Paroxetine, Cognitive Therapy or Their Combination in the Treatment of Social Anxiety Disorder with and without Avoidant Personality Disorder: A Randomized Clinical Trial

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Abstract

Background: The most efficacious treatments for social anxiety disorder (SAD) are the SSRIs and cognitive therapy (CT). Combined treatment is advocated for SAD but has not been evaluated in randomized trials using CT and SSRI. Our aim was to evaluate whether one treatment is more effective than the other and whether combined treatment is more effective than the single treatments. *Methods:* A total of 102 patients were randomly assigned to paroxetine, CT, the combination of CT and paroxetine, or pill placebo. The medication treatment lasted 26 weeks. Of the 102 patients, 54% fulfilled the criteria for an additional diagnosis of avoidant personality disorder. Outcomes were measured at posttreatment and 12-month follow-up assessments. *Results:* CT was superior to paroxetine alone and to pill placebo at the end of treatment, but it was not superior to the combination treatment. At the 12-month follow-up, the CT group maintained benefits and was significantly better than placebo and paroxetine alone, whereas there were no significant differences among combination treatment, paroxetine alone, and placebo. Recovery rates at 12 months were much higher in the CT group (68%) compared to 40% in the combination group, 24% in the paroxetine group, and 4% in the pill placebo group. *Conclusions:* CT was the most effective treatment for SAD at both posttreatment and follow-up compared to paroxetine and better than combined treatment at the 12-month follow-up on the Liebowitz Social Anxiety Scale. Combined treatment provided no advantage over single treatments; rather there was less effect of the combined treatment compared to CT alone.

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Introduction

Social anxiety disorder (SAD) is a common and debilitating condition, with a chronic course if left untreated [1]. SAD is best treated with psychotropic medication and cognitive behavioral therapies (CBT) [2]. The most effective treatments are monoamine oxidase inhibitors [3], the serotonin reuptake inhibitors (SSRI/SNRI) [4], benzodiazepines [5], and individual cognitive therapy

(CT) [6]. However, a substantial number of patients do not respond to drug treatment [7], and a meta-analysis suggested that severe forms of SAD with avoidant personality features do not respond well to psychological therapy [8]. Davidson et al. [9] found that exposure-based group CBT was not better than fluoxetine. However, individual CT [10] has been found superior to fluoxetine [11]. CT tested against applied relaxation and exposure was found to be more effective than the comparisons [12]. The results of a preliminary study suggest that CT enhanced with metacognitive techniques may be particularly efficacious and rapid [13].

There are 6 randomized trials of combined drug treatment in SAD [3, 14–18] but only 2 involve treatments with SSRI [9, 16]. In both of these studies medication was combined with exposure-based therapy but not CT [19]. The effects of combining the two most recent approaches in the treatment of SAD (CT and SSRI) have not been studied in a comprehensive randomized controlled trial. A recent meta-analysis showed there is a lack of studies combining psychological therapies and SSRI in most anxiety disorders [20]. This stands in contrast to typical clinical practice in SAD where a combination of some form of psychosocial treatment and SSRI is common and often recommended [21].

The present study aimed to investigate the comparative efficacy of these main treatments: SSRI (paroxetine), CT, and their combination. We compared them over the short and the long term (12 months). We aimed to test whether one treatment was more effective and whether combined treatment was more effective than individual treatment. We included patients with an additional avoidant personality disorder (APD) as these are highly common in samples of SAD. We also included a pill placebo with clinical management as the placebo effect is known to be high in most anxiety disorders [22].

Methods

Design and Procedure

We conducted a randomized, placebo-controlled comparative study of patients with primary SAD. Patients with an additional APD were included. We used 4 arms consisting of CT, paroxetine with clinical management, the combination of CT and paroxetine, and a pill placebo with clinical management. In the groups receiving pills, we applied triple masking, and the patient, the psychiatrists, and the principle investigator were blinded to which treatment (drug or placebo) was administered. The Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) [23] and SCID-II clinical interview [24] were used alongside a battery of self-report measures at pretreatment, posttreatment and the 12-month follow-up.

We made two changes to the registered trial protocol. We were unable to use the Social Phobia and Anxiety Inventory (SPAI) due to delays in obtaining a necessary authorization, and the Liebowitz Social Anxiety Scale (LSAS) was substituted instead. Also, the trial steering committee decided to drop the 6-month follow-up due to lack of capacity to deal with a 6-month assessment that coincided with end of treatment assessments.

The acute treatment phase consisted of 26 weeks of treatment with paroxetine or pill placebo, and the CT consisted of 12 sessions, each with a maximum duration of 60 min, with an opportunity for 2 booster sessions (approx. weeks 4 and 8 posttreatment). The combination condition consisted of CT for 12 sessions and paroxetine for 26 weeks, and during the first 12 weeks the patient had both treatments. All patients were assessed after 12 weeks of treatment (posttreatment assessment) and at a 12-month follow-up from the time the treatment ended.

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway (No. REK-018-03), the Norwegian Medicines Agency (SN 04-01998) and the Norwegian Data Inspectorate (ClinicalTrials.gov identifier: NCT00184106). All participants had to provide written informed consent before inclusion.

Sample and Eligibility Criteria

Participants were referred for treatment at the University Outpatient Unit, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. A total of 236 patients were referred to the trial. Of these, 102 patients were randomized into the 4 conditions. A total of 16 patients declined or did not show up at the trial after inclusion. The proportion of patients who declined or nonattendance at pretreatment was equally distributed among the treatment conditions (fig. 1).

Inclusion criteria were as follows: age of 18–65 years, fulfillment of DSM-IV criteria for SAD, and symptoms present for at least 6 months. Exclusion criteria were any form of physical disease, psychotic illness, acute suicidality, a primary diagnosis of major depressive disorder, diagnosis of body dysmorphic disorder, drug or alcohol dependence, and cluster A or cluster B personality disorders. Subjects not willing to accept random allocation were also excluded. We excluded patients who had been exposed to CT or to SSRIs previously in order to eliminate any bias of negative expectations to the treatment offered. Participants who were pregnant or were planning to become pregnant during the next 6 months were excluded due to the drug condition.

Therapists

The medication-based conditions were administered and managed by two experienced psychiatrists who were specialists in both psychopharmacology and psychiatry. Their mean duration of practice in psychiatry was 14 years. They received supervision with the principal investigator and the psychopharmacologists from St. Olav's University Hospital on a regular basis once a month. There were three therapists in the CT conditions. Their mean length of experience with CBT was 15 years. Each underwent extensive training in the basic CT protocol for social phobia [19], and they were trained and supervised by the author of the treatment manual (Adrian Wells). All therapists were trained clinical psychologists who had peer supervision every 2 weeks during the trial or monthly supervision with the originator of the CT protocol. Protocol adherence (check list) and competency ratings were routine-
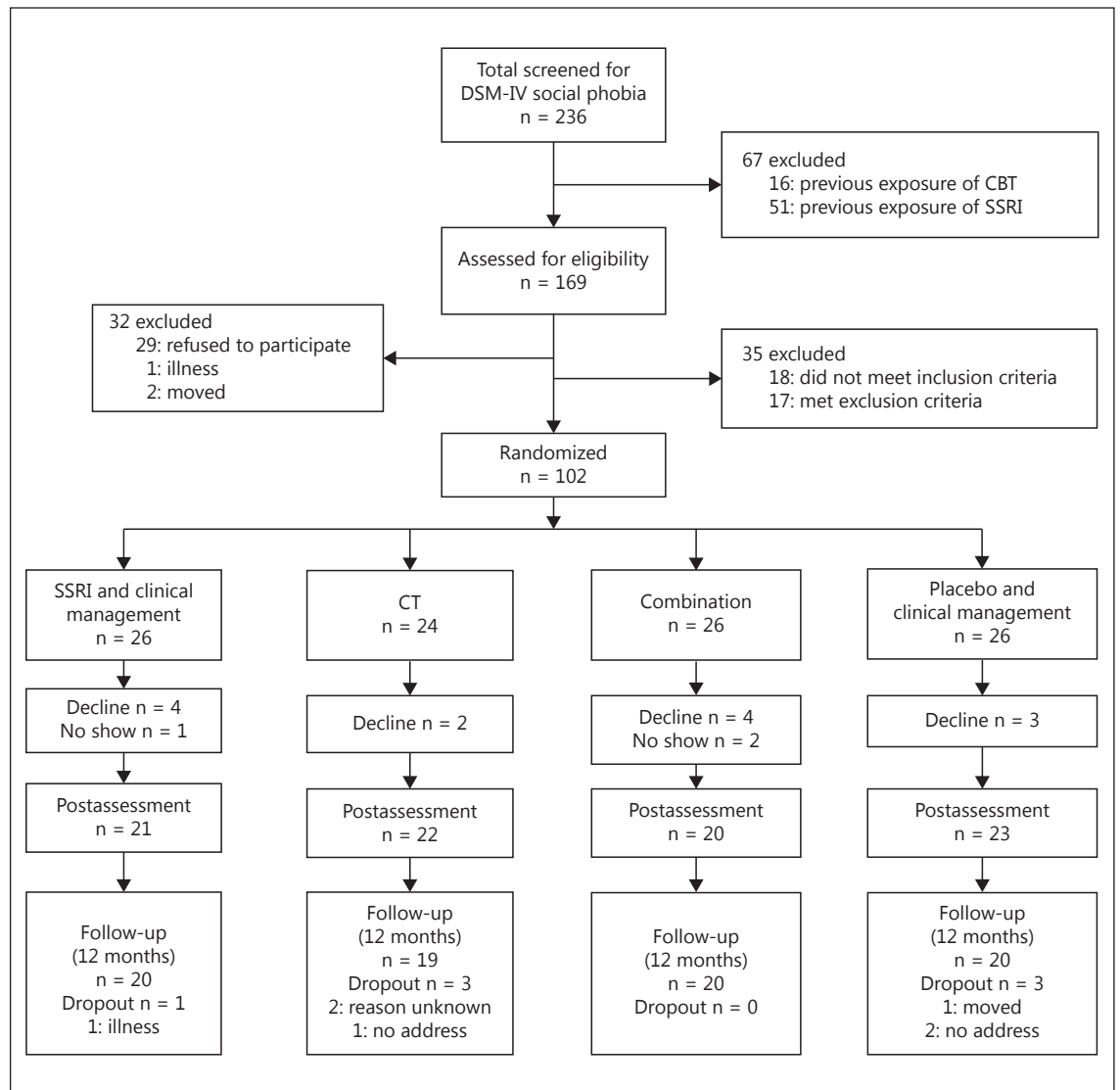
Fig. 1. CONSORT diagram of participant flow.

ly collected based on video recordings of all sessions. Competency was assessed by the protocol author and rated from 0 (no/low skills) to 6 (expert level). An overall evaluation indicated good (4) and very good (4.5 and 5.5) competency levels for the three therapists.

Randomization and Masking

The participants were randomly assigned to 1 of 4 conditions. The randomization used gender and diagnosis of APD as stratification variables in blocks of 10 to ensure equal distribution. The randomization lists were kept independently of the principle investigator, the psychiatrists, and the therapists. Blinding was conducted for the treatment conditions using medication or placebo and achieved for the primary outcome measures by using independent evaluators who were blinded to the treatment assignment. The Department of Clinical Psychopharmacology at St. Olav's

University Hospital administered the allocation sequence and assigned the patients to 1 of 4 treatment conditions in a randomized allocation format. The participants, independent diagnosticians, psychiatrists, and the principal investigator remained blinded to the paroxetine alone and pill placebo conditions. In addition, specific instructions were given to all participants to avoid disclosing information about their treatment to the evaluators.

Interventions

The medication used was paroxetine (paroxetine hydrochloride). It was administered as capsules manufactured by the pharmaceutical laboratory at St. Olav's University Hospital to make them identical to the placebo. The placebo capsules contained lactose. The paroxetine and the placebo were identical in size, color, smell, taste, and appearance. The pharmaceutical laboratory at St. Olav's University Hospital provided the medication to the psy-

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chiatrists. In addition to the medication they received clinical management. All patients were educated by the psychiatrists, and they provided information about the drugs and the management of it. All patients were asked for self-exposure during the psychopharmacological treatment and were able to discuss any problems related to drugs or side effects with their psychiatrist.

Following the clinical guideline by Stein et al. [25], drug treatment was administered over 26 weeks, and tapering of medications/placebo commenced at week 23, tapering 10 mg per week or alternatively 25% of dosage per week. Medication was administered adhering to best prescribing practices for social phobia as suggested by the manufacturer. The recommended initial dosage was 20 mg per day, and minimum–maximum dosage was 20–60 mg/day. The target range of paroxetine in the blood serum was set between 80 and 450 μmol/l. After 4 and 12 weeks of medication, blood serum was tested in all patients receiving paroxetine or pill placebo to monitor treatment compliance and ensure the target range of the drug was achieved. If needed, medication could be titrated upwards by 20 mg/day in steps until reaching the defined target level. The laboratory communicated serum levels outside the targeted range to the psychiatrist, and medications were added. Changes of medications were always counterbalanced in a 1:1 format so that changes in dosage were done simultaneously in both the active and the placebo arms in order to maintain the blinding of the treatment. The mean dosage of paroxetine in the overall group was 28 ± 5.5 mg/day.

The CT protocol for SAD followed the manual based on the model of Clark and Wells [10] but included specific enhancements based on metacognitive therapy [13]. Thus, there was greater systematic work on changing attention in social situations, more work on eliminating worry and rumination, and metacognitive experiments were used in each session, i.e. testing social performance while changing attention. Compared to the original version of the treatment, there was no work on reality testing underlying assumptions and beliefs about the self and social situations, limited work on imagery, and no work on memories of social situations. We replaced this with a greater focus on regulating attention and reducing threat monitoring. The main treatment elements in the manual were (a) developing and sharing a cognitive formulation of the problem, (b) reducing safety behaviors, (c) modifying the inner image of self as a social object (video feedback), (d) practicing external focus of attention in social situations, (e) carrying out behavioral experiments to test alternative mental strategies in social encounters and (f) using strategies for reducing worry, rumination, and threat monitoring associated with social situations.

Assessment and Outcome Measures

Patients were assessed pretreatment, posttreatment at 12 weeks (post-acute), and at the 12-month follow-up. Independent evaluators were trained and certified in the rating instruments and ADIS-IV and SCID-II assessments. The interrater reliability of the independent raters was based on 20 randomly selected video-taped assessments. For the diagnosis of SAD the kappa value was κ = 0.84, and for APD it was κ = 0.80. At posttreatment the evaluators were blinded to the treatment condition before reassessment.

The primary outcome measure was level of symptoms as measured by the Fear of Negative Evaluation Questionnaire (FNE) [26]. The reliable clinical change index (RCI) was used to establish the clinical significance of outcomes after treatment on the FNE following the procedure of Jacobson and Truax [27].

The secondary outcomes assessed anxiety by the LSAS [28] and the Beck Anxiety Inventory (BAI) [29], which have established validity for anxiety symptoms. For assessing interpersonal problems we used the Inventory of Interpersonal Problems (IIP-64) [30]. In addition, change in APD was measured by rediagnosis and severity ratings.

Power Calculations

Power calculations were based on the FNE (www.statisticalsolutions.net), and as the trial aimed to conduct a condition-by-time comparison, we weighted the active treatment conditions against the control condition (pill placebo). The mean standard deviation across trials using FNE is 5.78, and in an inferiority analysis with an expected difference, with an effect size of $d = 0.70$ (moderate effect), $\alpha = 0.05$, and β = at least 80%, the minimum number of participants in each condition was 18. Based on the calculation and an expected attrition rate of 25%, we estimated that the study should include at least 80 participants in 4 conditions. The sample comprised of 102 participants to increase the likelihood that the number exceeded thresholds at follow-up.

Data Analytic Strategy

All data were analyzed based on an intention-to-treat approach, and missing data were treated using last observation carried forward on the primary measure. We used a linear mixed model analysis [31]. Categorical data were analyzed using χ^2 tests, and pretreatment group differences on dimensional self-report measures were tested with ANOVA. Primary (FNE) and secondary (LSAS, BAI, IIP-64) outcome measures were subject to linear mixed model (repeated measures) with treatment condition as the between groups factor and time (pretreatment, posttreatment, 12-month follow-up) as the repeated measures factor. In each case the equality of variances of the repeated measures (sphericity) could not be assumed and so the Huyn-Feldt correction was applied. We also ran ANCOVA on the FNE and followed this with Sidak's pairwise post hoc comparisons on the adjusted means. Between-group effect sizes are reported as partial eta-squared (η_p^2). We also computed within-group effect sizes using Cohen's d and determined the clinical significance of findings by applying the criteria of Jacobson and Truax [27] for defining rates of reliable clinical change across groups. Significance in the overall study was defined to be $\alpha = 0.05$. We used IBM SPSS, version 22, to analyze the data.

Results

Pretreatment scores on the FNE, LSAS, BAI, and IIP-64 were similar across treatment groups with no statistical significant difference. Similarly, age, gender, occupational status, and ethnicity did not differ (table 1).

Results of the linear mixed-model ANOVAs demonstrated a significant effect for time on each of the self-report measures – unadjusted scores (table 2). There were significant interactions between treatment group and time on the FNE ($F_{4.4, 145.3} = 8.04$, $p < 0.0005$, $\eta_p^2 = 0.20$), demonstrating differences in the magnitude of symptom

Table 1. Demographic and clinical characteristics across conditions (n = 102)

Variable	SSRI	CT	Combination	Placebo	Total	p value
Subjects, n	26	24	26	26	102	0.911
Female, %	65	46	54	35	51	0.155
Mean age, years	31.0	27.0	34.5	30.7	30.9	0.080
Caucasian, %	95.0	95.2	94.7	85.7	92.6	0.594
Married/partner, %	60.0	44.0	46.4	45.1	48.8	0.180
Mean severity of SAD	5.7	5.4	5.5	5.5	5.5	0.352
Past major depression, %	18.0	14.0	10.5	27.2	17.6	0.510
Cluster C, %	54.0	50.0	55.0	59.0	54.0	0.985

p value: analysis of variance (for continuous variables) and χ^2 (for categorical variables).

Table 2. Unadjusted means and standard deviations at pretreatment, posttreatment, and 12-month follow-up with pairwise comparisons (Sidak) at each assessment (n = 102)

Measure	SSRI (n = 26)	CT (n = 24)	Combination (n = 26)	Placebo (n = 26)	F	p	Pairwise comparisons (p)					
							SSRI vs. CT	SSRI vs. combi	SSRI vs. placebo	CT vs. combi	CT vs. placebo	combi vs. placebo
FNE												
Pretreatment	24.81±3.86	25.25±3.66	23.88±4.52	23.19±3.85	1.34	0.264	0.697	0.407	0.148	0.231	0.072	0.534
Posttreatment	19.65±6.63	13.75±6.96	16.96±8.83	21.50±4.19	6.03	0.001	–0.003	–0.160	0.334	0.101	<0.0005	0.019
Follow-up	19.62±6.78	13.79±7.24	17.50±8.30	21.35±4.54	5.59	0.001	–0.003	–0.268	0.365	0.059	<0.0005	0.046
LSAS												
Pretreatment	69.23±23.98	69.08±20.66	61.77±11.24	63.19±15.88	1.12	0.341	0.981	0.160	0.290	0.133	0.267	0.711
Posttreatment	59.00±26.25	38.33±21.28	44.19±22.02	59.69±16.22	6.10	0.001	–0.004	–0.032	0.910	0.344	0.001	0.012
Follow-up	56.27±25.23	33.88±20.85	48.92±22.06	58.42±16.89	6.59	<0.0005	0.001	0.269	0.719	0.017	<0.0005	0.088
BAI												
Pretreatment	18.42±5.01	18.75±8.03	19.19±6.84	19.23±8.05	0.077	0.972	–0.871	–0.696	–0.682	–0.826	–0.811	–0.984
Posttreatment	15.23±6.59	7.33±5.68	10.46±9.75	14.65±9.06	5.41	0.002	0.001	0.034	0.795	–0.170	0.002	–0.062
Follow-up	15.65±6.27	6.42±5.94	10.69±6.89	16.08±9.55	9.69	<0.0005	–0.001	–0.016	–0.836	–0.042	<0.0005	–0.009
IIP-64												
Pretreatment	74.69±35.33	81.71±23.12	83.96±25.07	90.50±28.59	1.35	0.260	–0.407	–0.281	–0.083	–0.742	–0.236	–0.385
Posttreatment	68.04±37.34	55.83±30.71	67.46±33.84	86.99±25.35	4.06	0.009	–0.183	–0.949	–0.036	–0.204	–0.001	–0.031
Follow-up	67.69±37.53	51.17±28.16	68.88±37.78	83.50±26.67	3.99	0.010	0.080	–0.897	–0.088	–0.061	–0.001	–0.114

Follow-up: 12-month follow-up. Combi = Combination. Significance is two-tailed.

change across groups by posttreatment. As displayed in figure 2, the within-group analyses showed that in all active treatment conditions FNE scores improved significantly from pre- to posttreatment and from pretreatment to the 12-month follow-up.

We conducted ANCOVAs, utilizing pretreatment scores on the FNE as covariate, which demonstrated significant differences among groups posttreatment on FNE scores ($F_{3, 97} = 8.53$, $p < 0.0005$, $\eta_p^2 = 0.20$) and 12 month follow-up FNE score ($F_{3, 97} = 7.52$, $p < 0.0005$, $\eta_p^2 = 0.19$).

In each case the covariate had an effect posttreatment ($F_{1, 97} = 14.80$, $p < 0.0005$, $\eta_p^2 = 0.13$) and at follow-up ($F_{1, 97} = 10.89$, $p = 0.001$, $\eta_p^2 = 0.10$). Sidak's corrected pairwise tests on the adjusted means showed that at posttreatment the group receiving CT improved significantly more than the paroxetine group (mean difference = –6.180, SE = 1.819, p = 0.006, 95% CI: –11.065 to –1.294) and the placebo group (mean difference = –9.034, SE = 1.848, p < 0.0005, 95% CI: –13.998 to –4.071) but was not better than the combined treatment (mean difference =

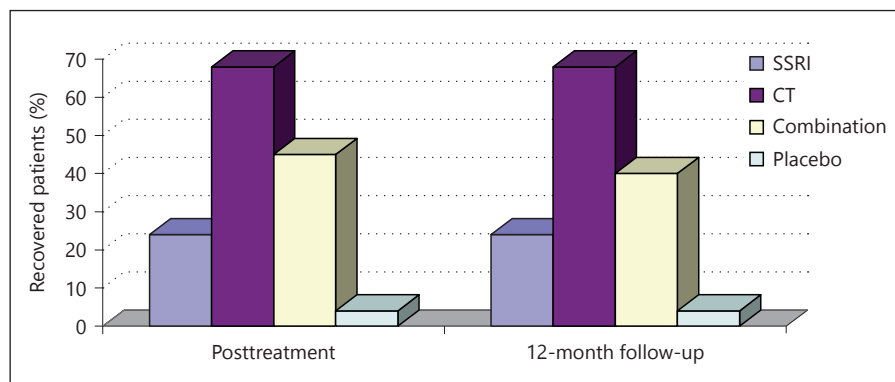Nordahl/Vogel/Morken/Stiles/Sandvik/
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Fig. 2. Histogram of the percentage of re-covered patients in the 4 treatment conditions.

−4.064, p = 0.161). Similarly, the combined treatment group improved more than the placebo group (mean difference = −4.971, SE = 1.784, p = 0.038, 95% CI: −9.763 to −0.178), but there were no differences between the combined group and the SSRI group (mean difference = −2.116, p = 0.806).

At the 12-month follow-up, pairwise tests demonstrated that CT was more effective than paroxetine (mean difference = −6.064, SE = 1.850, p = 0.009, 95% CI: −11.033 to −1.096) and placebo (mean difference = −8.675, SE = 1.879, p < 0.0005, 95% CI: −13.722 to −3.627). There were no differences between CT and the combination (mean difference = −4.452, p = 0.107). The combination treatment was no longer more improved than the placebo group (mean difference = −4.223, p = 0.125), and there were no differences between the combination and the SSRI (mean difference = −1.613, p = 0.942). Paroxetine and placebo did not differ (mean difference = −2.610, p = 0.641).

Effect Sizes, Reliable Improvement, and Recovery Rates

An effect size *(d)* indicates the magnitude of an observed effect in a standard unit of measurement [32]. In order to compare the magnitude of improvement in social anxiety symptoms, we calculated uncontrolled pretreatment to posttreatment and follow-up effect sizes using Cohen's formula on the primary measure: FNE. We found overall high effect sizes in the active treatments. A controlled effect size expresses the magnitude of a specific treatment effect compared to control conditions. It is calculated by subtracting the posttreatment mean of the control group (placebo) from the posttreatment mean of the treatment group divided by the pooled standard deviation. The controlled effect sizes (d_c) at posttreatment/12-month follow-up were as follows: paroxetine 0.59/0.39, CT 1.96/1.20, and combination 1.09/0.60.

In order to obtain an estimate of the clinical significance of the treatment effects on the FNE we calculated the RCI. Jacobson's criterion c, based on the revised methodology of Jacobson and Traux [27], was applied. The cutoff point c and the RCI were calculated using the following formulae:

$$c = \frac{S_1 M_2 + S_2 M_1}{S_1 + S_2},$$

$$RCI = \frac{X_2 - X_1}{S_{diff}},$$

where

$$S_{diff} = \sqrt{2\,S_E^2}$$

and

$$S_E = S_1 \sqrt{(1 - r_{xx})}.$$

For FNE: c = 15, RCI = 5.89. This means that to achieve recovery status, an individual's pre- to posttreatment/follow-up scores must change by 6 or more in the direction of the functional/normative group, and scores must be ≤15.

The number of patients meeting the criteria for recovery at posttreatment (n = 86) was 23% in the SSRI group, 68% in the CT group, 45% in the combination group, and 4% in the pill placebo group. There were significantly more patients recovered in the CT group compared to the combined group (p = 0.041). The same pattern of results was found at the 12-month follow-up (table 3).

Secondary Measures

Analyses were repeated on the secondary LSAS, BAI, and IIP-64. There was a significant interaction between group and time on the LSAS ($F_{4.28,\ 139.85} = 8.307$, p < 0.0005,

Table 3. Number of patients meeting criteria for reliable clinical improvement and recovery on the FNE at post-treatment and at the 12-month follow-up (n = 86)

	Paroxetine (n = 21)	CT (n = 22)	Combination (n = 20)	Placebo (n = 23)
Post-treatment, n (%)				
Recovered	5/21 (24)	15/22 (68)	9/20 (45)	1/23 (4)
Improved	4/21 (20)	4/22 (18)	3/20 (15)	2/23 (9)
No change	12/21 (56)	3/22 (14)	8/20 (40)	20/23 (87)
Deteriorated	0/21 (0)	0/22 (0)	0/20 (0)	0/23 (0)
12-month follow-up, n (%)				
Recovered	5/21 (24)	15/22 (68)	8/20 (40)	1/23 (4)
Improved	3/21 (14)	3/22 (14)	4/20 (20)	3/23 (9)
No change	13/21 (62)	4/22 (18)	8/20 (40)	19/23 (87)
Deteriorated	0/21 (0)	0/22 (0)	0/20 (0)	0/23 (0)

RCI ≥6 on the FNE and crossing cutoff score ≤15 (recovered).

$\eta_p^2 = 0.20$), the BAI ($F_{5.10, 166.88} = 4.923$, $p < 0.0005$, $\eta_p^2 = 0.13$), and the IIP-64 ($F_{4.74, 154.87} = 4.102$, $p = 0.002$, $\eta_p^2 = 0.11$), demonstrating differences in the magnitude of symptom change across groups. The results of the ANCOVAs for the LSAS showed significant group differences at posttreatment ($F_{3, 97} = 9.139$, $p < 0.0005$, $\eta_p^2 = 0.22$) and at follow-up ($F_{3, 97} = 9.073$, $p < 0.0005$, $\eta_p^2 = 0.22$). Group differences also emerged at posttreatment on the BAI ($F_{3, 97} = 6.087$, $p = 0.001$, $\eta_p^2 = 0.16$) and at follow-up ($F_{3, 97} = 10.373$, $p < 0.0005$, $\eta_p^2 = 0.24$). On the IIP-64 similar effects were found posttreatment ($F_{3, 97} = 5.899$, $p = 0.001$, $\eta_p^2 = 0.15$) and at follow-up ($F_{3, 97} = 4.823$, $p = 0.004$, $\eta_p^2 = 0.13$).

Pairwise tests on the LSAS scores at posttreatment showed that the CT group was more improved than the paroxetine group (mean difference = –20.574, p = 0.001, 95% CI: –34.583 to –6.564) and the placebo group (mean difference = –25.080, p < 0.0005, 95% CI: –39.179 to –10.981) but not more than the combination group (mean difference = –10.479, p = 0.262). The combination group did not do better than the paroxetine group (mean difference = –10.094, p = 0.281), but it was better than the placebo group (mean difference = –14.601, p = 0.031, 95% CI: –28.333 to –0.869). The paroxetine group did not perform better than the placebo group at posttreatment on the LSAS (mean difference = –4.507, p = 0.945). The pattern changed somewhat by the 12-month follow-up, where the CT group performed better than the combination group (mean difference = –18.607, p = 0.008, 95% CI: –33.654 to –3.560), better than paroxetine (mean difference = –22.322, p = 0.001, 95% CI: –37.223 to –7.422), and better than placebo (mean difference = –27.415, p < 0.0005, 95% CI: –42.410 to –12.419). By the 12-month

follow-up neither paroxetine (mean difference = –5.092, p = 0.928) or the combination (mean difference = –8.808, p = 0.498) were better than the placebo.

BAI at posttreatment showed that the CT group performed better than the paroxetine group (mean difference = –8.020, p = 0.002, 95% CI: –13.784 to –2.256) and the placebo group (mean difference = –7.140, p = 0.007, 95% CI: –12.905 to –1.376) but not better than the combination group (mean difference = –2.963, p = 0.675). The combination group was not more effective than the SSRI group (mean difference = –5.057, p = 0.104) or the placebo group (mean difference = –4.178, p = 0.264). The paroxetine group did not differ from placebo at posttreatment (mean difference = 0.879, p = 0.999). At the 12-month follow-up CT was significantly better than paroxetine (mean difference = –9.330, p < 0.0005, 95% CI: –14.717 to –3.942) and placebo (mean difference = –9.524, p < 0.0005, 95% CI: –14.913 to –4.136). However, it was not superior to combination treatment (mean difference = –4.150, p = 0.223). The combination was equivalent to paroxetine (mean difference = –5.179, p = 0.058) but was better than placebo (mean difference = –5.374, p = 0.044, 95% CI: –10.652 to –0.096). The paroxetine group did not perform better than the placebo group at the 12-month follow-up (mean difference = –0.194, p = 0.999).

For the IIP-64, at posttreatment, there were differences in favor of the CT group compared to the paroxetine group (mean difference = –18.167, p = 0.020, 95% CI: –34.377 to –1.957) and to the placebo group (mean difference = –23.696, p = 0.001, 95% CI: 39.941 to –7.450). The combination group did not differ from any other conditions. Paroxetine did not differ from placebo (mean

Table 4. The most commonly reported treatment-related adverse events during the trial in three groups (%); CT group not included (n = 63)

Adverse event	Placebo (n = 23)	Paroxetine (n = 21)	Combination (n = 19)
Nausea	8	24	21
Headache	4	24	21
Somnolence	4	24	26
Dry mouth	0	16	16
Sexual problems	0	8	10
Insomnia	12	20	16
Asthenia	8	24	26
Sweating	0	8	10
Tremor	0	0	0
Obstipation	4	8	5
Other: appetite loss	0	4	0

Sexual problems: lack of or difficulties with ejaculation.

difference = –5.529, p = 0.931). At the 12-month follow-up CT performed better than SSRI (mean difference = –21.699, p = 0.022, 95% CI: –41.244 to –2.155) and placebo (mean difference = –25.850, p = 0.004, 95% CI: –45.437 to –6.263). There were no other differences.

Adverse Effects and Safety

All patients underwent a thorough examination and medical test before inclusion in any of the drug conditions. The psychiatrists used a checklist in the case report form to inquire about the presence of SSRI adverse effects on each visit and rated a severity scale. The list of adverse effects was based on the National Medicines Agency guidelines for postmarketing studies (2001/20/EC). The most common adverse effects reported were nausea, headaches, and somnolence. Overall, the medications seemed to be well tolerated, and no serious side effects were reported in the trial, during the tapering of the drugs, or after the trial (table 4).

Discussion

The results showed that CT was significantly more effective than paroxetine and placebo at posttreatment and at follow-up on the primary social phobia outcome (FNE). CT did not perform better than the combined treatment on the main measure of FNE, but CT was significantly better on recovery rates. The combination of CT and paroxetine did not confer clinical advantages compared to CT alone at posttreatment and indeed appeared to impair long-term outcome at the 12-month follow-up, where CT led to significantly lower scores on the LSAS than the combination treatment.

The combination treatment was superior to placebo and demonstrated better recovery rates but was not superior to paroxetine on measures of anxiety and interpersonal behavior. CT also led to higher rates of recovery than the other conditions, and the presence of APD did not appear to reduce the outcome. There was no additional gain in effect over CT alone of combining SSRI and CT, but there was a trend suggesting that paroxetine detracted from efficacy compared to CT alone. We aimed to investigate any advantages of combining CT and paroxetine, but we were unable to find evidence supporting a benefit. In fact the combination yielded a lower effect size and significantly lower recovery rates than CT alone. This raises the possibility that the combined treatment is detrimental to CT alone. This finding concurs well with other studies showing that exposure therapy in combination with SSRI in SAD produces reduced effects [9, 33]. The same appears in studies of panic disorder where exposure or CBT is combined with alprazolam [34] or imipramine [35] and also impairs long-term effects compared to exposure therapy or CBT alone. These findings challenge the typical assumption that drugs and CBT should be integrated to improve outcome.

Our results are somewhat at variance with another recent study on SAD, which has reported advantages of combined treatment over and above the single treatments [3]. In that study group CBT was combined with phenelzine. The different pattern of results may reflect both the use of a different pharmacological treatment and the use of a different form of psychological treatment and treatment format.

Two recent meta-analyses of a large number of trials have compared pharmacological, psychological, and combined treatment. In the first meta-analyses a large pool of heterogeneous forms of psychotherapies and various types of SSRI were included, and larger effect sizes were found for the psychopharmacological drugs (SSRI and SNRI) than for psychological therapies [20]. This is in contrast to the meta-analysis of Mayo-Wilson et al. [6], showing large effect sizes for both pharmacological treatments as well as for psychological treatments, but they did not find evidence that any combination was more efficacious than the leading pharmacological or psychological interventions alone.

The results in our study showed that combined treatment is detrimental to CT alone. These findings concur

with results showing that exposure therapy in combination with SSRI [9, 33] in SAD produces reduced effects. This appears similar in panic disorder where exposure or CBT is combined with alprazolam [34] or imipramine [35], which impairs long-term effects compared to exposure therapy or CBT alone. These findings challenge the typical assumption that SSRI and exposure/CBT can be integrated to improve outcome for anxiety disorders.

There might be several explanations for the suppression effects of paroxetine on CT. Recently, Fava et al. [36] conducted a systematic review of SSRI withdrawal, showing that paroxetine might reduce outcome not only after suspension but during tapering of the drug. Also, rebound effects [37] and persistent postwithdrawal disorders [38] might occur with SSRIs, and these are often ignored and unrecorded in drug trials. An alternative hypothesis could be based on the cognitive model: that the patient's safety behaviors maintain anxiety by preventing reality testing of negative thoughts [10]. Specifically, drugs might act as a safety behavior and thus reduce the effect of CT. Consistent with this idea Basoglu et al. [39] showed that medications might well lead the person to attribute positive changes to the medications and not to the therapy, and this leaves the patient more vulnerable to relapse.

Our results are consistent with other studies comparing CT with SSRIs, although it is noteworthy that our effect sizes and recovery rates were larger than previously reported. As the competency of the therapists in other studies has also been high [11, 12], a plausible explanation of the strong effect sizes could be that in our study we used a modified form of CT with elements more consistent with metacognitive therapy [13]. Metacognitively enhanced CT seems to work more quickly and may increase outcomes of CT. In particular, it seems that basing treatment on reducing the emphasis on changing cognitive content and rather working on the worry, ruminations, and threat monitoring in social anxiety can enhance the outcome.

Both paroxetine and CT have both benefits and vulnerabilities as treatments for SAD. Paroxetine is a potent SSRI and is considered to be a safe treatment for SAD. It has demonstrated adverse side effects in a high proportion of patients and has strong withdrawal symptoms after it is discontinued [36]. In addition, paroxetine should not be used in children or in patients with increased suicidal risk. Also, there are problems with variability in effect across gender and with older age that make it difficult to provide optimal dosages as this must be monitored and adjusted in each case.

CT is considered to be a safe treatment for SAD. CT of SAD is dependent on the quality of and compliance with treatment [40] and is relatively costly and resource demanding. Availability of well-trained therapists in CT is low, and poorly performed CT, which normally includes video feedback and self-exposure techniques, may backfire and make the patient worse. The metacognitively enhanced CT used here requires additional skills in meta-CT and is new and not yet widely available. In addition, SSRIs or benzodiazepines can be considered a treatment option alone, but the first-line treatment should be CT. However, SSRIs or benzodiazepines may be considered for SAD when comorbid depressive disorder is present [41].

The strength of the current study includes the use of a rigorous randomized controlled design and evaluation of the best current treatments and their combinations. Triple blinding was used in the paroxetine and pill placebo conditions so that the principal investigator, the psychiatrist/therapist, and the patients had no knowledge about which patients were receiving the active drug treatment or the pill placebo. There was systematic control of the correct dosage of drugs (blood serum by 4 and 12 weeks), so we are reasonably sure that the dosage was within target level and the medication was taken as prescribed. Furthermore, any correction of drugs was counterbalanced in both the active and the placebo arms, so the blinding of the study was upheld. Finally, a notable aspect of this study is that it was independent of any sponsors with a special interest in the results and that the medication treatment lasted at least 6 months (26–28 weeks), which is longer than most comparable studies on SSRIs.

The study also has some important limitations. First, attrition is always a challenge in samples of SAD and avoidant behavior; however, attrition was equally distributed in all groups in the current study. Fifteen percent of the patients did not attend the reassessment, so we had to interview these patients at post-treatment by telephone. We are not sure whether a different setting of the interviews could bias the data, but this must be considered. Second, many patients with social phobia suffer from co-occurring depression; thus, we should be cautious about generalizing the findings to patients with both social phobia and major depression as patients with current major depressive disorder were excluded. There is a possibility that drug treatment in our study may have been adversely affected by bias produced by the blinding process. Specifically, in completing self-report measures, those in the drug arm may have doubted that they received the active treatment rather than placebo. No such conflict operated

in the unmasked CT condition. Fourth, psychotherapies might also provide adverse effects, and the current trial did not monitor these for the CT condition. This might have imposed more negative expectations of treatment outcome in patients receiving drugs compared to the patients receiving CT. Future studies should definitely monitor the adverse effects in psychological treatments as these are well known but underrecorded and underreported [42, 43]. Finally, the allegiance effect is always an important bias in any study. The cognitive therapists were all specialists and have a long track record of using CT in various forms of psychological disorders. The psychiatrists were experienced experts within psychopharmacological drugs and treatments; thus, the allegiance effects should be part of the effects demonstrated both in the therapy and the drugs.

The overall implications of the results are that CT should be considered, where available, as a first-line treatment of patients with SAD with and without an additional avoidant personality, with no apparent advantage of combining CT with paroxetine. However, in cases of SAD with comorbid depressive disorder, combination treatments involving SSRI or benzodiazepines should be considered. Contrary to what was expected, we did not find significant differences between paroxetine and placebo on average reduction on the FNE. However, there was clearly a greater percentage of patients meeting the criteria for reliable clinical improvement with paroxetine compared to placebo. This might reflect the high proportion of patients with APD, who seemed to respond less to medication alone.

The treatment effects were maintained at the 12-month follow-up, and the pill placebo showed no further improvement. The stability of treatment effects for the enhanced CT that we used shows that stability of change does not suffer due to the relatively short nature of the intervention, a finding which also is confirmed in a parallel randomized controlled study of adolescent social phobia [44]. However, the long-term effects of both paroxetine and CT in this trial are unknown. A long-term follow-up study of SAD using exposure therapy suggested that personality disorder might worsen the long-term outcome and predict a relapse of SAD [8, 45].

Conclusion

CT was the most effective treatment for SAD with and without APD. Paroxetine was associated with greater recovery rates posttreatment than placebo but not on the self-report FNE scores. There was a reduced effect of combining the treatments compared to CT alone. The detrimental effects of combining SSRI with exposure or CBT is reported in previous studies but should be explored further. The inclusion of patients with avoidant personality did not reduce outcomes as the results for CT or paroxetine compare well against other studies that have typically excluded such patients.

Acknowledgments

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