Moclobemide and cognitive behavioral therapy in the treatment of social phobia.

A six-month controlled study and 24 months follow up

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Abstract

The aim of the study was to asses the 6-months treatment efficacy and 24-month follow up of three different therapeutic programs (A. moclobemide and supportive guidance, B. group cognitive-behavioral therapy and pill placebo, and C. combination of moclobemide and group cognitive-behavioral therapy) in patients with a generalized form of social phobia. Eighty one patients (38 males and 43 females) were randomly assigned to three different therapeutic programs. Patients were regularly assessed on a monthly basis by an independent rater on the LSAS (Liebowitz Social Anxiety scale), CGI (Clinical Global Impression) for severity and change and BAI (Beck Anxiety Inventory). Altogether, sixty-six patients completed the six month treatment period and 15 patients dropped out. All therapeutic groups showed significant improvement. A combination of CBT and pharmacotherapy yielded the most rapid effect. Moclobemide was superior for the reduction of the subjective general anxiety (BAI) during the first 3 months of treatment, but its influence on avoidant behavior (LSAS avoidance subscale) was less pronounced. Conversely, CBT was the best choice for reduction of avoidant behavior while a reduction of subjective general anxiety appeared later than in moclobemide. After 6 months of treatment there were best results reached in groups treated with CBT and there was no advantage of the combined treatment. The relapse rate during the 24-month follow up was significantly lower in the group treated with CBT in comparison with the group A. formerly treated with moclobemide alone.

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ORIGINAL ARTICLE

INTRODUCTION

Social phobia is a chronic anxiety disorder with a low rate of remission which substantially decreases the quality of life and impairs numerous specific social roles (Davidson et al. 1994, Solyom et al. 1986, Regier et al. 1990). Findings based on large community samples from five sites in the Epidemiological Catchment Area study (Eaton et al. 1991) yielded lifetime prevalence estimates of 2,73% for social phobia. Estimates from the National Comorbidity Survey (NCS) (Kessler et al. 1994) indicated a lifetime prevalence of 13,3% (Kessler et al. 1994).

A number of studies have examined the efficacy of pharmacological and psychological treatments of this disorder. A growing body of evidence suggests that antidepressants, benzodiazepines and cognitive behavioral therapy are effective. Few studies have compared the effectiveness of pharmacotherapy and cognitive-behavioral therapy (Gelertner et al. 1991, Heimberg et al.1998, Oosterbaan et al. 2001, Haug et al 2000 and Blomhoff et al. 2001). It seems that pharmacological treatment may have an earlier onset of action and a more potent short-term effect, while the effect of cognitive-behavioral therapy may persist longer. Furthermore (Heimberg et al. 1993, Mattick et al. 1989), only very limited data are available on regarding the efficacy of combined treatment with CBT and pharmacotherapy (Gelertner et al. 1991, Clark and Agras 1991, Agras 1990, Andrews et al. 1994, Heimberg et al. 1993). Gelertner et al. (1991) compared CBT with pharmacotherapy by assigning 65 patients to one of four treatment conditions: 1) cognitive-behavioral group treatment (CBGT), 2) alprazolam with self-directed exposure, 3) phenelzine with self-directed exposure, or 4) placebo with self-directed exposure. The duration of the trial was 12 weeks for all treatments. Neither of the medication with self-directed exposure groups fared significantly better than the group receiving only CBGT. The phenelzine group performed better than the alprazolam group in some measures. At a 2-month follow up after the treatment discontinuation the phenelzine group maintained, the CBGT patients showed some additional improvement, and the alprazolam patients showed a higher relapse rate.

Heimberg et al. (1998) recruited 133 patients for a two-site study comparing monoamine oxidase inhibitor phenelzine, pill placebo, an educational-supportive group, or group CBT (CBGT) for 12 weeks. At the 12th week of the study phenelzine (77% treatment responders) and CBT (75% responders) were superior to the pill placebo (41% responders) or educational-supportive group therapy (35% responders). After 12 weeks, however, phenelzine patients were significantly more improved than CBGT patients on some measures. After 12 weeks of acute treatment patients who had a positive response to either phenelzine or CBGT, received monthly maintenance treatment for 6 months. After that there was a 6-month treatment-free follow up (Liebowitz et al. 1999). Patients who had received CBGT were less likely to relapse than patients who had received phenelzine. Thus, phenelzine may provide somewhat more immediate relief, but CBGT may provide greater protection against relapse. A study by Haug et al (2000) examined the effect of exposure therapy alone or in combination with sertraline for generalized social phobia in a primary care setting. Although exposure therapy and sertraline were effective alone, the combination of exposure therapy and sertraline showed some additional benefits.

After 15 weeks of active treatment in a randomized clinical trial comparing cognitive therapy to moclobemide for social phobia, Oosterbaan et al. (2001) found that cognitive therapy was significantly better than moclobemide but not placebo. After a 2-month follow-up period, cognitive therapy was significantly better than both moclobemide and placebo. In addition, treatment gains in the cognitive therapy group were maintained over a 15-month follow up period.

Moclobemide was the most studied antidepressant in the 90s for the treatment of social phobia. In the Versiani study, moclobemide was superior to placebo at the end of 8 weeks and was as effective as phenelzine on all measures, except for the social avoidance subscale of the LSAS (Versiani et al. 1992). The state of knowledge at the time of planning and beginning of our study was that moclobemide is an effective compound in the treatment of social phobia and yields the best results in a dose of 600 mg per day. Later, the data on moclobemide efficacy in social phobia started to be inconsistent. Other double-blind, placebo controlled studies of moclobemide have been published, with controversial results. A large multicenter 12-week, double-blind study compared two doses of moclobemide (300 and 600 mg) with placebo (Katschnig et al. 1997). The higher dose was superior to placebo on all measures of social phobia, general anxiety, and disability. The 300 mg dose was superior to placebo only in some measures. Noyes et al. (1997) compared five doses of moclobemide (75, 150, 300, 600 and 900 mg) with placebo in a 12-week double-blind study. None of the doses of moclobemide was superior to placebo. Schneier et al (1998) compared moclobemide with placebo in double-blind, flexible-dose design. Moclobemide was superior to placebo in just 2 of the 10 primary outcome measures. In summary of the four published double-blind, placebo controlled studies of moclobemide, one showed strong efficacy, one weak efficacy, and two showed no clinically significant efficacy. Numerous controlled trials across a range of SSRIs including sertraline, fluvoxamine and paroxetine have demonstrated their effectiveness in the treatment of social phobia (Stein et al. 1996, Allgulander et al. 1999, Vliet et al. 1994, Stein et al. 1999, van Ameringen et al. 2001). SSRIs are currently considered as the first-line medication treatment (for a meta-analysis of RCTs see Van der Linden et al. 2000).

When we started our study, the view on moclobemide efficacy was more optimistic in the treatment of

patients suffering from social phobia. Because it was the antidepressant of choice in the treatment of social phobia in 1995, we decided to compare its efficacy with group CBT program. The aim of the study was to compare the efficacy of three types of six-month treatment programs:

- A. Pharmacotherapy (moclobemide 600 mg) and clinical management
- B. Group cognitive-behavioural therapy with pill placebo
- C. Pharmacotherapy (moclobemide 600 mg) and group cognitive-behavioural therapy

SUBJECTS AND METHODS

Subjects

Eighty nine patients referred with the diagnosis of social phobia-generalized type to the out-patients department of the Psychiatric Centre Prague and to the Day Care Clinic Horní Palata were screened by an experienced psychiatrist according to a structured diagnostic interview (SCID – Structured diagnostic interview DiNardio et al. 1993) using the diagnostic criteria of ICD-10 for social phobia. Before the admission to the study the diagnosis was confirmed by a second independent psychiatrist.

Inclusion criteria:

- Age between 18–55 years
- Research diagnostic criteria (ICD-10) for Social phobia
- DSM-IV criteria for social phobia
- A score of at least 4 on the Clinical Global Impression scale
- Written informed consent

Excluding criteria:

- Major depressive disorder
- Total HAMD score (Hamilton Psychiatric Rating Scale for Depression) of more than 16
- Substance abuse disorder
- Organic mental disorder
- Personality disorders: dissocial, histrionic, borderline, paranoid
- History of schizophrenia
- Mental retardation
- Endocrine diseases
- Any contraindication for use of moclobemide (i.e. pregnancy)

The study project was approved by the Ethical Committee of the Psychiatric Centre Prague.

Methods

Patients were randomly assigned into three groups with different treatment strategies.

A. Group: Pharmacotherapy and supportive clinical management: After a one week wash-out period upon their admission to the study, moclobemide was administered to the patients in 600 mg daily doses two times per day. The duration of pharmacological treatment was six months. Supportive clinical management consisted of 14 individual therapeutic sessions, each lasting approximately 20–45 minutes. A psychiatrist allowed patients to express their concerns and provided them with reassurance. Patients were neither encouraged nor discouraged to confront phobic-avoided social situations. Psychotherapeutic interventions of any kind or additional medication were forbidden during the study. The doctor-patient relationship was limited to that of general support.

B. Group: Cognitive behavioural therapy and placebo pills: After a one week wash-out period upon the admission to the study, placebo pills (2 pills twice daily) were administered to the patients during a six-month treatment period. Cognitive behavioural therapy consisted of 12 group sessions, each lasting four hours, one session per week. There was an additional one booster session after three months. Every patient also had four individual sessions, each lasting approximately 45 minutes. All treatment steps were done according to the unified Treatment Protocol, which was co-ordinated with the patients' Self-help Manual. CBT consisted of education of a patient, cognitive reconstruction, communication training, graduated in vivo exposure, problem solving and relaxation training. Homework assignments were regularly included.

C. Group: Pharmacotherapy and group cognitive behavioural therapy: After a one week of wash-out period upon their admission to the study, moclobemide was administered to patients in 600 mg daily doses (2 pills twice a day). The duration of pharmacological treatment was six months. Cognitive behavioural therapy consisted of 12 group sessions with a 4-hour duration each. There was one session per week and one booster session after three months of the treatment. Every patient also had four individual sessions, each lasting approximately 45 minutes. No other medications or treatments were allowed in all three groups.

Main outcome measures

Patients were assessed under double blind conditions at the beginning of the study, and then every month within the six-month period. The efficacy of the treatments was evaluated by an rater who was blind to the treatment conditions. The following primary efficacy assessment instrument for assessing psychopathology was used:

Total score of Liebowitz Social Anxiety Scale – LSPS (Liebowitz et al.1988);

Secondary outcome measures were:

- Subscales of the LSAS (anxiety and avoidance subscales)

Clinical Global Impressions – CGI (Guy 1976).

- Beck Anxiety Inventory – BAI (Beck a Steer 1993), self-report scale for overall anxiety.

Relapse during the 24 month follow-up period was defined as a CGI score < 3, a necessity of changing the treatment or hospitalization of the patient for anxiety disorder or depression.

Statistical analysis

Descriptive statistics were applied to all demographic variables. Only patients, who completed the 6-month treatment, were included in the analysis. The data of the LSAS, CGI and BAI passed the normality testing (Kolmogorov-Smirnov (KS) with Dallal and Wilkinson approximation to Lilliefors' method). Analysis of variance (ANOVA) was used to evaluate the change in psychometric measures during the study. The interaction between group and time was evaluated by a two-way ANOVA. The Chi ^{2}-test was used in analyzing the change in the CGI score. For all statistical tests, a 5% significance level was chosen. Survival analysis with General Savage (Mantel-Cox) test and General Wilcoxon (Bresow) test was used for follow-up data (statistical software BMDP, programs 1D, 2D, 3D, 7D).

Table 1: Patient selection and drop outs

Patients screened and evaluated	89
Patients who did not meet inclusion criteria	4
Patients who refused study at the beginning	4
Patients who dropped out during the study	15
Adverse effects of medication	3
Non-compliance	8
Other diagnosis	4
Patients who completed the six-month study	66
Patients who completed the 24-month follow-up	64

RESULTS

Patient selection and withdrawal

During the first two years of the study 89 patients with the diagnosis of social phobia were referred to our center. Four patients were screened out at the beginning, because they did not fulfil the diagnostic criteria. Another 4 patients dropped out during the wash-out period, because they refused to participate in the study. The rest of the 81 patients were randomly assigned into the three groups. Fifteen patients dropped out later during the study. Three of them stopped taking the medication because of the adverse side effects (excitement, insomnia); the diagnosis of four patients was changed during the 6-month treatment (in two patients a depressive episode occurred, in one bipolar depression and one patient was diagnosed having schizophrenia). Another 8 patients refused further participation in the study. Altogether 66 patients completed the 6-month period of the study (Table 1).

Subjects characteristics

Demographic characteristics (sex, age, marital status, education) and characteristics of the disorder (age at the onset, duration, number of hospitalizations and comorbidity) of the three treatment groups were well matched (Table 2).

There was comorbidity observed in 74% of patients. Avoidant personality disorder dominated in comorbidity (41%). Amongst anxiety disorders, comorbid generalized anxiety disorder (18%) and panic disorder or/and agoraphobia (18%), and dysthymia (17%) were mainly present. There were no differences in the rates of comorbidity between the 3 treatment groups.

Table 2: Descriptive characteristics of patients completing the 6-month study

	A. Group MOCLOBEMIDE	B. Group CBT + PLACEBO	C. Group CBT + MOCLOBEMIDE	Drop outs
NUMBER	20	24	22	15 (A=7, B=3, C=5)
AGE	27.4	27.6	26,6	28,9
GENDER	8:12	10:14	11:11	10:5
MARITAL STATUS				
Single	16	19	18	12
Married	3	3	3	3
Divorced/widower	1	2	1	0
EDUCATION				
High school	4	3	6	1
College	14	18	12	13
Graduate in work	2	3	4	1
Age of onset of the disorder	14.15	15.13	16.64	13,93
Number of previous hospitalizations	0.40	0.25	0.40	0,53
Comorbidity	75%	79%	68%	86%
Comorbidity with personality disorder	45%	62%	59%	53%

There were not any significant statistical differences (t-tests and chi^2) between groups in descriptive characteristics.

Treatment efficacy

Liebowitz Social Anxiety Scale (LSAS)

During the six-month treatment, there was a significant decrease in total score (sum of anxiety and avoidance scores) of the Liebowitz Social Anxiety Scale (Liebowitz 1987) in all three groups (ANOVA: p<0,001). The total score of the LSAS showed more rapid decrease in both groups treated with CBT (B and C) compared to the group treated with moclobemide (A). The interaction between all groups (AxBxC) and time (0–6 months) is highly statistically significant (two-way ANOVA: F(12;378)=2,86:p<0,001). In comparison of the groups between each other a significant interaction was shown between A (moclobemide) versus B (CBT) (two-way ANOVA: F(6;252)=4,23: p<0,001) and A (moclobemide) versus C (combination) (F(6,240)=3,70:p<0,005). There was no difference between B (CBT) and C (combination) (see Table 3).

Post hoc analyses showed statistical differences between groups in the 3rd month (AxBxC: one way

Table 3: Efficacy of the treatments in rating scales

		A. group n=20		B. group n=24		C. group n=22		Statistics
Liebowitz Social Anxiety Scale (LSAS)								
subscale	time (months)	avarage	sd	average	sd	average	sd	two way ANOVA (group x time)
anxiety	before	48,2	9,9	48,2	6,5	48,6	8,3	AxBxC: F(12;378) =1,90: p < 0,05 AxB: F(6,252) = 2,93: p < 0,01 BxC: n.s. AxC: n.s.
	1.month	37,6	9,9	37,8	11,1	37,8	9,0	
	2.month	30,9	8,0	31,3	11,9	28,0	11,1	
	3.month	23,3	7,3	24,6	11,3	21,5	10,0	
	4.month	22,0	6,7	19,5	8,9	19,3	10,7	
	5.month	19,7	7,0	14,8	9,0	15,6	9,5	
	6.month	18,2	7,7	12,5	9,1	14,2	7,3	
avoidance	before	44,3	10,1	44,2	6,6	45,6	8,1	AxBxC: F(12;378)=3,74: p < 0,001 AxB: F(6;252) = 5,54: p < 0,001 BxC: n.s. AxC: F(6;240)= 5,79: p < 0,001
	1.month	37,4	7,3	32,8	13,4	32,1	9,8	
	2.month	31,8	7,4	24,8	12,6	24,4	8,4	
	3.month	25,6	6,3	19,3	11,2	19,3	7,1	
	4.month	23,9	6,7	14,0	7,8	16,6	7,4	
	5.month	21,2	6,8	10,2	7,3	11,9	7,5	
	6.month	19,1	8,0	8,4	6,2	11,0	6,6	
total	before	92,8	19,1	92,4	11,9	94,2	15,0	AxBxC: F(12;378)=2,86: p < 0,001 AxB: F(6;252)=4,23: p < 0,001 BxC: n.s AxC: F(6,240)=3,70: p < 0,005
	1.month	75,0	14,2	70,5	23,8	70,0	17,3	
	2.month	62,4	13,6	56,0	23,9	51,5	18,0	
	3.month	48,9	12,4	43,8	22,1	40,8	15,9	
	4.month	45,9	13,3	33,5	16,2	35,9	17,5	
	5.month	40,9	12,8	25,0	15,4	27,5	16,0	
	6.month	37,3	15,2	20,9	14,8	25,3	13,0	
Global clinical impression - severity								
CGI-severity	Before	4,60	0,82	5,00	0,66	4,86	0,56	AxBxC: F(12;378)=3,77: p < 0,001 AxB: F(6;252)=3,65: p < 0,005 AxC: F(6;240)=4,82: p < 0,001 BxC: F (6;264)=3,07: p < 0,01
	1.month	4,45	0,76	4,50	0,98	4,00	0,53	
	2.month	4,10	0,64	4,00	1,02	3,41	0,85	
	3.month	3,30	0,73	3,42	1,21	2,59	0,73	
	4.month	2,80	0,69	2,54	0,98	2,18	0,73	
	5.month	2,55	0,90	2,04	1,00	1,81	0,66	
	6.month	2,20	0,89	1,75	0,85	1,77	0,61	
Beck Anxiety Inventory								
BAI	before	26,2	3,7	26,7	3,8	25,2	3,8	AxBxC: F(12;378)=3,25: p < 0,001 AxB: F(6;252)=6,63: p < 0,001 AxC: F(6;240)=2,74 p < 0,05 BxC: ns.
	1.month	17,6	4,1	22,5	5,1	19,9	3,5	
	2.month	15,0	3,0	19,9	4,9	17,4	4,3	
	3.month	14,0	3,8	17,4	4,5	14,4	5,1	
	4.month	12,3	3,5	13,7	4,8	11,5	5,1	
	5.month	9,7	3,5	9,8	5,1	8,8	4,4	
	6.month	8,7	4,0	7,5	5,4	7,2	3,0	

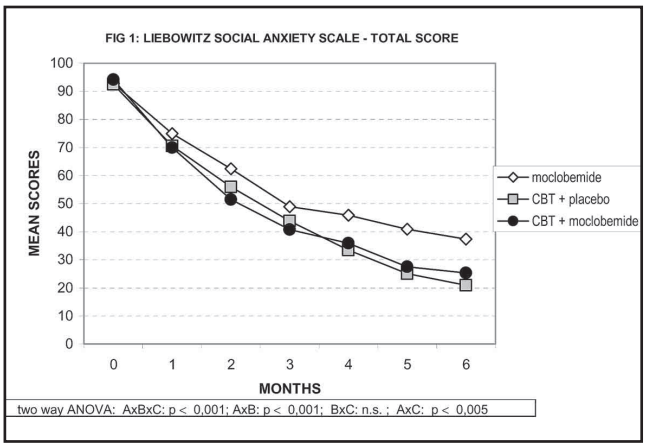

Fig. 1.

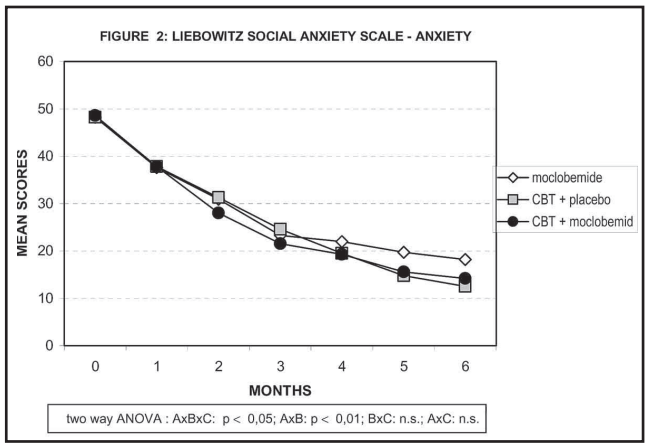

Fig. 2.

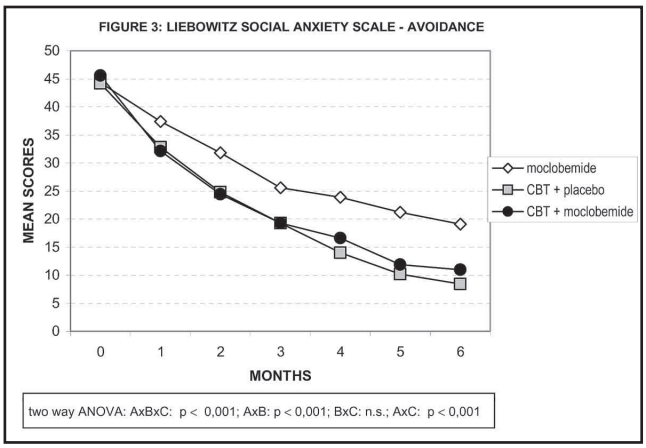

Fig. 3.

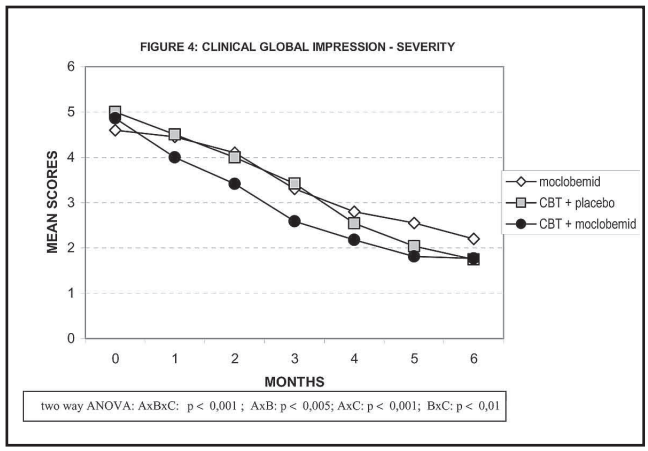

Fig. 4.

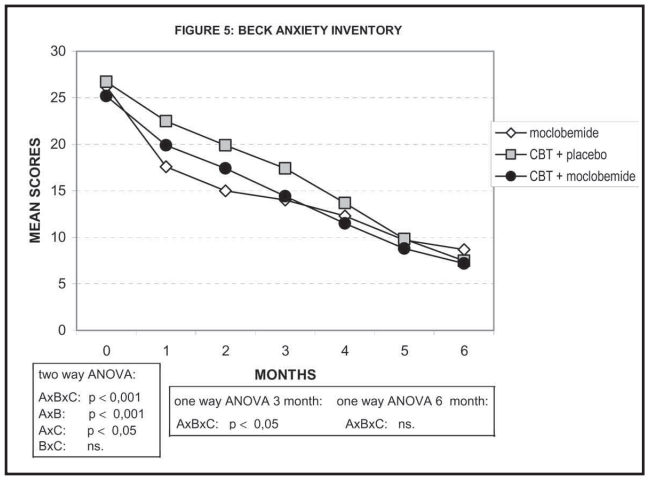

Fig. 5.

ANOVA: F(2;63)=1.14: p<0,05), and there were statistically significant differences in the 6th month (AxBxC: one way ANOVA: F(2;63)=7,42: p<0,001; t-tests: AxB p<0,001, AxC p<0,01, BxC: ns).

The analysis of an anxiety subscale of the LSAS showed that in groups A (moclobemide) and C (combination) anxiety in social situations decreased earlier than in group B (CBT) patients. However, the difference did not reach statistical significance. The results remarkably changed during the last three months of treatment. The anxiety subscale dropped down more in groups with CBT (group B and C), than in the group with moclobemide treatment (group A). The interaction between all groups (AxBxC) and time (0–6 months) is statistically significant (two-way ANOVA: F(12;378)=1,90: p<0,05). Separate comparison of the groups between each other showed a significant interaction between CBT alone (B) and moclobemide alone (A); CBT was superior to moclobemide (two-way ANOVA: F(6;252)=2,93; p<0,01), but no difference between moclobemide (A) and the combination (C) group, as well as CBT (B) and combination (C). Post hoc analyses did not showed any differences in the 3rd month, but there were some significant differences in

Table 4: Relapse rates during follow-up period in the three treatment groups
a) survival analysis

month of follow up	A group n=19		B group n=23		C group n=22		Statistics general Savage(Mantel-Cox) test	general Wilcoxon(Bresow) test
	n relapses	survive	n relapses	survive	N relapses	survive	F=8,795 p < 0,05	F=9,849 p < 0,01
3rd month	7	0,63	3	0,87	4	0,82		
6th month	11	0,42	5	0,78	7	0,68		
9th month	13	0,32	6	0,74	9	0,69		
12th month	15	0,21	7	0,70	12	0,45		
18th moth	15	0,21	8	0,65	13	0,41		
24th month	15	0,21	11	0,52	14	0,36		

b) Pearson's chi^2

month of follow up	A x B	B x C	A x C
3rd month	p < 0,05	n.s.	n.s
6th month	p < 0,01	n.s.	n.s (p=0,07)
9th month	p < 0,005	n.s.	n.s (p=0,06)
12th month	p < 0,001	n.s(p=0,07)	n.s (p=0,08)
18th moth	p < 0,005	n.s.(p=0,07)	n.s.
24th month	p < 0,05	n.s.	n.s

the 6th month (AxBxC: one way ANOVA: ns., t-tests: AxB: p<0,05, AxC: ns., BxC: ns.)

Evaluation of the LSAS subscale of avoidance behaviour gave slightly different results. From the beginning there was a more rapid decrease of the score in both groups (B and C) treated with CBT than in the group treated with moclobemide alone (A) (two-way ANOVA: (12; 378) = 3,74: p<0,001). A separate comparison between groups showed a significant interaction between CBT (B) and moclobemide (A) (two-way ANOVA: F(6;252)=5,54; p<0,001) and combination (C) and moclobemide (A) (F(6;240)=5,79:p<0,001). The combination (C) did not differ from CBT (B). Pos hoc analyses showed significant differences in the 3rd month (AxBxC: one way ANOVA: F(2;63)=13,72: p<0,005; t-tests: AxB: p<0,001, AxC: p<0,005, BxC: ns.)

Clinical Global Impression (CGI)

The Clinical global impression (CGI, Guy 1976) severity subscale reflects not only the severity of social anxiety, but a general clinical view on the severity of the disorder. All three groups showed significant decreases in CGI severity scores after six months of the treatment. A plot of mean group CGI – severity (AxBxC) against time (0–6 months) scores indicate a significant interaction (two-way ANOVA: F (12; 378) = 3,77; p< 0,001). A separate comparison of groups between each other showed a significant interaction between combination (C) and moclobemide (A) (two-way ANOVA: F(6;240)=4,82: p<0,001), between combination (C) and CBT (B) (two-way ANOVA: F (6;264)=3,07: p< 0,01), and between CBT (B) and moclobemide (A) (two-way ANOVA: F(6;252)=3,65: p<0,005). From this point of view the combination treatment is the best choice in the first 6 months of treatment, because from the first month of initial treatment there was a higher greater mean CGI score decrease in group C with combined treatment than in both groups A and B with monotherapy. The treatment with moclobemide (A) compared with CBT (B) did not differ during the first three months, but a difference developed after the fourth month in favor of CBT.

CGI improvement subscale was evaluated with the chi^2-test. We separated patients with a score of 1 or 2 from those with higher scores. The number of these patients differed significantly only in the 3rd month of treatment in favor of the group with the combination treatment (C: 50% improved patients), the group with CBT (B: 33,3% improved patients) against the moclobemide group (A: 10% improved patients) (AxBxC: Pearson chi^2: p<0,05; AxB: ns., AxC: p<0,01, BxC: ns.), but not on the 6th month (number of improved patients: A=90%, B=83,3%, C=95,5%).

Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory is a self-assessment of 21 symptoms of overall anxiety. It is not focused on social phobia itself. It is clear that the highest effectivity of moclobemide (A) and combination (C) is in the first 3 months of treatment in comparison with CBT (B) (interaction of group and time (0–3) in two-way ANOVA F(2,63)=3,72: p<0,05). This result independently influenced the whole interaction between groups and time hence this difference did not appear after 4 months of treatment. Post hoc analyses showed that the effect of CBT (B) during the first three months of

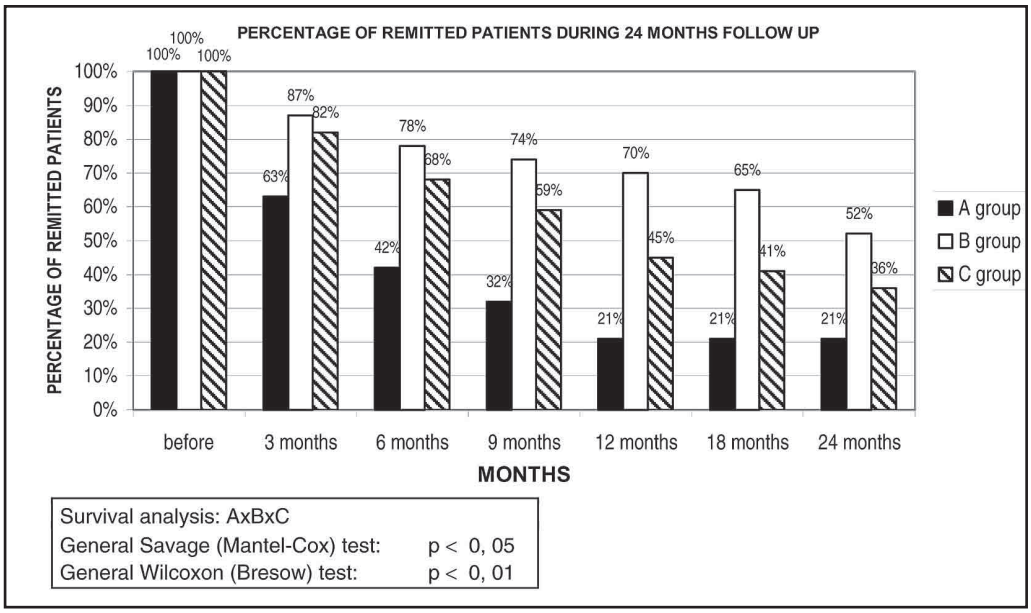

Fig. 6.

treatment did not appeared as rapidly on the subjective anxiety scale as moclobemide (A) or combination (C) (AxBxC: one way ANOVA: F(2;63)=3,72: p<0,05, t-tests: AxB: p<0,05, AxC: p<ns., BxC: p<0,05). There was not any difference after the 6th month of treatment in post hoc analyses. It seems that exposure treatment, which confronted the patient with the phobic situations, didn't allow as swift a decrease of subjective general anxiety. The mean scores did not significantly differ after 6 months of treatment.

Follow-up

After a 6-month period of the study treatment was stopped and the patients were observed and assessed for an additional 24-month period of follow-up; every 3 months during the first 12 months and every 6 months for the following 12 months. The 64 patients who had CGI –severity scores of 1, 2 or 3 at the end of 6-months period of acute treatment were enrolled for a follow-up study. The relapse was defined as a CGI-severity score < 3, the necessity of a new treatment or hospitalization of the patient. Relapse rates are shown in Table 4.

The group previously treated with moclobemide had a significantly higher relapse rate (79%) during the follow-up in comparison with the group treated with the combination treatment (64%) or CBT alone (48%). Survival analysis showed a significant difference between groups (General Savage (Mantel-Cox) test: F=8,795: p<0, 05 and General Wilcoxon (Bresow) test: F=9,849: p<0, 01). There was no significant difference between the CBT group and the combination treatment group (Fig 6).

DISCUSSION

The study has confirmed the efficacy of moclobemide, cognitive behavioural therapy, and their combination in the treatment of social phobia. Patients in all three groups improved significantly. The time course of the improvement, however, was different. Moclobemide alone was superior in reducing subjective anxiety measured with the BAI in the first three months of the study, but its influence on specified social anxiety measured with the LSAS was less impressive. CBT appeared to be the best choice for reduction of avoidance behaviour. The improvement was significantly higher in the two groups treated with CBT (alone or in combination with moclobemide) compared to the group treated with moclobemide alone during the six-month treatment period according to the LSAS and the CGI severity subscale. There was no significant difference between groups treated with CBT alone and CBT plus moclobemide within the whole six-month treatment period. However, efficacy of the combination) when compared with CBT treatment alone is more favorable from a short-term point of view because it occurs earlier (after 3 months).

Because of inconsistent results of moclobemide efficacy in multicenter double-blind studies (Noyes et al. 1997, Katschnig et al. 1997, Schneier et al. 1998), moclobemide itself does not seem to be the most effective drug in the treatment of social phobia. Furthermore, we cannot generalize the results of comparison of moclobemide with CBT to other drugs used in the treatment of social phobia.

The little effect of moclobemide in combination with group cognitive behavioral therapy may be due to the lack of its robust effectiveness. From the present study we cannot conclude how CBT would perform in comparison with a drug that has shown robust efficacy in the treatment of social phobia. Further studies

combining the SSRI with CBT treatment are needed to answer the question whether the combination treatment is better than monotherapy or not. Our data have shown a more prolonged effect of CBT in comparison with moclobemide.

We also found a high level of comorbidity in our out-patients, which is in accordance with other authors. Almost 60% of patients with social phobia had additional symptoms that met criteria for one or more additional diagnoses (Sanderson et al. 1990). The presence of comorbid disorders has been associated with a longer duration of social phobia as well as a more severe impairment before and after cognitive-behavioral therapy treatment (Erwing et al. 2002). It can be questioned whether comorbidity could have influenced the outcome of our study. We cannot sufficiently answer this question due to the sample size however, the proportion of comorbid patients did not differ among the study groups.

REFERENCES

1 Allgulander C: Paroxetine in social anxiety disorder: a randomized placebo-controlled study. Acta Psychiatr Scand 1999; **100**:193–198.
2 American Psychiatric Association. (1994): Diagnostic criteria from DSM-IV, Washington, DC: Author.
3 Barlow DH, Lehman CL: Advances in the psychosocial treatment of anxiety disorders. Arch Gen Psychiatry 1996; **53**:727–735.
4 Beck AT a Steer RA. Manual for the Beck Anxiety Inventory. Psychological Corporation. San Antonio TX 1993.
5 Blomhoff S, Tangen Haug T, Hellstrom K, Holme I, Humble M, Madsbu HP, Wold JE: Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. Br J Psychiatry 2001; **179**:23–30.
6 Clark DB, Agras WS: The assessment and treatment of performance anxiety in musicians. Am J Psychiatry 1991; **148**:598–605.
7 Davidson JRT, Hughes DC, George LK, Blazer DG: The boundary of social phobia. Arch Gen Psychiatry 1994; **51**:975–983.
8 DiNardio PA, Moras K, Barlow DH, Rapee RM, and Brown TA: Reliability of DSM-R-R anxiety disorder categories: using the Anxiety Disorders Interview Schedule-Revised. Arch Gen Psychiatry 1993: **50**:251–256.
9 Eaton et al. 1991
10 Erwing BA, Heimberg RG, Juster H et al: Comorbid anxiety and mood disorders among persons with social anxiety disorder. Behav Res Ther 2002; **40**:19–35.
11 Gelernter CS, Uhde TW, Cimbolic P, Arnkoff DB, Vittone BJ, Tancer ME, Bartko JJ. Cognitive-behavioral and pharmacological treatments of social phobia. Arch Gen Psychiat 1991; **48**:938–945.
12 Guy W (ed.): ECDEU Assessment manual for psychopharmacology. Rockville, U.S. DHEW 1976
13 Haug TT, Hellstrom K, Blomhoff S et al: The treatment of social phobia in general practice. Is exposure therapy feasible? Fam Pract 2000; **17**:114–118.
14 Heimberg RG, Salzman D, Holt CS et al: Cognitive-behavioural group treatment for social phobia: Effectiveness at five-year follows up. Cognitive Therapy and Research 1993: 17.
15 Heimberg RG, Liebowitz MR, Hope DA, Schneier FR, Holt CS, Welkowitz LA, Juster HR, Campeas R, Bruch MA, Cloitre M, Fallon B, Klein DF. Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. Arch Gen Psychiatry 1998; **55**:1133–41.
16 The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia. Moclobemide in social phobia. A double-blind, placebo-controlled clinical study. Eur Arch Psychiatry Clin Neurosci 1997; **247**:71–80.
17 Katschnig H, Stein MB, Buller R, on behalf of the International Multicenter Clinical Trial Group on Moclobemide in social phobia: a double-blind, placebo-controlled clinical study. Eur Arch Psychiatry Clin Neurosci 1997; **247**:71–80.
18 Katzelnick DJ, Kobak KA, Griest JH et al: Sertraline for social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 1995; **152**:1368–1371.
19 Kessler RC, McGonagle K, Zhao S, Nelson C, Hughes M, Eschleeman S, Wittchen HU and Kendler KS: Lifetime and 12-months prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 1994:**51**: 8–19
20 Liebowitz MR: Social phobia. Modern Problems in Pharmacopsychiatry 1987; **22**:141–173.
21 Liebowitz MR, Heimberg RG, Schneier RF et al: Cognitive-behavioral group therapy versus phenelzine in social phobia: long-term outcome. Depress Anxiety 1999; **10**:89–98.
22 Noyes R Jr, Moroz G, Davidson JR, Liebowitz MR, Davidson A, Siegel J, Bell J, Cain JW, Curlik SM, Kent TA, Lydiard RB, Mallinger AG, Pollack MH, Rapaport M, Rasmussen SA, Hedges D, Schweizer E, Uhlenhuth EH. Moclobemide in social phobia: a controlled dose-response trial. J Clin Psychopharmacol 1997; **17**:247–54.
23 Nutt D, Montgomery SA: Moclobemide in the treatment of social phobia. Int. Clin. Psychopharmacol. 1996; **11** (suppl 3):77–82.
24 Oosterbaan DB, van Balkon AJLM, Spinoven P et al. Cognitive therapy versus moclobemide in social phobia: A controlled study. Clin Psychol Psychother 2001; **8**:263–273.
25 Regier DA, Farmer ME, Rae DS et al.: Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. JAMA 1990; **264**:2511–2518.
26 Sanderson WC, Di Nardo PA, Rapee RM et al: Syndrome comorbidity in patients diagnosed with a DSM-III-R anxiety disorder. J Abnormal Psychol 1990; **99**:308–312.
27 Schneier FR, Goetz D, Campeas R, Fallon B, Marshall R, Liebowitz MR: Placebo-controlled trial of moclobemide in social phobia. Br J Psychiatry 1998; **172**:70–77.
28 Solyom L, Ledwige B, Solyom C: Delineating social phobia. Br J Psychiatry 1986; **149**:464–470.
29 Stein MB, Chartier MJ, Hazen AL et al: Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. J Clin Psychopharmacol 1996; **16**:218–222.
30 Stein MB, Fyer AJ, Davidson JRT et al: Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. Am J Psychiatry 1999; **156**:756–760.
31 van Ameringen MA, Lane RM, Walker JR et al: Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. Am J Psychiatry 2001; **158**:275–281.
32 Van der Linden GHH, Stein DJ, van Balkon AJLM: The efficacy of the selective serotonin reuptake inhibitors for social anxiety disorder (social phobia): A meta-analysis of randomized controlled trials. Int Clin Psychopharmacol 2000; **15**(Suppl 2) S15–S23.
33 van Vliet IM, den Boer JA, Westenberg HG: Psychopharmacological treatment of social phobia: a double-blind placebo controlled study with fluvoxamine. Psychopharmacology 1994; **115**:128–134.
34 Versiani M, Nardi AE, Mundim FD, Alves AB, Liebowitz MR, Amrein R. Pharmacotherapy of social phobia. A controlled study with moclobemide and phenelzine. Br J Psychiatry 1992; **161**:353–60).