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REVIEW

Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders

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Abstract

Background. A number of meta-analyses have led to contradictory results regarding the efficacy of the psychological and pharmacological treatment of anxiety disorders. The main reasons for these inconsistent results seem to be the inclusion of heterogeneous studies and influences of selection biases. We performed a meta-analysis, which only included studies using a direct comparison of pharmacological, psychological, or combined treatments. *Method.* Sixteen studies on panic disorder, six studies on social anxiety disorder, and two studies on generalized anxiety disorder have been analyzed. Effect sizes for differences between the different treatment modalities were calculated. Also, the effect sizes of the pre–post differences were calculated. *Results.* Pharmacological treatment, cognitive-behavioural treatment, and the combination of both treatment modalities all led to substantial improvement between pre- and post-treatment. Combined pharmacological and psychological treatment was superior to the monotherapies for panic disorder. For social anxiety disorder, there is only preliminary support for combined treatment. Due to lack of sufficient data, no final conclusions can be drawn for generalized anxiety disorder. *Conclusions.* While drug treatment and CBT showed equal efficacy, only in panic disorder the combination of pharmacological and psychological treatment was superior to either treatment alone. For the other anxiety disorders, the evidence for greater efficacy of combination treatment is still not sufficient due to lack of studies.

Key words: *Anxiety disorders, pharmacological treatment, cognitive-behavioural therapy, combined treatment, meta-analysis*

Introduction

Psychopharmacological drugs and psychological therapies have shown efficacy for the treatment of anxiety disorders (Bandelow et al. 2002; Baldwin et al. 2005). Selective serotonin reuptake inhibitors (SSRIs) and the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine are established treatments for panic disorder with or without agoraphobia (PDA), social anxiety disorder (SAD), and generalized anxiety disorder (GAD). Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines have proven to be effective in the treatment of anxiety disorders, but these drugs are not used as first line treatments due to the higher risk of adverse events. The reversible inhibitor monoamine oxidase A (RIMA) moclobemide is approved for social anxiety disorder in some countries.

Among psychological therapies, cognitive behaviour therapy has consistently shown to be effective in controlled studies. Proofs for other forms of psychotherapy are lacking.

There is conflicting evidence regarding the comparative efficacy of both modalities and the role of combination therapies. A number of meta-analyses on comparisons of both treatment modalities (Mattick et al. 1990; Cox et al. 1992a,b; Clum et al. 1993; van Balkom et al. 1997; Gould et al. 1997; Foa, 2000; Fedoroff and Taylor, 2001; Westen and Morrison, 2001; Mitte, 2005) led to diverging estimates of effect sizes (ES) (Table I). These studies used different effect calculations and the analyses are based on a varying number of studies, so that the results are not easily comparable. Accordingly, recommendations regarding the superiority of CBT, drug treatment, or the combination of both

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Table I. Results from meta-analyses on treatment of panic disorder/agoraphobia (PDA) and social anxiety disorder (SAD).

Meta-analysis	Diagnosis	*n*	*Effect size*	Main results
Clum et al. (1993)	PDA	29	Glass' Δ	CBT > Drug + CBT > Drug (AD) > Drug (BDZ)
Gould et al. (1995)	PDA	43	Glass' Δ	CBT > Drug + CBT = Drug
Mattick et al. (1990)	PDA	55	Glass' Δ	Drug + CBT > CBT > Drug
van Balkom et al. (1997)	PDA	106	Cohen's *d*	Drug + CBT > CBT > Drug
Mitte (2005)	PDA	124	Hedges' *g*	Drug + CBT = CBT = Drug
Gould et al. (1997)	SAD	24	Glass' Δ	Drug (SSRI) > CBT = Drug (BDZ)
Fedoroff and Taylor (2001)	SAD	108	Cohen's *d*	Drug (BDZ) = Drug (SSRI) > CBT

n, number of studies included; PDA, panic disorder with agoraphobia; SAD, social anxiety disorder; drug, pharmacological treatment; SSRI, selective serotonine re-uptake inhibitor; BDZ, benzodiazepine; CBT, cognitive-behavioural treatment.

showed striking differences. For instance, for PDA, Clum et al. (1993) found the highest effect sizes for CBT alone, very low effect sizes for drug treatment alone and intermediate results for the combination. In contrast, Mattick et al. (1990) and van Balkom et al. (1997) found the highest effect sizes for the combination.

The remarkable differences between these meta-analyses may partly be explained by the choice of studies included in the analysis. According to Klein (2000), some meta-analyses compared effect sizes from flawed studies that were not uniformly blind, random, controlled, or of high quality or lacked assay sensitivity.

The major problem with all previous meta-analyses is that many studies were included, which were no direct comparisons of both treatment modalities: some compared a drug with a placebo condition, and others compared a psychological treatment with a waiting-list control, a psychological placebo or a different kind of psychological treatment. Results may have been influenced by selection or sample biases. For example, there may be systematic differences in the characteristics of subjects recruited for a double-blind drug trial and those who consent to participate in a comparison of two forms of psychotherapy.

As placebo effects tend to be high in the anxiety disorders, treatment outcome is largely under the influence of expectancy effects. Patients consenting to a placebo-controlled study and receiving the active drug may assume that they have been randomized to the placebo condition, which may lead to a decrease of the observed effect size of the drug, while patients participating in a comparison of two different kinds of CBT may have the expectancy that both modalities could be effective, no matter what treatment arm they are randomized to. In studies comparing two different kinds of psychotherapy, outcome assessment may also be influenced by investigators' expectation biases when raters were not blind to the different conditions.

Moreover, concomitant drug treatment in CBT studies may lead to exaggerated effect sizes. Whereas in pure drug studies only patients may be included who have not undergone psychotherapy for a certain period, e.g. 6 months prior to the study, in most "pure" psychotherapy studies the inclusion criteria allowed the concomitant use of drugs (e.g. refs Mavissakalian et al. 1983b; Craske et al. 1989; McNamee et al. 1989; Borden et al. 1991; Beck et al. 1992; Gould et al. 1993; Margraf et al. 1993; Öst et al. 1993; Telch et al. 1993; Clark et al. 1994; Côté et al. 1994; Lidren et al. 1994; Gould and Clum, 1995; Öst and Westling, 1995; Swinson et al. 1995; Telch et al. 1995; Bouchard et al. 1996; Williams and Falbo, 1996; Brown et al. 1997; Craske et al. 1997; Newman et al. 1997). Up to 83% of the patients in some of these psychotherapy studies were receiving psychopharmacological treatment. When these studies are compared with drug therapies in a meta-analysis, a combined drug–psychotherapy effect is compared with the effect of pure drug therapy, which may lead to an overestimation of the CBT effect.

In order to avoid possible biases due to different study conditions, we conducted a meta-analysis of only those studies that included both a pharmacological treatment, a psychological treatment or combinations of both within one study design, so that patients were randomly assigned to different treatment conditions realized within each study.

Method

Selection of studies

Randomized treatment outcome studies were selected for patients with panic disorder and agoraphobia, social phobia, and generalized anxiety disorder that included both a cognitive-behavioural and a pharmacological treatment modality. Some studies also included a combination of both treatments. Treatments included pharmacological treatment alone, cognitive-behavioural treatment

alone, pharmacological and cognitive-behavioural treatment combined, cognitive-behavioural and pharmacological placebo treatment combined, pharmacological placebo, and "psychological placebo".

Pharmacological treatments included tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI), benzodiazepines, irreversible monoamine oxidase inhibitors (MAOIs) and reversible inhibitors of monoamine oxidase A (RIMAs). Cognitive-behavioural treatment included cognitive techniques, exposure, and anxiety-management techniques, in some cases conducted as group therapy. Despite differences in the cognitive-behavioural treatments employed, outcome data from all CBT treatments was used to calculate average effect sizes. Also, drug classes and classes of psychotherapy were grouped together instead of focusing on single treatments because of the small number of trials for each different type. Cognitive-behavioural treatment was combined with a pill placebo in several studies. Only data from drug treatment, CBT, combined drug plus CBT treatment, and CBT plus pharmacological placebo treatment were analyzed. Other comparisons would have been possible, but would have been beyond the scope of this article.

Journal articles were located using MEDLINE, psycINFO and EMBASE. Search was conducted from 1980 (when the modern concept of anxiety disorders was introduced in DSM-III (APA 1980) to the present. The following key words were used: *randomized controlled trial, treatment, drug, psychotherapy, cognitive behaviour therapy, panic disorder, social phobia, social anxiety disorder and generalized anxiety disorder*. The following methodological requirements were formulated for the inclusion of studies: It was required that subjects met DSM-III, DSM-III-R, or DSM-IV criteria for each anxiety disorder (PDA, SAD, and GAD). The quality of studies was assessed with regard to adequate description of the randomization and blinding process, an adequate sample size, the use of suitable rating scales and correct statistical calculations. Treatment outcome had to be presented in terms of self-report or clinician-rated measures. Outcome measures had to be presented with sufficient information to calculate effect sizes. Studies had to be published and those studies were excluded, which reported results of subsamples used in larger studies. Other disorders belonging to the anxiety disorders spectrum (post-traumatic stress disorder and obsessive–compulsive disorder) were not subject of this meta-analysis. An overview of study selection and inclusion is given in Figure 1.

Twenty studies since 1980 used a design which directly compared pharmacological, treatment, cognitive-behavioural treatment or a combination of both.

Some PDA studies could not be included due to missing information required to compute effect sizes or incomplete data presentation (Marks et al. 1983; Zitrin et al. 1983; Cohen et al. 1984; Mavissakalian and Michelson, 1986). In a recent study, a combination of drug therapy and CBT led to better results than the monotherapies (Bradwejn et al. 2005). However, since the CBT treatment realized in this study was a self-help program we did not include it into our analysis.

A total of 16 PDA studies were used for further analysis. Two SAD studies had to be excluded; one because of incomplete data presentation (Turner et al. 1994), the other because of a too small sample size (Falloon et al. 1981). In both of these studies, drugs were used, which had not shown efficacy in anxiety disorders in previous trials. A total of six studies were used for further analysis. One GAD study had to be excluded due to incomplete data

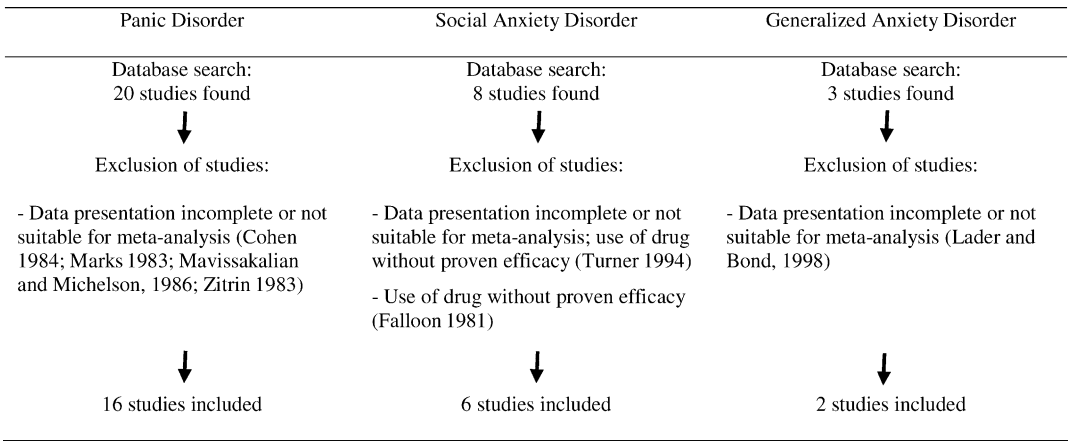


Figure 1. Inclusion of studies.

presentation (Lader and Bond 1998), so that only two studies could be used for the analysis.

Meta-analysis procedure

Panic disorder. The included studies used a wide range of dependent measures to assess treatment outcome. We performed separate analyses for both clinician-based ratings and self-report data. Not all studies used both self-report and clinician-rated data, so the separate analyses included 13 studies using clinician-ratings, or 12 studies using self-report questionnaires, respectively. Most studies included a variety of measures for anxiety, avoidance or depression. Only few studies indicated the primary efficacy measure. Calculation of effect sizes was based on data from the most frequently used instruments. Mostly, instruments specific for assessing the severity of anxiety-related symptoms were used. Only if unavailable, calculation of effect sizes was based data from less specific measures. Despite a certain amount of heterogeneity, this made it possible to obtain effect sizes from all studies available. To achieve a maximum of comparability we used the following algorithms for data calculation:

Clinician-based ratings:

1. CGI (Clinical Global Impression Scale; Guy 1976); if not available:
2. Hamilton Anxiety Scale (HAMA; Hamilton 1959); if not available:
3. Any other instrument.

Self-report questionnaires:

1. Fear Questionnaire (FQ) – Agoraphobia Subscale (Marks and Matthews 1979); if not available:
2. Any other anxiety questionnaire (for example MSPS; Sheehan 1983); if not available:

As far as possible, for each study one effect size based on self-report and one effect size based on clinician ratings was calculated for each treatment. Since data for the intent-to-treat (ITT) analysis were not reported in most studies, according-to-protocol (ATP) data was used for all analyses (with one exception: data from Loerch et al. 1999, used ITT data). Most studies had a duration of 12 weeks, while some studies reported data from 8-, 10- or 14-week treatment intervals.

Social anxiety disorder. All studies on social anxiety disorder included self-report measures, except one study (Gelernter et al. 1991), in which clinician-based ratings were reported. Again, only few studies indicated the primary measure of efficacy. We used the following algorithms for data calculation:

Clinician-based ratings:

1. CGI (Clinical Global Impression Scale; Guy 1976) measures; if not available:
2. ADIS (Anxiety Disorders Interview Schedule; DiNardo et al. 1983); if not available:
3. Any other instrument.

Self-report questionnaires:

1. Fear Questionnaire (FQ) – Social Phobia Subscale (Marks and Matthews 1979); if not available:
2. Fear of Negative Evaluation Scale (FNE; Watson and Friend 1969); if not available:
3. Any other anxiety questionnaire used.

As far as possible, for each study one effect size based on self-report and one effect size based on clinician ratings was calculated for each treatment.

Generalized anxiety disorder. For GAD, one study (Lindsay et al. 1987) did not report clinician ratings, so that it only could be used for analysis of self-ratings. Thus, effect sizes based on clinician and self-ratings cannot be directly compared with each other.

Calculation of effect sizes

Effect sizes were based on Cohen's d statistic (Cohen 1988). Effect sizes can be interpreted as small (≥ 0.20), medium (≥ 0.50), or large (≥ 0.80). We compared effect sizes for the following treatment conditions: drug, CBT, drug+CBT, and CBT+placebo. Each study is represented with one measure for anxiety. Effect sizes representing pre–post-differences are for short-term treatment outcome. In most cases, treatment duration was 12 weeks (range 8–16 weeks).

We calculated two kinds of effect sizes: the *comparison effect size,* reflecting the post-treatment differences between two treatments compared in one study, and the *pre–post effect sizes*, which measure the difference between scale scores before and after treatment of each condition.

Comparison effect sizes. The effect size d represents the difference between the pre- and post scale score reductions for the two treatments a and b, divided by the pooled standard deviation:

$$d = \frac{(a_{pre} - a_{post}) - (b_{pre} - b_{post})}{SD_{average}}$$

Alternatively, calculation of d was based on responder-analyses data. If no information on pre–post-differences was given, we calculated data for percentages P of improvement from responder analyses (Rosenthal's r ; Rosenthal, 1991).

	% Responder	% Non-Responder
Treatment a	P_{ar}	P_{an}
Treatment b	P_{br}	P_{bn}

$$r = \frac{P_{ar}P_{bn} - P_{br}P_{bn}}{\sqrt{(P_{ar} + P_{an})(P_{ar} + P_{br})(P_{an} + P_{bn})(P_{br} + P_{bn})}}$$

These r values were transformed into Cohen's d:

$$d = 2r\sqrt{(1 - r^2)}$$

Pre–post effect sizes. Pre–post effect sizes were calculated with the following formula, where a is the scale score, N the number of patients, and SD the standard deviation:

$$d = \frac{a_{pre} - a_{post}}{\sqrt{\frac{(N_{pre} - 1)SD^2_{pre} + (N_{post} - 1)SD^2_{post}}{N_{pre} + N_{post} - 2}}}$$

An effect size based on a study with large sample size is assumed to be a more precise estimate of the population effect size than is an effect size based on a small study. Therefore, larger studies should carry more weight in the meta-analyses than smaller studies. For this purpose, the *inverse variance weight* (Shadish and Haddock 1994) was used. The standard error (SE) is a direct index of effect size precision and is used to create confidence intervals (the smaller the SE, the more precise the effect size).

$$SE = \sqrt{\frac{N_1 + N_2}{N_1N_2} + \frac{d}{2(N_1 + N_2)}}$$

The inverse variance weight is:

$$w = \frac{1}{SE^2}$$

The weighted mean effect size is:

$$\overline{d} = \frac{\sum(w \times d)}{\sum w}$$

Confidence intervals were determined by:

$$Lower\ \ CI = \overline{d} - 1.96\ SE_{\overline{d}}$$

$$Upper\ \ CI = \overline{d} + 1.96\ SE_{\overline{d}}$$

In order to determine the level of significance, z values were calculated by:

$$z = \frac{\overline{d}}{SE_{\overline{d}}}$$

Differences between effect sizes were tested for significance by using ANOVA. *Post-hoc* comparisons were done using Bonferroni-corrected α-levels. *A priori* set α levels of 0.05 were regarded as statistically significant.

Results

Panic disorder

Comparison effect sizes. The comparison effect sizes for the single studies are listed in Table II and the weighted mean effect sizes are shown in Figure 2. Both on the clinician and the self ratings, there was no evidence for a difference between drugs and CBT. A combination of CBT and drug was superior to pure drug treatment on both the clinician and the self ratings. For both ratings, a combination of CBT and drug was more effective than CBT alone. However, the effect sizes were small and not statistically different (this was based on only two studies). A combination of CBT and drug was significantly more effective than CBT plus placebo both on the investigators' and the patients' rating. The effect sizes were small.

Pre–post effect sizes. Pre–post effect sizes for the various treatments are presented in Table III. The weighted mean effect sizes for the different types of treatment are shown in Figure 3.

All treatment modalities show large pre–post effect sizes. Combined treatment showed the largest effects in the clinician rating. However, analysis of variance (ANOVA) for data from clinician-based ratings showed no statistically significant differences between different types of treatment ($F_{(3,15)} = 0.61$; n.s.). Also, data from self-report questionnaires demonstrated superiority of the combined treatment. ANOVA showed significant differences among the treatments ($F_{(3,26)} = 3.09$, $P < 0.05$), and *post-hoc* comparisons using Bonferroni-corrected α levels yielded a statistically significant difference between combined cognitive-behavioural and pharmacological treatment and pharmacological treatment alone ($t_{(15)} = 3.02$, $P < 0.01$), while all other comparisons were non-significant.

Only few studies employed a "psychological placebo" treatment. The "applied relaxation" treatment (Clark et al. 1994) yielded pre–post-effect sizes of $d = 0.91$ (clinician rating), or $d = 0.43$ (self-rating), respectively. A 15-week waiting-list control group (Klosko et al. 1990) yielded an effect size of $d = 0.36$ (clinician rating). Pharmacological placebo alone has led to average effect sizes of $d = 0.81$ (clinician ratings, data from four studies) and $d = 0.45$ (self-ratings, three studies).

Social anxiety disorder (SAD)

Comparison effect sizes. For SAD, comparison effect sizes are summarized in Table IV. Weighted mean effect sizes are shown in Figure 4. A statistical significant difference was only found for the

Table II. PDA, clinician ratings and self-ratings. Effect sizes (Cohen's *d*) for direct comparisons of different treatments (Positive values: treatment 1 >treatment 2).

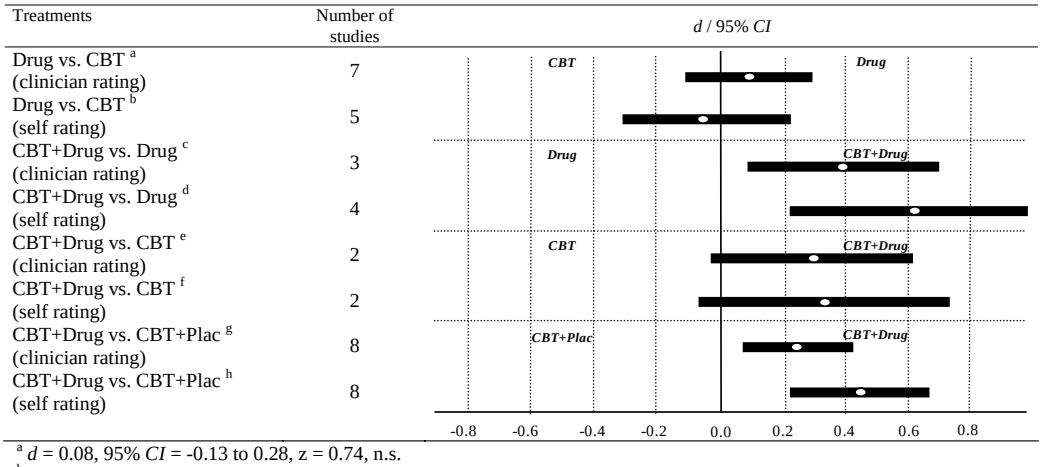
				Clinician ratings			Self-ratings		
Study	*n*	Drug	Weeks	Treatment	*d*	Measure	Treatment	*d*	Measure
Bakker et al. (1999)	28/26	Paroxetine	12	***Drug*** vs. CBT	0.88	CGI	***Drug*** vs. CBT	0.43	MSPS
Bakker et al. (1999)	29/26	Clomipramine	12	***Drug*** vs. CBT	0.09	CGI	Drug vs. ***CBT***	−0.01	MSPS
Barlow et al. (2000)	56/51	Imipramine	12	***Drug*** vs. CBT	0.09	CGI			
Black et al. (1993)	21/16	Fluvoxamine	8	***Drug*** vs. CBT	0.54	CGI	***Drug*** vs. CBT	0.19	PA Severity
Clark et al. (1994)	16/16	Imipramine	12	Drug vs. ***CBT***	−0.54	HAMA	Drug vs. ***CBT***	−0.50	FQ
Klosko et al. (1990)	16/15	Alprazolam	15	Drug vs. ***CBT***	−0.35	HAMA			
Sharp et al. (1997)	29/30	Fluvoxamine	12	Drug vs. ***CBT***	−0.37	CGI	Drug vs. ***CBT***	−0.43	GHQ
Barlow et al. (2000)	47/45	Imipramine	12	***Drug+CBT*** vs. CBT+Plac	0.07	CGI			
Cottraux et al. (1995)	21/27	Buspiron	16	Drug+CBT vs. ***CBT+Plac***	−0.15	CGI	***Drug+CBT*** vs. CBT+Plac	0.65	FQ
de Beurs et al. (1995)	19/19	Fluvoxamine	12				***Drug+CBT*** vs. CBT+Plac	1.24	Ag Comp
Kampman et al. (2002)	19/19	Paroxetine	8				***Drug+CBT*** vs. CBT+Plac	0.91	FQ
Loerch et al. (1999)	11/13	Moclobemid	10	***Drug+CBT*** vs. CBT+Plac	0.22	HAMA	Drug+CBT vs. ***CBT+Plac***	−0.68	FQ
Marks et al. (1993)	34/30	Imipramine	16	Drug+CBT vs. CBT+Plac	0.00	CGI	***Drug+CBT*** vs. CBT+Plac	0.42	PQ
Oehrberg et al. (1995)	55/52	Paroxetine	12	***Drug+CBT*** vs. CBT+Plac	0.59	CGI	***Drug+CBT*** vs. CBT+Plac	0.11	GHQ
Sharp et al. (1997)	29/33	Fluvoxamine	12	***Drug+CBT*** vs. CBT+Plac	0.12	CGI	Drug+CBT vs. ***CBT+Plac***	−0.01	FQ
Stein et al. (2000)	15/16	Paroxetine	12	***Drug+CBT*** vs. CBT+Plac	0.48	CGI			
Telch et al. (1985)	10/9	Imipramine	8				***Drug+CBT*** vs. CBT+Plac	0.88	FQ
Zitrin et al. (1980)	18/21	Imipramine	14	***Drug+CBT*** vs. CBT+Plac	0.49	CGI			
Barlow et al. (2000)	47/51	Imipramine	12	Drug+CBT vs. CBT	0.37	CGI			
de Beurs et al. (1995)	24/21	Fluvoxamine	12				Drug+CBT vs. CBT	1.07	Ag Comp
Sharp et al. (1997)	29/30	Fluvoxamine	12	Drug+CBT vs. CBT	0.16	CGI	Drug+CBT vs. ***CBT***	−0.16	GHQ
Barlow et al. (2000)	47/56	Imipramine	12	Drug+CBT vs. Drug	0.29	CGI			
Loerch et al. (1999)	11/9	Fluvoxamine	10				Drug+CBT vs. Drug	0.67	FQ
Mavissakalian et al. (1983a)	8/7	Imipramine	12	Drug+CBT vs. Drug	0.69	GAS	Drug+CBT vs. Drug	0.71	FQ
Sharp et al. (1997)	29/29	Fluvoxamine	12	Drug+CBT vs. Drug	0.51	CGI	Drug+CBT vs. Drug	0.26	GHQ
Telch et al. (1985)	10/10	Imipramine	8				Drug+CBT vs. Drug	1.85	FQ

n, number of patients (treatment 1/treatment 2); drug, pharmacological treatment; CBT, cognitive-behavioural treatment; Plac, pharmacological placebo; *d*, effect size (Cohen's *d*); CGI, Clinical Global Impression Scale; HAMA, Hamilton Anxiety Scale; GAS, Global Assessment of Severity; FQ, Fear Questionnaire; GHQ, General Health Questionnaire; Ag Comp., Agoraphobia composite score; MSPS, Marks–Sheehan Phobia Scale; PA severity, severity rating of panic attacks; superior treatment is printed ***bold***.

comparison between drug plus placebo versus CBT plus placebo in the clinician rating (small effect size), whereas no differences were found between drug or CBT alone or between drugs alone and drugs combined with CBT.

Pre–post effect sizes within treatment groups. Again, the selected studies were analyzed in order to compute pre–post differences for each class of treatment employed. Differences between pre- and post measures for social phobia are presented in Table V, and weighted mean effect sizes are shown in Figure 5.

All treatments lead to large effect sizes, while effect sizes based on clinician ratings tend to be larger than effect sizes from self-ratings. Clinicians saw the largest pre–post-differences under drug



[a] d = 0.08, 95% *CI* = -0.13 to 0.28, z = 0.74, n.s.
[b] d = -0.05, 95% *CI* = -0.31 to 0.21, z = -0.37, n.s.
[c] d = 0.39, 95% *CI* = 0.09 to 0.69, z = 2.59, p < 0.01
[d] d = 0.61, 95% *CI* = 0.22 to 0.99, z = 3.10, p < 0.01
[e] d = 0.29, 95% *CI* = -0.02 to 0.61, z = 1.81, n.s.
[f] d = 0.33, 95% *CI* = -0.06 to 0.73, z = 1.65, n.s.
[g] d = 0.23, 95% *CI* = 0.05 to 0.41, z = 2.46, p < 0.05
[h] d = 0.43, 95% *CI* = 0.21 to 0.66, z = 3.79, p < 0.01

Figure 2. PDA, clinician ratings and self-ratings. Mean weighted comparison effect sizes (d) and confidence intervals (*CI*) for differences between treatment modalities.

treatment, while patients rated the combined treatment as most effective. Drug treatment yields larger effect sizes than CBT.

ANOVAs based on the drug, CBT, drug plus CBT and CBT plus placebo conditions yielded no statistically significant differences for data from clinician-based ratings ($F_{(3,19)} = 0.14$, n.s.) and data from self-report questionnaires ($F_{(3,12)} = 0.43$, n.s.).

General anxiety disorder

Only two studies on GAD were available, both of which had small sample sizes. Data from clinician-based ratings and self-report questionnaires is presented in Table VI. Because of the few studies available and the low statistical power of these studies, we did not calculate mean effect sizes. In one study (Lindsay et al. 1987), the ES for CBT was higher than for lorazepam (high ES; patient rating). In the other study (Power et al. 1990), CBT was associated with a numerically higher effect size than diazepam on both the clinician and patient ratings. While the drug plus CBT combination was superior to drug alone (medium ES), there was only a small effect in favour of CBT + drug over CBT + placebo on both the clinician and patient ratings. CBT + drug was not superior to CBT alone on the clinician rating and less effective on the patient rating.

Discussion

Although a number of meta-analyses exists, which compare pharmacological and psychological therapies in the treatment of anxiety disorders, this is the first analysis that only included studies employing both a drug and a cognitive behaviour therapy arm or a combination of these treatments. In contrast to earlier meta-analyses, this kind of examination keeps the conditions comparable for all patients by avoiding possible influences caused by the inheterogeneity of study samples, selection biases, and expectation effects.

No difference was found between drug and CBT conditions in direct comparisons.

In general, results for panic disorder with or without agoraphobia (PDA) show the superiority of combined pharmacological and cognitive-behavioural treatment over pharmacological treatment alone, cognitive-behavioural treatment alone and combined cognitive-behavioural and pharmacological placebo treatment. Effect sizes range between $d = 0.23$ and $d = 0.61$ (which corresponds to small to medium effect sizes, Cohen 1988), thus indicating that combined therapy is the most effective treatment strategy. This was found for clinician-based ratings as well as for self-report questionnaires.

In general, effect sizes tended to be higher for data from clinician-based ratings, which corresponds to earlier findings (Lambert et al. 1986). This may be due to an interviewer bias (expectation of lower symptom scores at post-treatment rating), or to differences in the sensitivity of instruments used. This discrepancy does not necessarily mean that the investigators tend to overestimate the efficacy of their treatment, while patients have a more realistic view. It is also possible that patients retrospectively

Table III. PDA, clinician ratings and self-ratings. Pre–post effect sizes.

					Clinician ratings		Self-ratings	
Treatment	Study	*n* pre/*n* post	Drug	Weeks	*d*	Measure	*d*	Measure
Drug	Bakker et al. (1999)	32/28	Paroxetine	12	2.69	CGI	1.33	MSPS
Drug	Bakker et al. (1999)	32/29	Clomipramine	12	1.42	CGI	0.58	MSPS
Drug	Black et al. (1993)	25/21	Fluvoxamine	8			1.21	PA Severity
Drug	Barlow et al. (2000)	77/56	Imipramine	12	1.90	PDSS		
Drug	Clark et al. (1994)	16/16	Imipramine	12	0.75	HAMA	0.66	Ag Fear
Drug	Klosko et al. (1990)	17/16	Alprazolam	15	0.79	HAMA		
Drug	Loerch et al. (1999)	16/9	Moclobemid	10			0.43	FQ Ag
Drug	Mavissakalian et al. (1983a)	9/7	Imipramine	12	2.39	GAS	1.35	FQ Ag
Drug	Sharp et al. (1997)	29/29	Fluvoxamine	12			0.71	GHQ
Drug	Telch et al. (1985)	12/19	Imipramine	8			0.29	FQ Ag
CBT	Bakker et al. (1999)	35/26		12	1.23	CGI	0.83	MSPS
CBT	Barlow et al. (2000)	83/51		12	1.47	PDSS		
CBT	Black et al. (1993)	25/16		8			0.86	Pa Severity
CBT	Clark et al. (1994)	16/16		12	1.78	HAMA	1.04	Ag Fear
CBT	de Beurs et al. (1995)	21/18		12			0.98	Ag Comp
CBT	Klosko et al. (1990)	18/15		15	1.33	HAMA		
CBT	Sharp et al. (1997)	30/30		12			1.41	GHQ
Drug+CBT	Barlow et al. (2000)	65/47	Imipramine	12	2.15	PDSS		
Drug+CBT	Cottraux et al. (1995)	37/21	Buspirone	16			1.08	FQ Agora
Drug+CBT	de Beurs et al. (1995)	24/19	Fluvoxamine	12			2.04	AG Comp
Drug+CBT	Kampman et al. (2002)	22/19	Paroxetine	8			1.18	FQ GA
Drug+CBT	Loerch et al. (1999)	14/11	Moclobemid	10	1.30	HAMA	1.30	FQ Ag
Drug+CBT	Marks et al. (1993)	40/34	Alprazolam	8	1.00	HAMA	2.06	PQ
Drug+CBT	Mavissakalian et al. (1983a)	9/8	Imipramine	12	2.61	GAS	2.05	FQ Ag
Drug+CBT	Sharp et al. (1997)	29/29	Fluvoxamine	12			1.06	GHQ
Drug+CBT	Stein et al. (2000)	16/15	Paroxetine	12			0.75	FQ Ag
Drug+CBT	Telch et al. (1985)	13/10	Imipramine	8			2.34	FQ Ag
Drug+CBT	Zitrin et al. (1980)	29/29	Imipramine	14	3.63	CGI		
CBT+Plac	Barlow et al. (2000)	63/45		12	2.15	PDSS		
CBT+Plac	Cottraux et al. (1995)	40/27		16			0.56	FQ Agora
CBT+Plac	de Beurs et al. (1995)	24/19		12			1.31	Ag Comp
CBT+Plac	Kampman et al. (2002)	21/19		8			0.50	FQ GA
CBT+Plac	Loerch et al. (1999)	14/13		10	1.39	HAMA	2.35	FQ Ag
CBT+Plac	Marks et al. (1993)	38/30		8	0.60	HAMA	1.37	PQ
CBT+Plac	Sharp et al. (1997)	33/33		12			1.01	GHQ
CBT+Plac	Stein et al. (2000)	17/16		10			0.55	FQ Ag
CBT+Plac	Telch et al. (1985)	12/9		8			1.63	FQ Ag
CBT+Plac	Zitrin et al. (1980)	24/24		14	2.41	CGI		

See Table II. CGI, Clinical Global Impression Scale; HAMA, Hamilton Anxiety Scale; GAS, Global Assessment of Severity; PDSS, Panic Disorder Severity Scale; FQ, Fear Questionnaire; GHQ, General Health Questionnaire; Ag Comp., Agoraphobia composite score; MSPS, Marks–Sheehan Phobia Scale; PA severity, Severity rating of panic attacks.

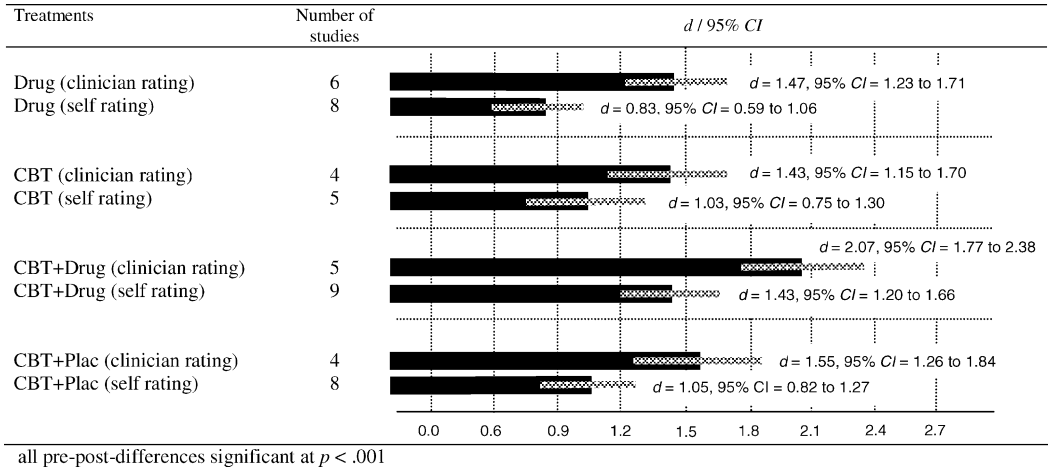


Figure 3. PDA, clinician ratings and self-ratings. Mean weighted pre–post effect sizes.

Table IV. SAD, clinician ratings and self-ratings: effect sizes (Cohen's *d*) for direct comparison of different treatments (Positive values: treatment 1 > treatment 2).

				Clinician ratings			Self-ratings		
Study	*n*	Drug	Weeks	Treatment	*d*	Measure	Treatment	*d*	Measure
Clark et al. (2003)	17/20	Fluoxetine	16	Drug vs. ***CBT***	−0.85	ADIS	Drug vs. ***CBT***	−0.98	FQ
Davidson et al. (2004)	39/48	Fluoxetine	14	***Drug*** vs. CBT	0.12	CGI	Drug vs. ***CBT***	−0.09	BSPS
Gelernter et al. (1991)	14/17	Alprazolam	12				***Drug*** vs. CBT	0.19	FQ
Gelernter et al. (1991)	13/17	Phenelzine	12				Drug vs. CBT	0.00	FQ
Heimberg et al. (1998)	26/28	Phenelzine	12	***Drug*** vs. CBT	0.60	ADIS	***Drug*** vs. CBT	0.75	FQ
Otto et al. (2000)	15/15	Clonazepam	12	***Drug*** vs. CBT	0.64	CGI	***Drug*** vs. CBT	1.02	FNE
Blomhoff et al. (2001)	88/87	Sertraline	24	Drug+CBT vs. Drug	0.17	CGI	Drug+CBT vs. Drug	0.01	FQ
Davidson et al. (2004)	42/39	Fluoxetine	14	Drug+CBT vs. Drug	0.00	CGI	Drug+CBT vs. Drug	−0.01	BSPS
Blomhoff et al. (2001)	88/91	Sertraline	24	***Drug+CBT*** vs. CBT+Plac	0.58	CGI	***Drug+CBT*** vs. CBT+Plac	0.28	FQ
Davidson et al. (2004)	42/46	Fluoxetine	14	***Drug+CBT*** vs. CBT+Plac	0.12	CGI	***Drug+CBT*** vs. CBT+Plac	0.04	BSPS
Davidson et al. (2004)	42/48	Fluoxetine	14	***Drug+CBT*** vs. CBT	0.12	CGI	Drug+CBT vs. ***CBT***	−0.10	BSPS

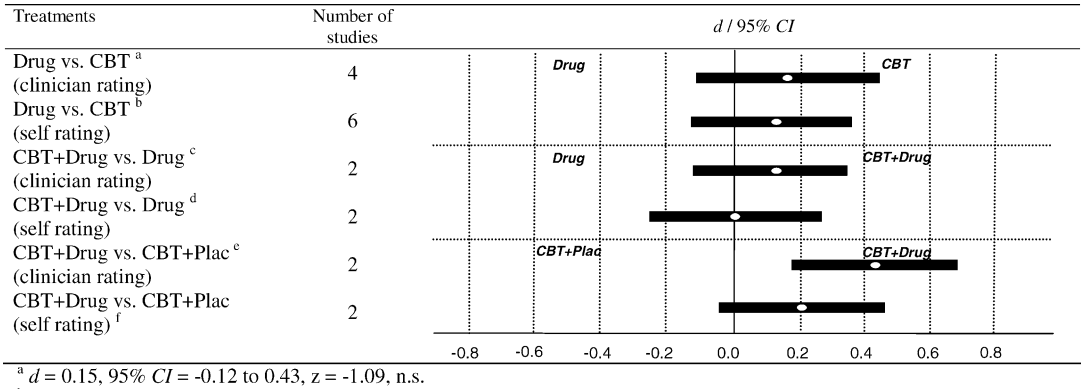
See Table II. CGI, Clinical Global Impression Scale; HAMA, Hamilton Anxiety Scale; GAS, Global Assessment of Severity; FQ, Fear Questionnaire; FNE, Fear of Negative Evaluation Scale; BSPS, Brief Social Phobia Scale.

underestimate their illness severity before treatment, while investigators have a more objective estimate of the actual improvement by having access to the pre-trial severity scores.

When looking at the pre–post differences, pharmacological, cognitive-behavioural, and combined treatments were highly effective in the treatment of PDA (large effect sizes between $d = 0.83$ and $d = 2.07$), with the largest effect sizes coming from combined pharmacological and cognitive-behavioural treatment. Although pre–post changes in placebo conditions (pharmacological and psychological) yielded medium to large effect sizes, the amount of symptom change was substantially smaller than in all other treatment conditions.

While clinicians saw higher pre–post differences for drug treatment alone than for CBT alone, the patients reported higher effect sizes for CBT alone. It has to be taken into account that patients were not blind to CBT treatment, but were blind to the drug they received.

Results from studies in social anxiety disorder (SAD) are less clear. Only two studies had a combined treatment arm (Blomhoff et al. 2001; Davidson et al. 2004). Data from these studies show higher effect sizes for combined pharmacological and cognitive-behavioural treatment when compared to cognitive-behavioural treatment plus pill placebo. While self-report data show a small effect ($d = 0.20$) in favour of a combined treatment,



[a] $d = 0.15$, 95% *CI* = -0.12 to 0.43, z = -1.09, n.s.
[b] $d = -0.12$, 95% *CI* = -0.31 to 0.37, z = 0.96, n.s.
[c] $d = 0.12$, 95% *CI* = -0.13 to 0.36, z = 0.93, n.s.
[d] $d = 0.00$, 95% *CI* = -0.24 to 0.25, z = 0.03, n.s.
[e] $d = 0.42$, 95% *CI* = 0.18 to 0.68, z = 3.42, $p < 0.01$
[f] $d = 0.20$, 95% *CI* = -0.04 to 0.44, z = 1.63, n.s.

Figure 4. SAD, clinician ratings and self-ratings. Mean weighted effect sizes (*d*) and confidence intervals (CI) for differences between treatment modalities.

Table V. SAD, clinician ratings and self-ratings. pre-post effect sizes.

					Clinician ratings		Self-ratings	
Treatment	Study	*n* pre/*n* post	Drug	Weeks	*d*	Measure	*d*	Measure
Drug	Blomhoff et al. (2001)	96/87	Sertraline	24	1.78	CGI	1.45	FQ
Drug	Clark et al. (2003)	20/17	Fluoxetine	16	0.61	ADIS	0.72	FQ
Drug	Davidson et al. (2004)	57/39	Fluoxetine	14	2.22	CGI	1.57	BSPS
Drug	Gelernter et al. (1991)	15/14	Alprazolam	12			1.27	FQ
Drug	Gelernter et al. (1991)	15/13	Phenelzine	12			1.10	FQ
Drug	Heimberg et al. (1998)	31/26	Phenelzine	12	2.72	ADIS	1.59	FQ
Drug	Otto et al. (2000)	25/15	Clonazepam	12	2.24	CGI	1.48	FNE
CBT	Clark et al. (2003)	20/20		16	1.43	ADIS	1.93	FQ
CBT	Davidson et al. (2004)	60/48		14	1.99	CGI	1.83	BSPS
CBT	Gelernter et al. (1991)	20/17		12			1.53	FQ
CBT	Heimberg et al. (1998)	36/28		12	2.23	ADIS	0.76	FQ
CBT	Otto et al. (2000)	20/15		12	1.71	CGI	0.34	FNE
Drug+CBT	Blomhoff et al. (2001)	98/88	Sertraline	24	1.96	CGI	1.50	FQ
Drug+CBT	Davidson et al. (2004)	59/42	Fluoxetine	14	2.19	CGI	1.58	BSPS
CBT+Plac	Blomhoff et al. (2001)	98/91		24	1.4	CGI	1.29	FQ
CBT+Plac	Davidson et al. (2004)	59/46		14	2.01	CGI	1.57	BSPS

See Table II. CGI, Clinical Global Impression Scale; HAMA, Hamilton Anxiety Scale; ADIS, Anxiety Disorders Interview Schedule; FQ, Fear Questionnaire; FNE, Fear of Negative Evaluation Scale; BSPS, Brief Social Phobia Scale.

the difference is more evident in data from clinician ratings ($d = 0.42$). However, it is questionable whether the study by Blomhoff et al. (2001) employed adequate cognitive-behavioural therapy, as the patients only received 15–20-min sessions by general practitioners with a special training but not by experienced CBT therapists. Both clinicians and patients saw a very small advantage of pharmacotherapy compared to CBT.

All other direct comparisons between different treatments for SAD show no clear superiority of one treatment over another and do not support the use of combined treatment.

When looking at pre–post differences, all treatments analyzed showed large effect sizes between $d = 0.88$ and $d = 2.18$, with highest effect sizes reported for pharmacological treatment in the clinician ratings and combined pharmacological and cognitive-behavioural treatment in self-report questionnaires, respectively.

For generalized anxiety disorder (GAD) the database is too small to draw final conclusions. The small set of data available from only one study (clinician ratings) and two studies (self-ratings) indicates a superiority of cognitive-behavioural treatment over pharmacological treatment, while the combination of pharmacological and cognitive-behavioural treatment is on the one hand better than cognitive behavioural treatment combined with pharmacological placebo, on the other hand inferior to cognitive-behavioural treatment alone.

The present analysis only looked at acute treatments. It is believed that gains from CBT are maintained after termination of treatment, while patients on drugs immediately have a reoccurrence of anxiety symptoms after medication is stopped.

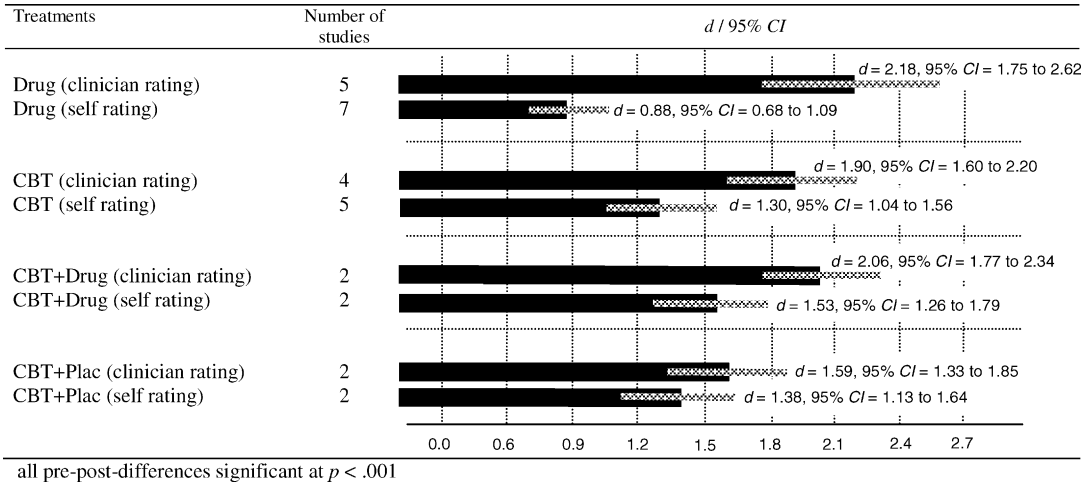


Figure 5. SAD, clinician ratings and self-ratings. Mean weighted pre–post effect sizes.

Table VI. GAD, clinician ratings and self-ratings. Effect sizes (Cohen's *d*) for direct comparisons (Positive values: treatment 1 > treatment 2).

				Clinician ratings			Self-ratings		
Study	*n*	Drug	Weeks	Treatment	*d*	Measure	Treatment	*d*	Measure
Lindsay et al. (1987)	10/10	Lorazepam	4				Drug vs. ***CBT***	−1.10	Zung
Power et al. (1990)	22/19	Diazepam	10	Drug vs. ***CBT***	−0.78	CGI	Drug vs. ***CBT***	−0.79	CGI*
Power et al. (1990)	21/19	Diazepam	10	Drug+CBT vs. Drug	0.78	CGI	Drug+CBT vs. Drug	0.62	CGI*
Power et al. (1990)	21/19	Diazepam	10	***CBT*+Drug** vs. CBT+Plac	0.34	CGI	***Drug*+CBT** vs. CBT+Plac	0.21	CGI*
Power et al. (1990)	21/18	Diazepam	10	CBT+Drug vs. CBT	0.00	CGI	Drug+CBT vs. ***CBT***	−0.25	CGI*

See Table II. CGI, Clinical Global Impression Scale.
*CGI, Clinical Global Impression Scale (self rating); Zung, Zung Self-rating Anxiety Scale.

This would offer CBT considerable advantage over drug treatment. However, an analysis of available follow-up studies comparing the durability of CBT with drug therapy does not show clearly longer "durability" of CBT. A longer-lasting effect of CBT could be demonstrated in only one of six panic disorder studies (Marks et al. 1993). One study showed superiority of CBT, but the patients in this group were allowed to use benzodiazepines, making the results difficult to interpret (Clark et al. 1994). In one study, drug treatment was superior to CBT (Loerch et al. 1999). Three studies (Mavissakalian et al. 1983a; Cohen et al. 1984; Barlow et al. 2000) did not show a difference between drugs and psychological therapies. Studies reporting follow-up data for social anxiety disorder had mixed results. In one study, CBT was superior to fluoxetine at follow up (Clark et al. 2003). One study reported only a trend for superiority of CBT over phenelzine (Liebowitz et al. 1999), and in a third study, exposure therapy was not superior to sertraline at follow-up (Haug et al. 2003; Bandelow and Haug, 2004).

Conclusions

Altogether, our data support the use of a combination of CBT and drug treatment for panic disorder. For social phobia, combined treatment is as yet only supported by preliminary results, and more studies are warranted. For generalized anxiety disorder, final conclusions cannot be drawn due to lack of sufficient data.

The present analysis has some limitations: the meta-analysis was not controlled for study duration. Moreover, we could not differentiate between different drug classes or CBT methods without having a problem with multiple testing. Finally, the number of available studies is still not large enough to draw reliable conclusions.

The differential indication for psychopharmacological or psychological treatment of the different anxiety disorders also depends on the preference of the patient, unwanted side effects, onset of efficacy, comorbidity (e.g. with depression), economic considerations, time availability and commitment of the patient, availability of psychiatric and psychological treatment resources, and qualification and experience of the therapist. It has also to be taken into account that combined treatment is associated with increased expenditures in time and money.

In summary, both pharmacological and psychotherapeutic treatment were shown to be highly effective in the treatment of anxiety disorders. In patients with insufficient response to monotherapy, a trial with combined treatment is warranted.

Statement of interest

In the last 5 years and in the near future, Dr Bandelow has been/will be on the speakers/advisory board for: AstraZeneca, Bristol-Myers-Squibb, Janssen-Cilag, Lilly, Lundbeck, Pfizer, Roche, Sanofi-Aventis, Solvay, Wyeth. The remaining authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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