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Psychological treatment of generalized anxiety disorder: A meta-analysis

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HIGHLIGHTS

- Cognitive behavior therapy (CBT) is effective in the treatment of GAD.
- CBT also has considerable effects on depression in GAD.
- There are not enough studies examining the long-term effects.
- There are not enough studies comparing CBT with care-as-usual or placebo.

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ABSTRACT

Recent years have seen a near-doubling of the number of studies examining the effects of psychotherapies for generalized anxiety disorder (GAD) in adults. The present article integrates this new evidence with the older literature through a quantitative meta-analysis. A total of 41 studies (with 2132 patients meeting diagnostic criteria for GAD) were identified through systematic searches in bibliographical databases, and were included in the meta-analysis. Most studies examined the effects of cognitive behavior therapy (CBT). The majority of studies used waiting lists as control condition. The pooled effect of the 38 comparisons (from 28 studies) of psychotherapy versus a control group was large ($g = 0.84$; 95% CI: 0.71–0.97) with low to moderate heterogeneity. The effects based on self-report measures were somewhat lower than those based on clinician-rated instruments. The effects on depression were also large ($g = 0.71$; 95% CI: 0.59–0.82). There were some indications for publication bias. The number of studies comparing CBT with other psychotherapies (e.g., applied relaxation) or pharmacotherapy was too small to draw conclusions about comparative effectiveness or the long-term effects. There were some indications that CBT was also effective at follow-up and that CBT was more effective than applied relaxation in the longer term.

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1. Introduction

Generalized anxiety disorder (GAD) is a highly prevalent, chronic, costly and disabling mental disorder (Tyrer & Baldwin, 2006). It is characterized by excessive and persistent worry and anxiety about everyday internal and external events, in combination with various psychological and somatic complaints, such as autonomic arousal, restlessness, fatigue, problems with concentrating, irritability, and sleep problems (American Psychiatric Association, 2000). Because most patients are still affected after 6 to 12 years, GAD is usually considered to be a chronic disorder (Yonkers, Dyck, Warshaw, & Keller, 2000). The 12-month prevalence rate of GAD has been estimated to be between 1.2 and 1.9% and the lifetime prevalence between 4.3 and 5.9% (Tyrer & Baldwin, 2006).

Since the introduction of GAD in the DSM in 1980, several randomized trials and meta-analyses have shown that pharmacotherapies can be effective in the treatment of GAD (Baldwin & Polkinghorn, 2005; Mitte, 2005a,b). However, psychological treatments are usually considered by clinicians as well as patients to be preferable to drug treatment in GAD (Tyrer & Baldwin, 2006). Several types of psychological treatments have been developed in the past decades. Most of these belong to the family of cognitive behavioral therapies (CBT), and include a mix of one or more specific techniques, such as cognitive restructuring; exposure; problem-solving; applied relaxation and biofeedback. Contemporary CBT treatments for GAD, such as metacognitive therapy (Wells & King, 2006) and acceptance-based behavior therapy (Treanor, Erisman, Salters-Pedneault, Roemer, & Orsillo, 2011), emphasize the function of worry as an avoidance strategy of internal experiences (Behar, Dobrow DiMarco, Hekler, Mohlman, & Staples, 2009). However, aside from CBT, other types of psychotherapies for GAD have also been developed, such as psychodynamic therapies (Leichsenring et al., 2009; Levy Berg, Sandell, & Sandahl, 2009), non-directive supportive therapy (Stanley, Beck, & DeWitt Glassco, 1996), and spiritual therapy (Koszycki, Raab, Aldosary, & Bradwejn, 2010). Most of the therapies are delivered as individual face-to-face treatments, although a number of studies have examined group treatments of GAD (e.g., Dugas et al., 2003) and guided self-help therapies (Bowman, Scogin, Patton, & Gist, 1997). In recent years Internet-based treatments for GAD have also been developed and tested (Andersson et al., 2012; Paxling et al., 2011; Titov et al., 2009).

A considerable number of randomized controlled trials examining the effects of psychological treatments have been conducted in the past three decades, and several recent meta-analyses have integrated the results of these trials (Covin, Ouimet, Seeds, & Dozois, 2008; Gonçalves & Byrne, 2012; Haby, Donnelly, Corry, & Vos, 2006; Hunot, Churchill, de Lima, & Teixeira, 2007; Mitte, 2005a, 2005b; Siev & Chambless, 2007). However, most of these previous meta-analyses were rather narrow in focus, by aiming at one specific outcome (worry; Covin et al., 2008), at one specific target group (older adults; Gonçalves & Byrne, 2012), or at one specific comparison (direct comparisons between cognitive therapy and applied relaxation; Siev & Chambless, 2007). We found two broader meta-analyses that were aimed at all psychotherapies for GAD that were conducted in the past ten years (Hunot et al., 2007; Mitte, 2005). However, the latter meta-analyses were both conducted several years ago (deadlines of the searches were on February 2006 and May 2002), and, as a result, we were unable to include more recent studies. Our literature search revealed 41 relevant trials, almost twice as many trials as in the largest earlier meta-analysis (Hunot et al., 2007).

In view of the considerable growth of the literature since the last broad meta-analysis, we decided to conduct a new meta-analysis of randomized trials examining the effects of psychological treatments of GAD. We included trials comparing psychotherapy with untreated controls, with other psychotherapies and with pharmacotherapy. This new meta-analysis had several goals. First we wanted to examine whether we could assess the overall effects of psychotherapies for GAD more precisely, because a larger number of trials is expected to result in a better estimate of the effect size. Second, because earlier meta-analyses could not examine longer-term effects of psychotherapies (the number of studies was too small in these meta-analyses), we aimed to examine whether there are now enough studies to evaluate the long-term effects of GAD treatments. Third, most studies have examined the effects of traditional face to face CBT and relatively few studies have examined other types of therapy, such as Internet-based CBT or pharmacological treatment. Therefore, we wanted to examine whether enough studies are now available to compare the differential effects between types of therapy. Finally, we wanted to examine the quality of psychotherapy studies. Although the association between quality and outcome has been examined in one earlier meta-analysis (Hunot et al., 2007), we think it is important to examine this in more detail. Since recent trials tend to meet quality criteria more often, we also examined the association between publication year and outcome.

2. Methods

2.1. Identification and selection of studies

We used several methods to identify studies for possible inclusion. First, we conducted systematic searches in major bibliographical databases: PubMed, PsycInfo, Embase and the Cochrane Central Register of Controlled Trials (up to April 2012). In the searches we combined terms indicative of generalized anxiety (worry, generalized anxiety) and randomized trials. Because we did not want to miss studies on specific types of psychotherapy, and to increase the sensitivity of the searches, we did not limit the searches further to search terms indicating psychological treatments. Both text words and key words were used. Second, we examined the reference lists of earlier reviews and meta-analyses of psychological treatments of GAD (Covin et al., 2008; Gonçalves & Byrne, 2012; Haby et al., 2006; Hunot et al., 2007; Mitte, 2005a, 2005b; Siev & Chambless, 2007; Westen & Morrison, 2001). Third, we checked the references of the included primary studies.

We included (a) randomized trials in which the effects of (b) a psychological treatment for (c) generalized anxiety disorder (d) in adults were compared with (e) a control group (waiting list, care-as-usual, placebo, or any other), with another psychological treatment or with a pharmacological treatment. We only included studies when included patients met diagnostic criteria for GAD according to a formal diagnostic interview.

We excluded studies in which a psychological treatment was compared with the same treatment with one component added or removed (dismantling studies; e.g., Borkovec, Mathews, Chanbers, Ebrahimi, & Nelson, 1987; Fava et al., 2005; Westra, Arkowitz, & Dozois, 2009), unless the treatments were also compared to a control group or a fully different type of psychotherapy. We also excluded studies in which

insufficient data were reported to calculate the effect size, and studies in children and adolescents below 18 years of age. No language restrictions were applied. Selection of the studies was carried out by two independent raters, and disagreements were solved by discussion.

2.2. Quality assessment and data extraction

The validity of included studies was assessed with four criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (Higgins & Green, 2008) to assess possible sources of bias in randomized trials: 1) adequate generation of allocation sequence; 2) concealment of allocation to conditions; 3) prevention of knowledge of the allocated intervention; and 4) dealing with incomplete outcome data. Assessment of the validity of the studies was conducted by two independent researchers and disagreements were solved by discussion.

The quality of the interventions was assessed according to three criteria from an authoritative review of empirically supported psychotherapies (Chambless & Hollon, 1998): (1) the study referred to the use of a treatment manual (either a published manual, or a manual specifically designed for the study); (2) the therapists who conducted the therapy were trained for the specific therapy, either specifically for that study or as a general training; (3) treatment integrity was checked during the study (by supervision of the therapists during treatment or by recording of treatment sessions or by systematic screening of protocol adherence by a standardized measurement instrument).

We coded several aspects of the included studies, including the following participant characteristics: Recruitment method (through the community or only from clinical samples in primary care or specialized mental health care) and target group (adults in general or older adults). We also assessed the following intervention characteristics: Format (individual, group, or Internet-based), and number of sessions. Additionally, we categorized the types of psychotherapy. This was complicated because the large majority of therapies included a mix of cognitive–behavioral intervention components. For the included studies we rated whether they belonged to the broad family of cognitive–behavioral interventions, which means they included at least one of the following components: cognitive restructuring; exposure; problem-solving; applied relaxation; acceptance and commitment therapy; and biofeedback. Within these CBT interventions, we rated whether the intervention used cognitive restructuring as one of the components or not. Within the CBT family we also found several studies that used only (applied) relaxation techniques. These were also rated separately. Non-CBT psychotherapies were categorized as psychodynamic, non-directive supportive therapy or other. As general study characteristic, we rated the type of control group (waiting list, care-as-usual, other).

2.3. Meta-analyses

For each comparison between a psychotherapy group and a comparison group, the effect size indicating the difference between the two groups at post-treatment was calculated (Cohen's d or standardized mean difference). Effect sizes were calculated by subtracting (at post-treatment) the average score of the psychotherapy group from the average score of the comparison group, and dividing the result by the pooled standard deviations of the two groups. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are considered to be small (Cohen, 1988). Because several studies had small sample sizes, we adjusted the effect size for small sample bias according to the procedures suggested by Hedges and Olkin (1985; Hedges' g). When available we used the intention-to-treat data to calculate the effect sizes, if not we used the completers-only data.

In the calculation of effect sizes, we distinguished between three categories of outcome measures: (a) self-report measures of worry and anxiety; (b) clinician-rated instruments of anxiety; and (c) measures of depression. The inclusion of depression measures was motivated by the high level of comorbidity between GAD and depression. We calculated effect sizes for the most used instruments, but also effect sizes in which all instruments in the three categories were pooled for each study. In these pooled analyses, each study provided only one effect size.

To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis (CMA; version 2.2.021). If means and standard deviations were not reported, or any other precise test-statistic, we used the procedures of CMA to calculate the effect size using dichotomous outcomes. As we expected considerable heterogeneity among the studies, we decided to calculate mean effect sizes using a random effects model. In the random effects model it is assumed that the included studies are drawn from 'populations' of studies that differ from each other systematically (heterogeneity). In this model, the effect sizes resulting from included studies not only differ because of the random error within studies (as in the fixed effects model), but also because of true variation in effect size from one study to the next.

The standardized mean difference (Hedges' g) is not easy to interpret from a clinical perspective. Therefore, we transformed the standardized mean differences into the numbers-needed-to-treat (NNT), using the formulae provided by Kraemer and Kupfer (2006). The NNT indicates the number of patients that have to be treated in order to generate one additional positive outcome (Laupacis, Sackett, & Roberts, 1988).

As a test of homogeneity of effect sizes, we calculated the I^2-statistic which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). We calculated 95% confidence intervals around I^2 (Ioannidis, Patsopoulos, & Evangelou, 2007) using the non-central chi-squared-based approach within the heterogi module for Stata. We also calculated the Q-statistic, but only report whether this was significant or not.

Subgroup analyses were conducted according to the mixed effect model. In this model, studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model. For continuous variables, we used meta-regression analyses to test whether there was a significant relationship between the continuous variable and the effect size, as indicated with a Z-value and an associated p-value.

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000), which yields an estimate of the effect size after the publication bias has been taken into account (as implemented in Comprehensive Meta-Analysis). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant.

3. Results

3.1. Selection and inclusion of studies

The systematic searches resulted in a total of 2565 abstracts (1562 after removal of duplicates). A total of 136 full-text papers were retrieved, of which 96 were excluded because they did not meet the inclusion criteria. Fig. 1 presents a flowchart describing the inclusion process, and includes an overview of the reasons for exclusion for the 96 excluded studies. A total of 41 studies (described in 40 papers) met all the inclusion criteria and were included in the analyses.

3.2. Characteristics of included studies

In the 41 included studies 2132 patients participated (1375 in the psychotherapies conditions, 607 in the control conditions, 103 in the pharmacotherapy conditions and 47 in the combined conditions of psychotherapy and pharmacotherapy).

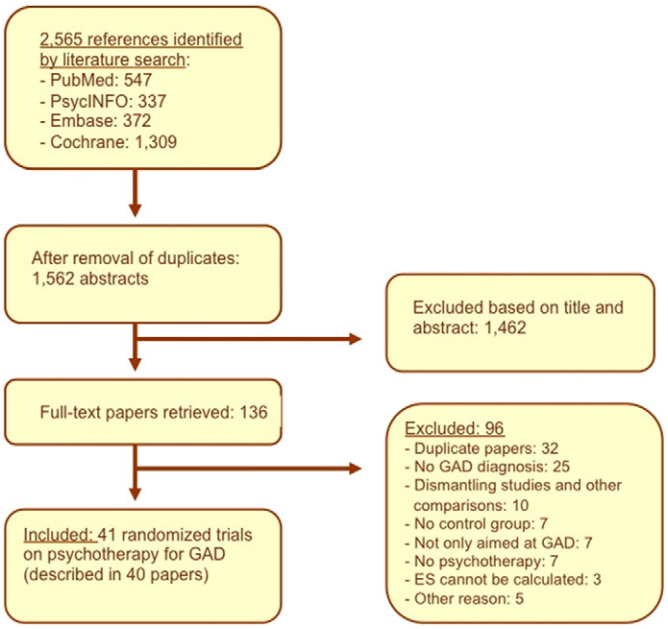

Fig. 1. Flowchart of inclusion of studies.

Patients were recruited from clinical samples in 16 studies, in 22 studies patients were (also) recruited through community referrals, and 3 studies did not report the recruitment method. Most studies were aimed at adults in general (N = 32), while 8 studies were specifically aimed at older adults, and one study did not report the age group.

In 35 of the 41 included studies, CBT was examined as psychotherapy, six studies (also) examined relaxation, three examined biofeedback, three behavior therapy (without cognitive restructuring), two supportive therapy, two psychodynamic therapy, two acceptance-and-commitment therapy (which can also be seen as another therapy from the broad CBT family of therapies), and in 5 studies another type of psychotherapy was examined. In most studies the therapies had an individual treatment format (N = 29), while a group format was used in 5 studies, and another 5 used an Internet-based treatment format (one study did not report the format, and another used a guided self-help non-Internet format). In most studies (N = 27) the treatments had 12 or less treatment sessions (range of treatment sessions: 4 to 37).

Of the 26 studies that compared a psychotherapy with a control group, 19 used a waiting list control, three used a pill placebo control group and another used (enhanced) usual care as control condition (one study used a minimal contact control condition and another study used both a waiting list and a discussion group as control group). Fifteen studies were conducted in the US, 14 in Europe, and 12 in other countries.

3.3. Quality assessment

The quality of the studies varied (Table 1). Eleven reported an adequate sequence generation, while the other 30 did not. Nine studies reported allocation to conditions by an independent (third) party. Twenty one studies reported blinding of outcome assessors whereas thirteen did not and seven used only self-report outcomes. Twenty-eight studies conducted intention-to-treat analyses (a post-treatment score was analyzed for every patient even if the last observation prior to attrition had to be carried forward or that score was estimated from earlier response trajectories). Eight studies met all four quality criteria, while 15 studies met two or three criteria, and the remaining 18 studies met only one or none of the criteria.

The quality of the interventions also varied (Table 1). In most studies (39) a treatment manual was used. In 23 studies the therapists who conducted the therapy were trained for the specific therapy. Treatment integrity was checked in 24 studies. Nineteen studies met all three criteria, eight met two criteria, 12 met one criterion, and two met none of the criteria.

3.4. Effects of psychotherapy compared with control groups

We could compare the effects of psychotherapies with control groups in 38 comparisons from 28 studies. The overall effect was $g = 0.84$ (95% CI: 0.71–0.97), with low to moderate, but significant heterogeneity ($I^2 = 33$; 95% CI: 0–55). This corresponds with a NNT of 2.23. Effect sizes and 95% confidence intervals of each study are presented in Fig. 2. After removal of a potential outlier (of which the 95% CI of the effect size did not overlap with the 95% CI of the pooled effect size; Levy Berg et al., 2009) the effect size increased to $g = 0.87$ (95% CI: 0.74–0.99), while heterogeneity was low and non-significant ($I^2 = 24$; 95% CI: 0–50).

In this meta-analysis, we included seven studies in which two or more psychological treatments were compared with the same control group. This means that multiple comparisons from these studies were included in the same analysis. These comparisons are not independent of each other and this may have resulted in an artificial reduction of heterogeneity and may have affected the pooled effect size. We examined the possible effects of this by conducting an analysis in which we included only one effect size per study. First, we included only the comparisons with the largest effect size from these studies and then we conducted another analysis in which we included only the smallest effect sizes. As can be seen from Table 2, the resulting effect sizes were almost the same as in the overall analyses. Heterogeneity was zero in these analyses.

The effect size based on self-report measures ($g = 0.78$; 95% CI: 0.66–0.90; $I^2 = 25$) was somewhat lower than the effect size based on clinician-rated instruments ($g = 1.09$; 95% CI: 0.88–1.30). As can be seen in Table 2, the effect sizes based on severity ratings by clinicians were even larger ($g = 1.23$; 95% CI: 1.00–1.46).

We could examine the effects of therapies for GAD on depression in 28 comparisons from 17 studies. The overall effect size was $g = 0.71$ (95% CI: 0.59–0.82), which corresponds with a NNT of 2.6. Heterogeneity was zero and not significant. Effect sizes based on the Beck Depression Inventory resulted in an effect size of $g = 0.80$, and the Hamilton Depression Rating Scale in an effect size of $g = 0.91$. Limiting the sample of studies to one effect size per study did not affect the overall effect size considerably, nor did it result in much higher levels of heterogeneity.

Visual inspection of the funnel plot, as well as Duval and Tweedie's trim and fill procedure, pointed at some possible publication bias. After adjustment for publication bias, the mean effect size was reduced from $g = 0.84$ to $g = 0.75$ (95% CI: 0.61–0.88; number of missed studies: 7). Egger's test showed a trend ($p = 0.05$) for possible publication bias (intercept: 1.13; 95% CI: −0.25–2.52).

3.5. Subgroup analyses

In the subgroup analyses (Table 2), we found no significant differences between studies in which studies were recruited from clinical samples compared with studies in which patients were also recruited from the community; studies with adults in general versus specific target groups; studies in which CBT was used, compared with behavioral therapies only and relaxation only; nor did we find a significant difference between studies with higher (meeting ≥ 3 criteria) versus lower quality; studies in which waiting list control groups were used compared with other control groups; studies in different countries; or between studies conducted before 2006 (when the latest meta-analysis was done; Hunot et al., 2007) compared with studies after 2006. We did find that studies in which the psychological treatment met all three quality criteria had a smaller effect ($g = 0.72$) than studies in which the treatment did not meet all quality criteria ($g = 0.99$) ($p < 0.05$).

Table 1
Selected characteristics of randomized controlled trials examining the effects of psychological treatments of generalized anxiety disorders.

Study	Recr	Target group	Conditions	N	Format	N sessions	Contents of treatment	Instruments measuring anxiety	Study qual[a]	Tx qual[b]	C
1. Arntz (2003)	Clin	Adults	CBT Applied relaxation	25 20	Ind	12	Cognitive restructuring Applied relaxation (Öst, 1987)	STAI-trait	− − sr −	+ + +	NL
2. Bakhshani, Lashkaripour and Sadjadi (2007)	Clin	Adults	CBT Pharmacotherapy Placebo	7 7 6	Ind	8	CBT protocol (Clark, 1990) Benzodiazepines + TCA (imipramine)	BAI; HAMA	− − − +	+ − −	IR
3. Barlow et al. (1984)	Clin	Adults	CBT Waiting list	5 4	Ind	18	Applied relaxation + biofeedback + cognitive restructuring + coping strategies	CSR	− − − +	+ − +	US
4. Barlow, Rapee and Brown (1992)	Clin	Adults	CBT Applied relaxation CBT + appl relaxation Waiting list	13 10 11 10	Ind	15	Cognitive restructuring	CSR/ADIS-R; HAMA; STAI-trait; CSAQ-cogn; CSAQ-som; FQ	− − + −	+ + +	US
5. Biswas and Chattopadhyay (2001)	NR	Adults	CBT Biofeedback	15 15	Ind	12?	Cognitive restructuring	Significant improvement (dichotomous)	− − − +	+ − −	IND
6. Biswas, Biswas and Chattopadhyay (1995)	NR	Adults	CBT Biofeedback Benzo	5 5 5	Ind	12?	Cognitive restructuring Benzodiazepines	HAMA; STAI-trait; STAI-state	− − − +	+ − −	IND
7. Borkovec and Costello (1993)	Comm	Adults	CBT Applied relaxation Nondirective supp th	19 18 18	Ind	12	Cognitive restructuring and self-control desensitization	CSR/ASGAS; HAMA; STAI-trait; Zung SRA; PSWQ	− − + +	+ + +	US
8. Bowman et al. (1997)	Comm	Adults	PST Waiting list	17 18	Gsh	4	Self-examination/ problem-solving therapy	HAMA; STAI-trait; STAI-state	− − + −	+ − −	US
9. Butler et al. (1991)	Clin	Adults	CBT Behavior therapy Waiting list	19 19 19	Ind	12	BT: relax + exposure + behavioral activation CBT: cognitive restructuring	CSR/Watson; BAI; STAI-trait; Leeds; HAMA	− − + +	+ + +	UK
10. Crits-Christoph et al. (2011)	Comm	Adults	CBT + venlafaxine Venlafaxine	26 34	Ind	12	Relaxation techniques; coping self-statements; cognitive restructuring	CSR/CGI; HAMA; HADS-A; PSWQ	− − + −	+ + +	US
11. Dugas et al. (2010)	Clin	Adults	CBT Relaxation Waiting list	23 22 20	Ind	12	Cognitive restructuring; exposure; problem-solving; relaxation techniques	CSR/ADIS; PSWQ; WAQ-som; STAI-trait	− − + +	+ + +	CAN
12. Dugas et al. (2003)	Comm	Adults	Group CBT Waiting list	25 27	Grp	14	Cognitive restructuring; exposure; problem-solving	CSR/ADIS; PSWQ; WAQ; BAI	− − + +	+ + +	CAN
13. Durham et al. (1994)	Clin	Adults	CBT — high contact CBT — low contact Psychoan ther — high c Psychoan ther — low c Anx manag — low c	15 20 14 15 16	Ind	9 or 18	CT: cognitive restructuring Anx man: education and coping techniques	CSR; HAMA; STAI-trait; BAI	− − + +	+ + −	UK
14. Hoyer et al. (2009)	Clin	Adults	Worry exposure Applied relaxation Waiting list	29 28 29	Ind	15	Worry exposure: avoidance reduction (no cogn restruct)	HAMA; STAI-trait; PSWQ	+ + + +	+ + +	GER
15. Johnston, Titov, Andrews, Spence and Dear (2011)	Comm	Adults	i-CBT WL	39 20	Web	8	Transdiagnostic: cognitive restructuring; exposure; assertiveness skills	GAD-7; PSWQ	+ + sr +	+ + −	AU
16. Koszycki et al. (2010)	Comm	Adults	Spiritual therapy CBT	11 11	Ind	12	Spiritual therapy: meditation, spiritual techniques; CBT (Zinbarg et al., 2007)	HAMA; BAI; PSWQ	− − + +	+ − −	CAN
17. Ladouceur et al. (2000)	Comm	Adults	CBT Waiting list	14 12	Ind	16	Cognitive restructuring; problem-solving; cognitive exposure; relapse prevention	CSR/ADIS; PSWQ; WAQ; BAI	− − + +	+ + +	CAN
18. Leichsenring et al. (2009)	Comm	Adults	CBT Psychodynamic	29 28	Ind	30	Psychodynamic: based on supp expressive therapy CBT: relaxation; cognitive restructuring, worry exposure; problem-solving	HAMA; PSWQ; STAI-trait; BAI; HADS-A	− − + +	+ + +	GER
19. Levy Berg et al. (2009)	Clin	Adults	Affect foc body ther Standard outpatient	33 28	Ind	37	AFBT: psychodynamic ther. with bodily techniques	SCL-90-anx; BAI	+ − sr +	+ + +	SWE
20. Linden, Zubraegel, Baer, Franke and Schlattmann (2005)	Clin	Adults	CBT Contact + waiting list	36 36	Ind	22	Cognitive restructuring; relaxation; problem-solving; behavioral activation	HAMA; STAI-state	− − − +	+ + +	GER
21. Mohlman et al. (2003)	Comm	Older adults	CBT Waiting list	11 10	Ind	13	Relaxation; cognitive restructuring; exposure; problem-solving sleep hygiene	CSR/SCID; Composite; BAI; SCL-90-anx	− − + −	+ + +	US
22. Mohlman et al. (2003)	Comm	Older adults	Enhanced CBT Waiting list	8 7	Ind	13	Relaxation; cognitive restructuring; exposure; problem-solving sleep hygiene;	CSR/SCID; Composite; STAI-trait	− − + +	+ + +	US
23. Ost and Breitholtz (2000)	Comm	Adults	CBT Applied relaxation	18 15	Ind	12	Applied relaxation Cognitive restructuring	CSR; HAMA; BAI; PSWQ; CSAQ; STAI-trait; STAI-state	− − + −	+ − −	SWE
24. Paxling et al. (2011)	Comm	Adults	i-CBT WL	44 45	Web	8	Applied relaxation; cognitive restructuring; cognitive	PSWQ; GADQ-IV; STAI-state; STAI-trait; BAI	+ + sr +	+ + −	SWE

Table 1 (*continued*)

Study	Recr	Target group	Conditions	N	Format	N sessions	Contents of treatment	Instruments measuring anxiety	Study qual[a]	Tx qual[b]	C
							distancing; problem-solving, worry exposure				
25. Power, Jerrom, Simpson, Mitchell and Swanson (1989)	Clin	Adults	CBT Diazepam Placebo	10 10 11	Ind	4	Cognitive restructuring; applied relaxation	HAMA	− − − −	+ − −	UK
26. Power et al. (1990)	Clin	Adults	CBT Benzo (diazepam) Diazepam + CBT Placebo + CBT Placebo	21 22 21 18 19	Ind	7	Cognitive restructuring; applied relaxation; exposure	HAMA	− − − −	+ − −	UK
27. Robinson et al. (2010)	Comm	Adults	i-CBT technician i-CBT clinician Waiting list	50 47 48	Web	6	Cognitive restructuring; exposure; problems-solving; mood management	PSWQ; GAD-7	+ + sr +	+ − −	AU
28. Sarkar, Rathee and Neera (1999)	NR	NR	Biofeedback Pharmacotherapy	25 25	NR	NR	NR	HAMA	− − − −	− − −	IND
29. Stanley, Beck, et al. (2003)	Comm	Older adults	CBT minimal contact control	29 35	Grp	15	Relaxation; cognitive restructuring; exposure	CSR/ADIS-R; PSWQ; Worry Scale; STAI-trait; HAMA	− − + +	+ − +	US
30. Stanley et al. (1996)	Comm	Older adults	CBT Supportive	18 13	Grp	14	Relaxation; cognitive restructuring; exposure	CSR/ADIS-R; PSWQ; Worry Scale; STAI-trait; HAMA	− − − −	+ − +	US
31. Stanley, Hopko, et al. (2003)	Comm	Older adults	CBT Usual care	6 6	Ind	8	Relaxation; cognitive restructuring; exposure; problem-solving	CSR/ADIS-R; PSWQ; BAI	− − − −	+ − +	US
32. Stanley et al. (2009)	Comm	Older adults	CBT Enhanced UC	70 64	Ind	10	Motivational interviewing; relaxation; cognitive restructuring; exposure; problem-solving	PSWQ; GADSS; SIGH-A/HAMA	+ + + +	+ + +	US
33. Titov et al. (2009)	Comm	Adults	i-CBT Waiting list	24 21	Web	6	Cognitive restructuring; exposure	GAD-7; PSWQ	+ + sr +	+ − −	AU
34. Titov et al. (2010)	Comm	Adults	i-CBT Waiting list	18 16	Web	6	Transdiagnostic: cognitive restructuring; exposure; assertiveness skills	PSWQ	+ + sr +	+ − −	AU
35. Treanor et al. (2011)	Clin	Adults	ACT Waiting list	15 16	Ind	16	Avoidance reducing; relaxation; acceptance	CSR/ADIS; PSWQ	+ − − +	− − −	US
36. van der Heiden, Muris and van der Molen (2012)	Clin	Adults	Metacogn ther Intol-uncert ther Waiting list	54 52 20	Ind	14	MCT: Reduction of metacognitions. IUT: reduction of uncertainty; problem-solving; worry exposure	PSWQ; STAI-trait	+ + + +	+ + +	NL
37. Wells et al. (2010)	Clin	Adults	Metacogn ther relaxation	10 10	Ind	11	MCT: Reduction of metacognitions. AR: applied relaxation	PSWQ; STAI-trait; BAI	+ + − +	+ + +	UK
38. Wetherell et al. (2003)	Comm	Older adults	CBT Discussion group Waiting list	18 18 21	Grp	12	Relaxation; cognitive restructuring; worry exposure	CSR/ADIS; PSWQ; HAMA; BAI	− − + +	+ + +	US
39. Wetherell et al. (2011)	Comm	Older adults	ACT CBT	7 9	Ind	12	ACT: Avoidance reducing; relaxation; acceptance CBT: relaxation; attention training; cognitive restructuring; problem-solving; coping strategies	HAMA; PSWQ	− − + +	+ − +	US
40. White et al. (1992)	Clin	Adults	CT Behavior therapy CBT Subconsc retraining Waiting list	31 31 26 10 11	Grp	6	CT: cognitive restructuring BT: relaxation; functional analysis; exposure; CBT: CT + BT	STAI-state; STAI-trait; FSS	− − sr −	+ − −	UK
41. Zinbarg, Lee and Yoon (2007)	Comm	Adults	CBT Waiting list	8 10	Ind	12	Cognitive restructuring; relaxation and imagery exposure	CSR/SCID; PSWQ; BAI	− − + −	+ + +	US

Abbreviations: ACT: Acceptance and commitment therapy; ADIS-R: Anxiety Disorders Interview Schedule—Revised; AFBT: Affect-focused body therapy; Affect foc body ther: Affect focused body therapy; Anx manag: anxiety management; Appl: applied; ASGAS: Assessor Severity of GAD Anxiety Symptoms scale; AU: Australia; BAI: Beck Anxiety Instrument; Benzo: benzodiazepines; BT: behavior therapy; C: country; CAN: Canada; CBT: cognitive behavior therapy; CGI: Clinical Global Impressions Severity and Improvement scale; Clin: clinical samples; Comm: at least in part recruitment through the community; CSAQ-cogn: Cognitive–somatic anxiety questionnaire—cognitive subscale; CSAQ-som: Cognitive–somatic anxiety questionnaire—somatic subscale; CSAQ: Cognitive–somatic anxiety questionnaire; CSR: clinician severity rating; FQ: Fear questionnaire; FSS: Fear Survey Schedule; GAD-7; Generalized Anxiety Disorder 7-Item Scale; GADQ-IV; Generalized Anxiety Disorder Questionnaire—IV; GADSS; Generalized Anxiety Disorder Severity Scale; GER: Germany; Grp: group format; HADS-A: Hospital Anxiety and Depression scale—anxiety; HAMA: Hamilton Rating Scale for Anxiety; High c: high contact; i-CBT: Internet-based CBT; IND: India; Ind: individual format; Intol-uncert ther: intolerance uncertain therapy; IR: Iran; Leeds: Leeds Scale; Low c: low contact; Metacogn ther: metacognitive therapy; NL: Netherlands; NR: not reported; PST: problem-solving therapy; PSWQ: Penn State Worry Questionnaire; Psychoan ther: psychoanalytic therapy; Recr: recruitment; SCID: Structured Clinical Interview for the DSM; SCL-90-anx: Symptom Checklist 90—anxiety; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale; Sr: only self-report measures; STAI-state: State-Trait Anxiety Inventory—state; STAI-trait: State-Trait Anxiety Inventory—trait; Subconsc retraining: subconsciousness training; Supp th: supportive therapy; SWE: Sweden; UK: United Kingdom; US: United States; WAQ-som: Worry and Anxiety Questionnaire—somatic subscale; WAQ: Worry and Anxiety Questionnaire; Web: web-based treatment format; Zung SRA: Zung Self-Rating of Anxiety scale.

[a] In this column a positive (+) or negative (−) sign is given for four quality criteria of the study, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; intention-to-treat analyses; and selective outcome reporting. Sr in the third criterion indicates that only self-report measures were used (and no assessor was used).

[b] In this column a positive (+) or negative (−) sign is given for three quality criteria of the intervention in the study, respectively: use of a treatment manual; training of therapists; check of treatment integrity.

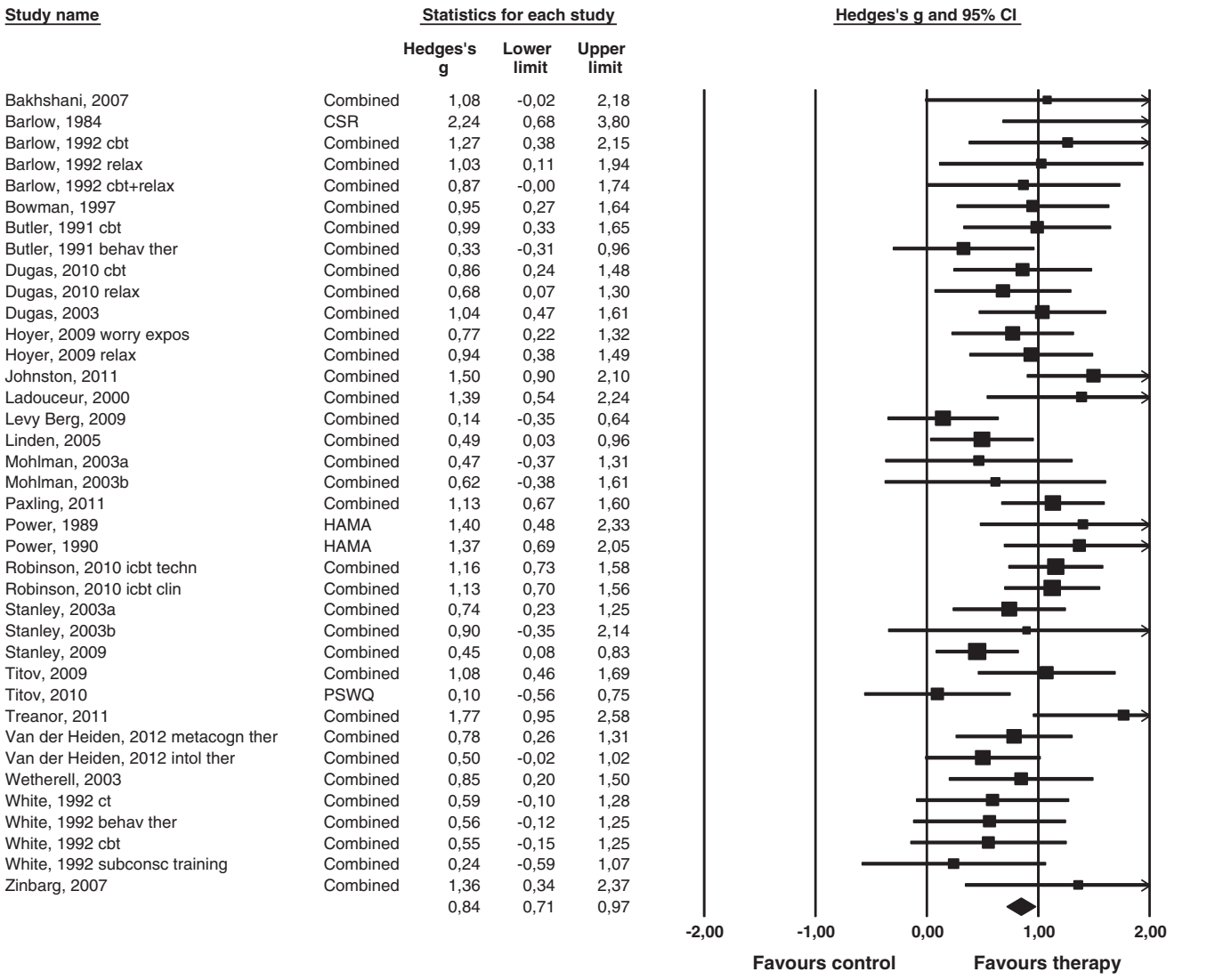

Fig. 2. Standardized effect sizes of psychotherapies for GAD in adults compared with control conditions: Hedges' g.

3.6. Other comparisons

All direct comparisons between psychotherapies compared CBT with another type of therapy. No study was included in which two non-CBT treatments were compared with each other. The comparisons between CBT and other psychotherapies with at least two studies are presented in Table 3 (all anxiety outcomes pooled). CBT was compared with relaxation in six studies. Three other studies compared CBT with another type of therapy (Koszycki et al., 2010: spiritual therapy; Wetherell et al., 2011: acceptance and commitment therapy; White, Keenan, & Brooks, 1992: subconsciousness training). There were also several studies that compared CBT with another form of (C)BT in which one or more modules were added or removed (e.g., Butler, Fennell, Robson, & Gelder, 1991; White et al., 1992). The distinction of the components of these interventions was not clear enough, however, and we decided not to conduct subgroup analyses, or examine these comparisons further. Because of the small number of studies in each of the comparisons, no definite conclusions can be drawn from these analyses. For the comparison with the largest number of studies (CBT vs relaxation) only six studies were available. The effect size indicating the difference between CBT and relaxation was $g = 0.19$ (95% CI: −0.22–0.60). In one of the six studies the CBT condition also included relaxation (Borkovec & Costello, 1993). Removing this study from the analyses resulted in comparable outcomes for the remaining five studies ($g = 0.20$; 95% CI: −0.28–0.68). A post-hoc power calculation showed that the statistical power (1 − beta) of this analysis was only 0.15 ($g = 0.19$; procedures according to Borenstein, 2009, chap. 29). This means that there is insufficient evidence for direct comparisons between CBT and other psychotherapies.

CBT and pharmacotherapy were directly compared with each other in four studies which resulted in a small, non-significant effect in favor of CBT ($g = 0.18$; 95% CI: −0.22–0.60; NNT = 9.43; Table 3). In two studies biofeedback was compared with pharmacotherapy ($g = -0.55$; 95% CI: −1.75–0.64), and two other studies compared pharmacotherapy with the combination of pharmacotherapy and CBT ($g = -0.25$; 95% CI: −1.25–0.76). Because the number of studies in these comparisons was too small, we did not conduct any additional subgroup analyses.

3.7. Long-term outcomes

The majority of studies used a waiting list control group that received treatment between the post-treatment assessment and follow-up, and only limited studies were available to examine the effects of psychotherapies at follow-up. We could calculate the Odds Ratio (OR) for a positive outcome of psychotherapy versus a control group at

Table 2
Effects of psychotherapies for GAD compared with control groups: Hedges' g.

		N	g	95% CI	I^2	95% CI[a]	p[b]	NNT
Outcomes on anxiety								
Overall outcomes								
All studies		38	0.84	0.71–0.97	33	0–55*		2.23
1 possible outlier removed[c]		37	0.87	0.74–0.99	24	0–50		2.16
One effect size per study (highest)		28	0.91	0.75–1.07	40	6–62*		2.08
One effect size per study (lowest)		28	0.85	0.68–1.01	44	12–64**		2.21
Outcomes for specific instruments								
Self-report measures								
All self-report instruments		35	0.78	0.66–0.90	25	0–51		2.39
All, with 1 possible outlier removed[c]		34	0.81	0.69–0.92	15	0–44		2.30
BAI		11	0.65	0.43–0.86	12	0–53		2.82
PSWQ		20	0.95	0.78–1.11	38	0–64*		2.01
STAI-state		7	0.73	0.42–1.04	41	0–75		2.54
STAI-trait		19	0.64	0.50–0.79	0	0–49		2.86
Clinician-rated instruments								
All clinician rated instruments		25	1.09	0.88–1.30	54	27–70**		1.79
Clinician's severity ratings		17	1.23	1.00–1.46	32	0–62		1.62
HAMA		14	1.02	0.78–1.25	38	0–67		1.89
Subgroup analyses[d]								
Recruitment	Clinical	22	0.77	0.60–0.94	29	0–58	0.238	2.42
	Community	16	0.93	0.74–1.11	34	0–64		2.04
Target group	Adults in general	32	0.88	0.74–1.02	37	4–59*	0.159	2.15
	Older adults	6	0.63	0.31–0.95	0	0–75		2.91
Format	Individual	23	0.80	0.64–0.96	35	0–61	0.150	2.34
	Group	8	0.70	0.42–0.98	0	0–68		2.63
	Web-based/self-help	7	1.05	0.80–1.29	44	0–77		1.85
Type	CBT	28	0.90	0.75–1.05	26	0–54	0.452	2.10
	Behavioral only	3	0.57	0.13–1.01	0	0–90		3.18
	Relaxation only	3	0.86	0.40–1.32	0	0.520 2		2.19
	Other	4	0.68	0.27–1.08	77	36–91**		2.70
Study quality	Meets ≥3 criteria	10	0.84	0.63–1.06	67	36–83**	0.987	2.23
	Meets <3 criteria	28	0.84	0.68–1.01	3	0–43		2.23
Treatment quality	Meets 3 criteria	20	0.72	0.56–0.88	38	0–65	0.028	2.56
	Meets <3 criteria	18	0.99	0.81–1.16	0	0–48		1.94
Control group	Waiting list	31	0.87	0.73–1.01	23	0–51	0.330	2.16
	Other[d]	7	0.71	0.42–1.00	53	0–80*		2.60
Country	US	13	0.89	0.65–1.13	22	0–59	0.114	2.13
	EU	15	0.70	0.52–0.89	30	0–62		2.63
	Other	10	1.01	0.78–1.24	30	0–66		1.91
Publication year	<2006	21	0.82	0.63–1.02	0	0–47	0.787	2.28
	≥2006	17	0.86	0.68–1.04	55	22–74**		2.19
Outcomes on depression								
All studies		28	0.71	0.59–0.82	0	0–42		2.60
BDI only		19	0.80	0.64–0.96	0	0–49		2.34
HAMD only		7	0.91	0.60–1.22	34	0–72		2.08
One effect size per study (highest)		17	0.75	0.60–0.89	5	0–54		2.48
One effect size per study (lowest)		17	0.63	0.48–0.77	14	0–51		2.91

* $p < 0.05$.
** $p < 0.01$.
[a] The p-value in this column indicates whether the Q-test for heterogeneity is significant.
[b] The p-value in this column indicates whether the effect sizes of subgroups differ significantly from each other in the subgroup analyses.
[c] Levy Berg et al. (2009).
[d] The 4 "other" control groups were: 2 care-as-usual, 1 pill placebo, and 1 minimal contact.

follow-up in three studies, with follow-up periods ranging from 3 to 15 months (Levy Berg et al., 2009; Stanley et al., 2009; Wetherell, Gatz, & Craske, 2003). When we pooled all outcomes for all time points together the OR for a positive outcome was OR = 1.53 (0.91–2.58) indicating a trend ($p < 0.1$) that psychotherapy may result in a better outcome than the control groups ($I^2 = 0$; 95% CI: 0–90). Because the statistical power to detect significant differences was too small, we did not conduct any additional analyses with these studies.

We could compare the long-term effects of CBT with those of applied relaxation in five studies, with follow-up periods ranging from 6 to 24 months. The OR of a positive outcome for all follow-up periods together was OR = 1.97 (1.02–3.82; $I^2 = 11$; 95% CI: 0–81), in favor of CBT ($p < 0.05$). At 6 months (N = 4; OR = 1.84; 95% CI: 0.77–4.40; $I^2 = 37$; 95% CI: 0–78) and at 24 months (N = 2; OR = 1.59; 95% CI: 0.71–3.56; $I^2 = 0$) there was no significant difference between CBT and applied relaxation, but at 12 months (N = 4; OR = 3.00; 95% CI: 1.45–6.22; $I^2 = 0$; 95% CI: 0–85) there was a significantly better outcome for CBT than for applied relaxation ($p < 0.01$).

4. Discussion

This meta-analysis investigated the effects of psychological treatments for GAD. We found a considerable number of studies examining the effects of psychological treatments for GAD in adults, especially CBT. When compared to waiting list control groups, these treatments have large effects on worrying, anxiety and depression, regardless of whether effects were measured with self-report measures or with clinician-rated instruments. These effect sizes correspond to NNTs of

Table 3
Comparisons of psychotherapies with other psychotherapies and pharmacotherapy: Hedges' g.

	N	g	95% CI	I^2	95% CI[a]	NNT
CBT versus other psychotherapies						
CBT vs applied relaxation only	6	0.19	−0.22–0.60	65	17–86	9.43
CBT vs psychodynamic therapy	3	0.46	−0.09–1.01	41	0–82	3.91
CBT vs biofeedback	2	0.68	−0.18–1.54	0	[a]	2.70
CBT vs supportive therapy	2	0.48	−0.21–1.17	35	[a]	3.76
Psychotherapy and pharmacotherapy						
CBT vs pharmacotherapy[b]	4	0.18	−0.76–1.12	77	36–91	
Biofeedback vs pharmacotherapy[c]	2	−0.55	−1.75–0.64	69	[a]	
Pharmacotherapy vs combined	2	−0.25	−1.25–0.76	81	[a]	

[a] 95% CI cannot be calculated when df = 1.
[b] A positive effect size indicates a superior effect of CBT over pharmacotherapy.
[c] A positive effect size indicates a superior effect of biofeedback over pharmacotherapy.

about 2, indicating that two patients have to be treated in order to generate one positive outcome, which is in line with earlier research.

We also found some indications that CBT may be more effective than applied relaxation at the longer term, while both were equally effective at the short term. Although these results are based on a limited number of studies and should be confirmed in future research, this suggests that CBT may be preferable over applied relaxation as a first line treatment of GAD. We also found some indications that CBT may have longer-lasting effects compared to usual care, but the number of studies reporting effects at follow-up was still limited and more research is needed before definite conclusions can be drawn.

Another goal of the current study was to examine whether the recent studies examining Internet-based treatments result in effects comparable to those of face-to-face therapies. Although the number of studies on this type of treatment is relatively small, the resulting effect sizes were comparable with those found for face-to-face therapies. This is in line with other research showing that both treatment formats have comparable outcomes (Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010).

Another goal of this meta-analysis was to examine whether enough studies are now available to explore the differential effects of different types of therapy and pharmacotherapy more closely. Unfortunately, the number of studies was still very small and we still cannot answer the question whether some treatments may be better than others.

We found no indication that more recent studies, which more often report to meet more quality criteria, had a higher or lower effect size than older studies. It may be possible that earlier studies met the quality criteria but did not report this as this was not considered relevant at that time, or there is no association between these quality criteria and outcome. It is also possible, however, that the number of studies was too small to find a significant association between quality and outcome, and that in the future when more studies are available, we will find such an association.

In the moderator analyses we found that studies in which the psychological treatment met all quality criteria had a smaller effect than studies in which the treatment did not meet all of these criteria. One would expect that a higher quality of interventions resulted in higher effect sizes. However, the criteria we used are difficult to estimate from the published papers, and it is very well possible that this is a chance finding.

No other significant moderator of outcome was found. We also could not confirm that psychotherapy is less effective in older than in younger adults, as was found in an earlier meta-analysis (Covin et al., 2008). The problem with moderator analyses in meta-analyses is that the power to detect differences between subgroups is typically small and that the association between the different characteristics can be considerable. This means that the results of such analyses are unstable, uncertain, and may be influenced considerably by one new study. These analyses should, therefore, be considered with caution.

The main results of this meta-analysis should also be considered with caution. Only a few studies used control groups other than waiting lists. This might be problematic as waiting lists have been known to produce stronger effect sizes than active control groups (Mohr et al., 2009). Our results suggest that psychological treatment may be at least as effective as medication, although the number of comparative studies may be too small to draw definite conclusions.

A striking finding of the present meta-analysis was the large overall effect size for the treatment effects on depression ($g = 0.71$). This effect size is very similar to the effects of psychological treatment for depression in general (Cuijpers, Andersson, Donker, & van Straten, 2011). There is evidence showing that GAD often precedes depression (Schoevers, Deeg, van Tilburg, & Beekman, 2005). Thus, it is possible that if GAD symptoms remit following treatment, this may lead to a reduction in depression symptoms as well.

Another interesting finding was that outcomes based on self-report assessments were lower as compared to clinician ratings. The causes of this difference are not clear. It is possible that clinicians are positively biased or that patients are negatively biased, and there are no methods available to examine which of the two is true. It is also possible that this difference is caused by the instruments used, with some instruments being more sensitive to change than others. In a meta-analysis of psychotherapies for depression we also found more conservative findings for self-report measures (Cuijpers, Li, Hofmann, & Andersson, 2010).

Earlier meta-analyses have concluded that applied relaxation and cognitive behavioral therapy may have comparable effects on GAD (Siev & Chambless, 2007). The number of studies directly comparing the two treatments was small, and hence the power of our analyses to detect smaller differential effects was limited. Whether the two treatments are indeed equally effective can only be determined when more research is available. However, it is important to note that the method of applied relaxation (Öst, 1987), used in the majority of the studies, includes more components than progressive relaxation only (e.g., encouraging exposure when instructing participants to apply relaxation in real life settings). This suggests that direct comparisons between applied relaxation and CBT could result in a different outcome than CBT against relaxation treatment only. As indicated earlier, our results also suggest that CBT and relaxation may be equally effective in the short-term, but that CBT may be more effective in the longer-term. This is important, both from a scientific and a clinical point of view. However, more research is needed to determine whether there is a real difference.

Overall, there is a large overlap in techniques and approaches used in CBT for GAD, as can be seen in Table 1. For example, many treatment protocols include relaxation as a component and some include sleep management. This was one reason why we decided not to include the dismantling studies (e.g., Borkovec, Newman, Pincus, & Lytle, 2002) as the relative effects of different forms of CBT are hard to study given the heterogeneity of the treatment components. Adding to this are the new acceptance oriented treatments that are grounded in behavior therapy (Hayes, Luoma, Bond, Masuda, & Lillis, 2006), but that also include other techniques such as defusion.

The effects of the psychotherapies may also have been overestimated because of publication bias. Therefore, although the results of this meta-analysis point at large and clinically relevant effects of psychotherapy, caution is also needed.

This study has several limitations. We already mentioned several limitations related to the included studies, such as the small number of studies using other than waiting list control groups, and the lack of follow-up measurements. The low quality of many of the included studies is also one of the weaknesses of the set of included studies. Furthermore, we had very few studies examining differential effects of different treatments, or pharmacotherapy. Another limitation concerns the role of treatment manuals used in the trials and the limited information about the treatment components presented in the trials. Due to limited information we were not able to include information on adherence to

treatment manuals and given the heterogeneity of the treatments this would most likely be hard to interpret anyway. Hence, the situation for GAD studies differs markedly from the depression field where many studies exist using the same manual (e.g., interpersonal psychotherapy for depression according to Klerman, Weissman, Rounsaville, & Chevron, 1984).

We also want to point at a general limitation of this kind of meta-analyses in general. Our meta-analysis can make an estimate of the effects of treatments compared with control groups or other interventions, but it gives very little information about how these therapies work. Although it is possible to examine moderators of outcome in meta-analyses, a much better design to examine the effective components of treatments is the dismantling study (Behar & Borkovec, 2003). In dismantling studies a therapy with a specific component is compared with the same therapy without this component. This allows us to examine whether that component is an essential element for a therapy to be effective. Unless a considerable number of dismantling studies have examined the same component, dismantling studies cannot be included in a meta-analysis, as these focus on broader questions about the effects compared with control groups or other treatments. To understand how therapies work, however, dismantling studies are of vital importance.

Despite the limitations of this meta-analysis, it seems safe to conclude that psychotherapies, especially CBT, are effective in the treatment of GAD in adults. This is an important conclusion, in view of the great personal and societal costs of GAD. Several psychologists have suggested that psychotherapy is the treatment of choice in combating GAD (Tyrer & Baldwin, 2006). The findings of the present meta-analysis are consistent with this, by demonstrating large and clinically relevant effects of psychotherapy in treating GAD in adults.

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