each NOED severity level could not be generalized.

5. The study lacks a control group so the effects of CBST should be generalized cautiously.

Recommendations
The study makes the following recommendations:

1. There should be compulsory age-appropriate sex education available to men during their teenage and early adulthood years so that they may not believe in myths and should be able to develop adaptive sexual attitudes.

2. The physicians and surgeons working as sexual health professionals should be imparted training in the administration of CBST so that men with erectile difficulties should access a therapist easily.

3. The CBST should be administered to men with NOED for a minimum duration of 8 weeks. It is better to administer CBST to men with NOED irrespective of their NOED severity.

4. There should be compulsory screening of depression and PE in individuals presented with NOED and vice versa.23,29

5. The future studies on the efficacy of CBST should involve the couples in the therapy sessions and a significant number of participants to make the results more generalizable.

CONCLUSION
It is concluded that there should be proper medical investigations carried out before making a distinction between organic or nonorganic ED. The NOED could be benefitted by the administration of both CBST and SC. However, the 8wCBST was more significant in reducing anxiety scores than other treatments. The 8wCBST or 12wCBST was more effective in reducing NOED severity, depression, and anxiety scores than 4wCBST or 6wCBST. The CBST has the added benefit of reducing anxiety scores associated with NOED compared with SC. Moreover, CBST may be a preferred treatment option for NOED in Pakistani context where the availability of SC is sometimes difficult than scheduling consultation with a psychotherapist practicing cognitive behavior therapy. Hence, the CBST is an emerging and effective therapeutic approach to aid in the management of this condition.

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REFERENCES

1. Nasim MAF. Comprehensive treatment of male psychogenic erectile dysfunction by sex therapy and psychotropic drugs (without Pde5 Inh.). JSM 2017;14:e338; Supplement 4.
2. Khanzada U, Khan SA, Hussain M, et al. Evaluation of the causes of erectile dysfunction in patients Undergoing penile Doppler Ultrasonography in Pakistan. WJMH 2017;35:22-27.
3. Rastrelli G, Maggi M. Erectile dysfunction in fit and healthy young men: psychological or pathological? Transl Androl Urol 2017;6:79-90.
4. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men— a review of the prevalence and risk factors. Sex Med Rev 2017;5:508-520.
5. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. Nat Rev Dis Primers 2016;2:16003.
6. Capogrosso P, Colicchia M, Ventimiglia E, et al. One patient out of four with newly diagnosed erectile dysfunction is a young man- worrisome picture from the everyday clinical practice. J Sex Med 2013;10:1833-1841.
7. Ou YC, Lin YM. Psychogenic cause is not the main risk factor for erectile dysfunction in young men compared to the aging group. Urol Sc 2015;26:532.
8. Jannini EA, Sternbach N, Limoncin E, et al. Health-related characteristics and unmet needs of men with erectile dysfunction: a survey in five European countries. J Sex Med 2014;11:40-50.
9. McCabe MP, Althof SE. A systematic review of the psycho-social outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man’s inability to have sex? J Sex Med 2014;11:347-363.
10. Plumb JM, Guest JF. Annual cost of erectile dysfunction to UK Society. Pharmacoeconomics 1999;16:699-709.
11. Wessells H, Joyce GF, Wise M, et al. Erectile dysfunction. J Urol 2007;177:1675-1681.
12. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of sexual dysfunctions in Women and men: a Consensus Statement from the Fourth International consultation on sexual medicine 2015. J Sex Med 2016;13:135-143.
13. Jannini EA, McCabe MP, Salonia A, et al. Controversies in sexual medicine: organic vs. psychogenic? The Manichean diagnosis in sexual medicine. J Sex Med 2010;7:1726-1733.
14. Hsu GL, Johnson H, Huang HM, et al. Is the psychogenic factor an exclusive contributor to erectile dysfunction in a man under Thirty? Neuropsychiatry 2018;8:1815-1827.
15. Shamloul R, Ghanem H. Erectile dysfunction. Lancet 2013; 381:153-165.
16. Rajkumar RP. The impact of disrupted childhood attachment on the presentation of psychogenic erectile dysfunction: an exploratory study. J Sex Med 2015;12:798-803.
17. Papagiannopoulos D, Nehra A, Khare NAOA. Evaluation of young men with organic erectile dysfunction. Asian J Androl 2015;17:11-16.
18. Rajkumar RP, Kumaran AK. Depression and anxiety in men with sexual dysfunction: a retrospective study. Compr Psychiatry 2015;60:114-118.
19. Mourikis I, Antoniou M, Matsouka E, et al. Anxiety and depression among Greek men with primary erectile dysfunction and premature ejaculation. Ann Gen Psychiatry 2015;14:34.
20. Son H, Song SH, Lee JY, et al. Relationship between premature ejaculation and depression in Korean males. J Sex Med 2011;8:2062-2070.
21. Althof SE, O’Leary MP, Cappelleri JC, et al. Impact of erectile dysfunction on confidence, self-esteem and relationship satisfaction after 9 months of sildenafil citrate treatment. J Urol 2006;176:2132-2137.
22. Rosen RC, Althof S. Impact of premature ejaculation: the psychological, quality of life, and sexual relationship consequences. J Sex Med 2008;5:1296-1307.
23. Tsai W-K, Chiang P-K, Lu C-C, et al. The Comorbidity between premature ejaculation and erectile dysfunction—a Cross-Sectional Internet survey. Sex Med 2019;7:451-458.

24. Lewis RW, Fugl-Meyer KS. Definitions, classification, and epidemiology of sexual dysfunction. In: Lue TF, Basson R, Rosen R, et al., eds. Sexual medicine: sexual dysfunctions in men and women. Paris: Health Publications; 2004. p. 37-72.

25. Jannini EA, Lombardo F, Lenza A. Correlation between ejaculatory and erectile dysfunction. Int J Androl 2005;2:40-45.

26. Waldinger MD. Ejaculatio praecox, erectio praecox, and detumescencia praecox as symptoms of a hypertonic state in lifelong premature ejaculation: a new hypothesis. Pharmacol Biochem Behav 2014;121:189-194.

27. EL-Sakka AI. Severity of erectile dysfunction at presentation: effect of premature ejaculation and low desire. Urology 2008;71:94-98.

28. Brody S, Weiss P. Erectile dysfunction and premature ejaculation: interrelationships and psychosexual factors. J Sex Med 2015;12:398-404.

29. Liu Q, Zhang Y, Wang J, et al. Erectile dysfunction and depression: a systematic review and meta-analysis. J Sex Med 2018;15:1073-1082.

30. Chou PS, Chou WP, Chen MC, et al. Newly diagnosed erectile dysfunction and risk of depression: a population-based 5-year follow-up study in Taiwan. J Sex Med 2015;12:804-812.

31. Pollack MH, Reiter S, Hammerness P. Genitourinary and sexual adverse effects of psychotropic medication. Int J Psychiatry Med 1992;22:305-327.

32. Madeo B, Bettica P, Milleri S, et al. The effects of citalopram and fluoxetine on sexual behavior in healthy men: evidence of delayed ejaculation and unaffected sexual desire. A randomized, placebo-controlled, double-blind, double-dummy, parallel group study. J Sex Med 2008;5:2431-2441.

33. Safarinejad MR. Evaluation of endocrine profile and hypothalamic-pituitary-testis axis in selective serotonin reuptake inhibitor-induced male sexual dysfunction. J Clin Psychopharmacol 2008;28:418-423.

34. Yang C, Tang K, Wang B. Clinical value of serum 5-HT level in diagnosis and treatment of premature ejaculation. Urol Int 2013;90:214-218.

35. McCabe MP, Connaughton C. Psychosocial factors associated with male sexual difficulties. J Sex Res 2013;51:31-42.

36. Nobre PJ, Pinto-Gouveia J. Cognitions, emotions, and sexual response: analysis of the relationship among automatic thoughts, emotional responses, and sexual arousal. Arch Sex Behav 2008;37:652-661.

37. Nobre PJ. Psychological determinants of erectile dysfunction: testing a cognitive-emotional model. J Sex Med 2010;7(4 PART 1):1429-1437.

38. Banner LL, Anderson RU. Integrated sildenafil and cognitive-behavior sex therapy for psychogenic erectile dysfunction: a pilot study. J Sex Med 2007;4(4 Pt 2):1117-1125.

39. Boddi V, Castellini G, Casale H, et al. An integrated approach with vardenafil orodispersible tablet and cognitive behavioral sex therapy for treatment of erectile dysfunction: a randomized controlled pilot study. Andrology 2015;3:909-918.

40. Khan S, Amjad A, Rowland D. Cognitive behavioral therapy as an adjunct treatment for Pakistani men with ED. Int J Impot Res 2017;29:202-206.

41. Khan S, Amjad A, Rowland D. Potential for long-term benefit of cognitive behavioral therapy as an adjunct treatment for men with erectile dysfunction. J Sex Med 2019;16:300-306.

42. Rowland DL, Gutierrez B. Psychosexual therapy in perspective: strategies for the non-specialist counselor. In: Brewer D, ed. Psychotherapy: Methods, outcomes, and future directions. Hauppauge, NY: Nova Science Publishers; 2016. p. 15-44.

43. Schmidt HM, Munder T, Gerger H, et al. Combination of psychological intervention and phosphodiesterase-5 inhibitors for erectile dysfunction: a narrative review and meta-analysis. J Sex Med 2014;11:1376-1391.

44. Binik Y, Meana M. The future of sex therapy: Specialization or marginalization. Arch Sex Behav 2009;38:1016-1027.

45. Bossio JA, Basson R, Driscoll M, et al. Mindfulness-based group therapy for men with situational erectile dysfunction: a mixed-Methods feasibility analysis and pilot study. J Sex Med 2018;15:1478-1490.

46. Brotno LA. Mindful sex. Can J Hum Sex 2013;22:63-68.

47. Kimmes JG, Mallory AB, Cameron C, et al. A treatment model for anxiety-related sexual dysfunctions using mindfulness meditation within a sex-positive framework. Sex Relatsh Ther 2015;30:286-296.

48. Mize SJS. A review of mindfulness-based sex therapy interventions for sexual desire and arousal difficulties: from research to practice. Curr Sex Heal Rep 2015;7:89-97.

49. Sommers FG. Mindfulness in love and love making: a way of life. Sex Relatsh Ther 2013;28:84-91.

50. Jenkins LC, Hall M, Deveci S, et al. An evaluation of a clinical Care Pathway for the management of men with Nonorganic erectile dysfunction. J Sex Med 2019;16:1541-1546.

51. Wang H, Yuan J, Hu X, et al. The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis. Curr Med Res Opin 2014;30:1565-1571.

52. Ferguson JE III, Carson CC III. Phosphodiesterase type 5 inhibitors as a treatment for erectile dysfunction: current information and new horizons. Arab J Urol 2013;11:222-229.

53. Wiggins A, Tsambarlis PN, Abdelsayed G, et al. A treatment algorithm for healthy young men with erectile dysfunction. BJU Int 2018;123:173-179.

54. Munk NE, Knudsen JS, Comerma-Steffensen S, et al. Systematic review of oral combination therapy for erectile dysfunction when phosphodiesterase type 5 inhibitor Monotherapy fails. Sex Med Rev 2019;7:430-441.

55. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319-326.
56. Mahmood MA, Rehman KU, Khan MA, et al. Translation, Cross-cultural Adaptation, and Psychometric Validation of the 5-item International Index of erectile function (IIEF-5) into Urdu. J Sex Med 2012;9:1883-1886.

57. Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales. 2nd Ed. Sydney: Psychology Foundation; 1995.

58. Aslam N. Psychological disorders and resilience among earthquake affected individuals (Unpublished MPhil Dissertation). Islamabad: Pakistan: National Institute of Psychology, QAU; 2007.

59. Cohen J. Statistical power analysis for the behavioral sciences. revised edition. New York: Academic Press; 1977.

60. Mulhall JP, Luo X, Zou KH, et al. Relationship between age and erectile dysfunction diagnosis or treatment using real-world observational data in the USA. Int J Clin Pract 2016; 70:1012-1018.

61. Matic H, McCabe MP. Duration of erectile dysfunction and its relationship to treatment seeking and satisfaction with treatment using PDE5 inhibitors. Int J Urol 2008; 15:346-349.

62. Nobre P, Gouveia JP. Erectile dysfunction: an empirical approach based on Beck’s cognitive theory. Sex. Relationship Ther 2000;15:351-366.