

The effects of cognitive and behavioural therapies for anxiety disorders on depression: a meta-analysis

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Background. The effects of cognitive behavioural therapy of anxiety disorders on depression has been examined in previous meta-analyses, suggesting that these treatments have considerable effects on depression. In the current meta-analysis we examined whether the effects of treatments of anxiety disorders on depression differ across generalized anxiety disorder (GAD), social anxiety disorder (SAD) and panic disorder (PD). We also compared the effects of these treatments with the effects of cognitive and behavioural therapies of major depression (MDD).

Method. We searched PubMed, PsycINFO, EMBASE and the Cochrane database, and included 47 trials on anxiety disorders and 34 trials on MDD.

Results. Baseline depression severity was somewhat lower in anxiety disorders than in MDD, but still mild to moderate in most studies. Baseline severity differed across the three anxiety disorders. The effect sizes found for treatment of the anxiety disorders ranged from $g = 0.47$ for PD, $g = 0.68$ for GAD and $g = 0.69$ for SAD. Differences between these effect sizes and those found in the treatment of MDD ($g = 0.81$) were not significant in most analyses and we found few indications that the effects differed across anxiety disorders. We did find that within-group effect sizes resulted in significantly ($p < 0.001$) larger effect sizes for depression ($g = 1.50$) than anxiety disorders ($g = 0.73$ – 0.91). Risk of bias was considerable in the majority of studies.

Conclusions. Patients participating in trials of cognitive behavioural therapy for anxiety disorders have high levels of depression. These treatments have considerable effects on depression, and these effects are comparable to those of treatment of primary MDD.

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Introduction

Cognitive and behavioural therapies (CBT) have been found to be effective in the treatment of anxiety disorders, including social anxiety disorders (SAD; Acarturk *et al.* 2009), generalized anxiety disorders (GAD; Hunot *et al.* 2007; Cuijpers *et al.* 2014) and panic disorder (PD; Sánchez-Meca *et al.* 2010). Although some other types of treatment have been developed for the treatment of anxiety disorders, like psychodynamic (Milrod *et al.* 2007; Beutel *et al.* 2013) and interpersonal psychotherapies (Cuijpers *et al.*

2016), cognitive and behavioural therapies have been examined in dozens of randomized trials and have consistently been shown to be effective in the treatment of anxiety disorders with large effect sizes across disorders. Treatment guidelines typically advise use of cognitive and behavioural therapies as first-line treatments of anxiety disorders (NICE, 2011).

The majority of patients suffering from an anxiety disorder also suffer from depression, either as a comorbid depressive disorder or as subclinical depressive symptoms (Goldberg *et al.* 2009). It is therefore not surprising that in many randomized trials on cognitive and behavioural therapies for anxiety disorders, depression is included as one of the outcome measures. Although most trials use symptoms of anxiety as the primary outcome measure, depression is typically used as one of the most important secondary outcome measures.

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Meta-analyses of cognitive behavioural treatments of anxiety disorders have examined the effects of these treatments on depression. When these treatments were compared with care-as-usual or waiting-list control groups, effect sizes typically found were between $d=0.60$ and 1.00 for GAD, SAD and PD (Mitte, 2005; Hunot *et al.* 2007; Acarturk *et al.* 2009; Sánchez-Meca *et al.* 2010; Cuijpers *et al.* 2014). These effect sizes correspond well with effect sizes found for cognitive behavioural interventions aimed at depression (Cuijpers *et al.* 2013; Ekers *et al.* 2014), suggesting that treatment of anxiety disorders is also effective in reducing depressive symptoms that are co-morbid with anxiety. It should be noted that CBT for depression and the anxiety disorders are not identical. Although both include techniques aimed at cognitive restructuring, behavioural activation, for example, has been found to be effective in depression (Ekers *et al.* 2014), but is not assumed to work in anxiety disorders. Exposure has been developed for anxiety disorders, and relaxation works well in GAD, but less so in panic and depression (Siev & Chambless, 2007).

What has not been examined so far, however, is whether the effects of treatment of anxiety disorders on depression differ for each of the specific anxiety disorders. Previous meta-analyses suggest that the effects of CBT of anxiety disorders result in comparable effect sizes on depression, but this has not been tested. It has also not been examined whether the effects of treatment of anxiety disorders on depression differ significantly from the effects of cognitive behavioural treatment of depressive disorders. Previous meta-analyses suggest that these effects are also comparable, but again, this has not been tested.

Whether CBT for anxiety disorders also has an effects on depression is important, because if these effects are comparable across depression and anxiety disorders, it would not be necessary to treat depression separately from the anxiety disorder and clinicians can assume that when an anxiety disorder is treated, depression is also improved. It is also important because it may simplify transdiagnostic treatments (Craske, 2012). From a theoretical point this is also an interesting question, because if treating anxiety also affects depression this could be seen as support for the notion that both anxiety and depressive disorders should be considered as variants of a broader category of neurotic disorders (Goldberg *et al.* 2009).

We decided, therefore, to conduct a meta-analysis of trials examining the effects of cognitive and behavioural therapies for GAD, SAD and PD, in which we also examined the effects of these treatments on depression. We compared these outcomes with those of trials examining the effects of cognitive and behavioural therapies for major depressive disorder (MDD) in adults.

Method

Identification and selection of studies

We searched four major bibliographical databases (PubMed, PsycINFO, EMBASE and the Cochrane database of randomized trials) by combining terms (both MeSH terms and text words) indicative of SAD (such as social phobia, social anxiety, public-speaking anxiety), GAD (such as worry and generalized anxiety), and PD (such as panic, panic disorder), with filters for randomized controlled trials. We also checked the references of earlier meta-analyses of psychological treatments for the included disorders. The deadline for the searches was 14 August 2015.

For the identification of trials on CBT for depression, we used an existing database of 1756 papers on the psychological treatment of depression. This database has been described in detail elsewhere (Cuijpers *et al.* 2008), and has been used in a series of earlier published meta-analyses (www.evidencebasedpsychotherapies.org). The database is continuously updated and was developed through a comprehensive literature search (from 1966 to January 2015) in which 17 061 abstracts in PubMed (4007 abstracts), PsycINFO (3147), EMBASE (5912) and the Cochrane Central Register of Controlled Trials (3995) were examined. These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words).

We included (a) randomized trials (b) in which a cognitive or behavioural treatment (c) for adults (d) with PD (with or without agoraphobia), generalized anxiety disorder (GAD), social anxiety disorder (SAD), or major depressive disorder (MDD) (e) was directly compared to a control group (waiting list, care as usual, placebo or other) and (f) in which the effects of the treatment on depression [according to the Beck Depression Inventory (BDI; Beck *et al.* 1961), the BDI-II (Beck *et al.* 1996) or the Hamilton Rating Scale for Depression (HAM-D-17; Hamilton, 1960) was measured. Only studies in which subjects met diagnostic criteria for the disorder according to a structured diagnostic interview (such as SCID, CIDI, or MINI) were included. We focused only on depressive symptoms as measured with BDI, the BDI-II and HAM-D-17 because these are by far the most used outcome instruments for depression in trials on anxiety disorders, and because this focus allowed a direct comparison with studies on the treatment of depression, where these instruments are also the most used outcome measures.

Cognitive and behavioural therapies were defined as therapies aimed at cognitive restructuring or at changing current anxiety behaviour. For depression we included trials in which CBT (Cuijpers *et al.* 2013) or

behavioural activation therapy (Ekers *et al.* 2014) was examined. Studies on therapies delivering only (applied) relaxation were excluded, as were studies on eye movement desensitization and reprocessing, interpersonal or psychodynamic therapies. Co-morbid mental or somatic disorders were not used as an exclusion criterion. Studies on inpatients, adolescents and children (age <18 years) were excluded. We also excluded maintenance studies, aimed at people who had already recovered or partly recovered after an earlier treatment. We excluded these studies because their aim is different from acute treatments and because including them would lead to an increased level of clinical and probably statistical heterogeneity. Studies that did not report sufficient data to calculate standardized effect sizes were excluded as well. Studies in English, German, and Dutch were considered for inclusion.

Quality assessment and data extraction

We assessed the validity of included studies using four criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (Higgins *et al.* 2011). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). Assessment of the validity of the included studies was conducted by two independent researchers, and disagreements were solved through discussion.

We also coded participant characteristics (disorder, recruitment method, target group); characteristics of the psychotherapies (treatment format, number of sessions); and general characteristics of the studies (country where the study was conducted, year of publication).

Meta-analyses

For each comparison between a psychotherapy and a control condition, the effect size indicating the difference between the two groups at post-test was calculated (Hedges' *g*). Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the control group, and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes we corrected the effect size for small sample bias (Hedges & Olkin, 1985). If means and standard deviations were not reported, we used the procedures of the Comprehensive Meta-analysis software (version 3.3070; CMA) to calculate the effect size using

dichotomous outcomes; and if these were not available either, we used other statistics (such a *t* value or *p* value) to calculate the effect size. We also calculated (unstandardized) mean differences that indicate the difference between treatment and control groups in terms of points on the specific scale that was used (BDI, BDI-II, HAMD-17). Furthermore, we calculated effect sizes indicating the improvement from baseline to post-test for the treatment groups in the studies. Because the values at baseline and post-test are not independent of each other, we assumed a conservative correlation between baseline and post-test score of $r = 0.70$.

To calculate pooled mean effect sizes, we used the Comprehensive Meta-Analysis computer program. Because we expected considerable heterogeneity among the studies, we employed a random-effects pooling model in all analyses.

In order to assess baseline difference among patients with GAD, SAD, PD and MDD, we pooled the mean on BDI, BDI-II, HAMD-17 at baseline using the means, standard deviations and number of the treatment groups according to the procedures implemented in CMA. Numbers needed to treat (NNT) were calculated using the formulae provided by Kraemer & Kupfer (2006).

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 indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins *et al.* 2003). We calculated 95% confidence intervals around I^2 (Ioannidis *et al.* 2007), using the non-central χ^2 -based approach within the heterogi module for Stata (Orsini *et al.* 2006).

We conducted subgroup analyses according to the mixed-effects model, in which 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 effect size, as indicated by a *Z* value and an associated *p* value. Multivariate meta-regression analyses, with the effect size as the dependent variable, were conducted in CMA.

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

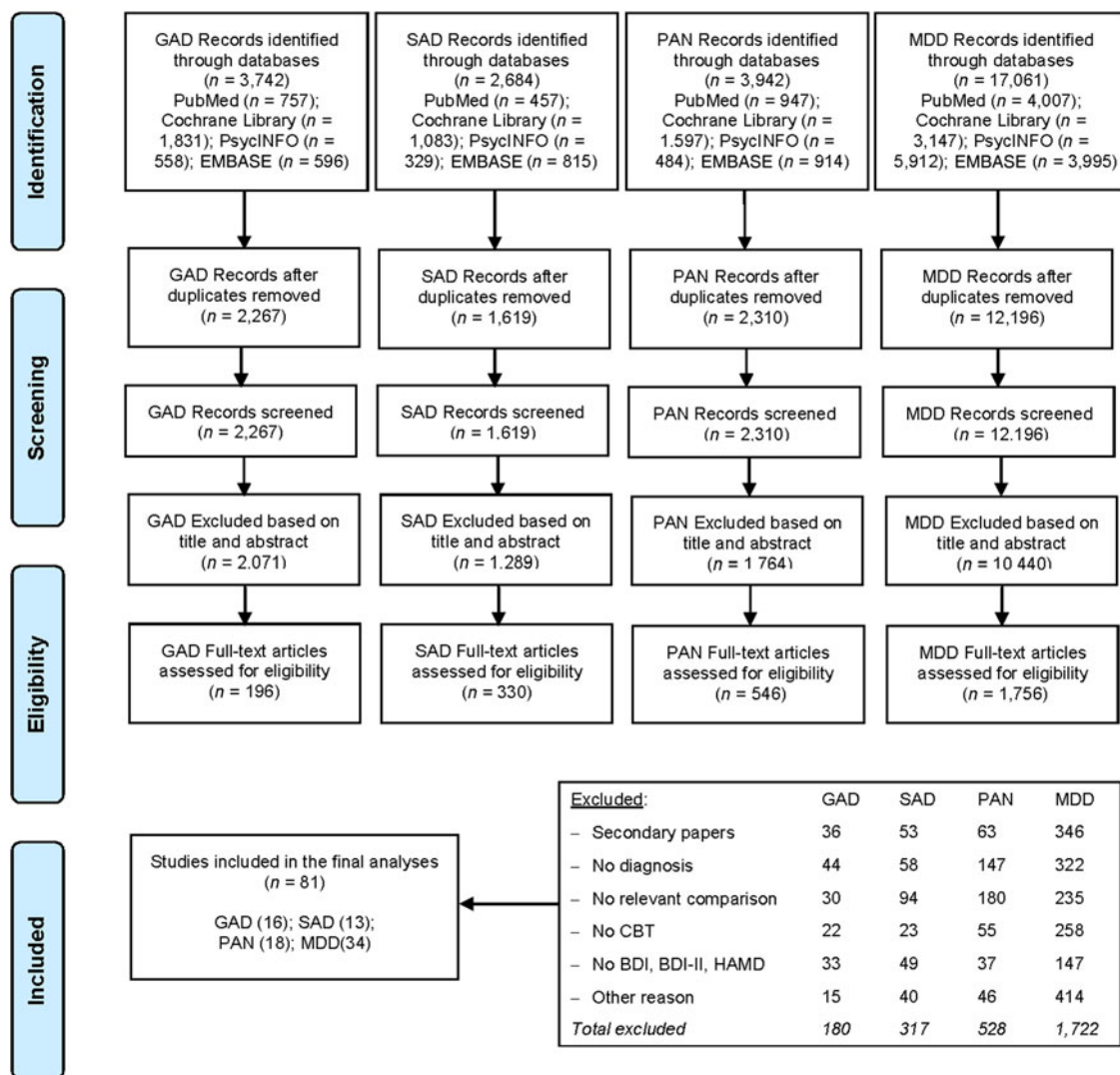


Fig. 1. PRISMA flowchart for the inclusion of studies. (Adapted from Moher *et al.* 2009.)

Results

Selection and inclusion of studies

After examining a total of 27 429 abstracts (18 392 after removal of duplicates), we retrieved 2928 full-text papers for further consideration. We excluded 2747 of the retrieved papers. The PRISMA flowchart describing the inclusion process, including the reasons for exclusion, is presented in Fig. 1. A total of 47 studies met inclusion criteria for this meta-analysis, 16 studies on GAD, 18 studies on PD, and 13 on SAD. Apart from the studies on anxiety disorders, we included 34 studies on MDD that used the BDI, BDI-II and/or HAMD-17. Selected characteristics of the included studies (81 in total) are reported in Supplementary Appendix A and references are given in Supplementary Appendix B.

Characteristics of included studies

The 81 studies included a total of 110 comparisons between a treatment and a control group (21 comparisons for GAD, 19 for SAD, 28 for panic, and 42 for MDD) and included a total of 5486 patients (3187 in the CBT groups and 2299 in the control groups).

Sixty-three studies were aimed at adults in general, seven were aimed at older adults and 11 at other more specific target groups. Twenty-three studies recruited patients exclusively from clinical populations, 46 recruited (also) from the community, and 12 used other recruitment methods.

In the 110 CBT conditions, the treatment was delivered in individual format in 60 studies, in group format in 29 studies, in guided self-help format in 19 studies and five studies used a mixed format. The number of treatment sessions ranged from 3 to 26. In 55 studies

Table 1. Pooled mean baseline scores on the BDI, BDI-II and HAMD-17 in patients participating in cognitive and behavioural therapies for GAD, SAD, PD and MDD^a

	N_{cmp}	Mean	95% CI	I^2	95% CI	$p_{\text{MDD}}^{\text{b}}$	$p_{\text{no MDD}}^{\text{c}}$
BDI							
GAD	16	16.77	15.14–18.40	69	43–80	0.01	0.06
SAD	11	13.82	11.95–15.69	70	34–82		
PD	26	16.00	14.71–17.28	73	58–81		
MDD	22	23.68	17.03–30.32	100	–		
BDI-II^d							
GAD	5	19.79	15.92–23.66	89	76–94	<0.001	0.18
SAD	4	15.88	11.71–20.05	79	11–90		
PD							
MDD	12	27.86	25.50–30.21	85	75–90		
HAMD-17							
GAD	5	14.42	11.29–17.56	85	60–92	<0.001	<0.001
SAD	4	8.18	7.23–9.14	30	0–76		
PD	4	11.73	8.95–14.51	68	0–87		
MDD	20	19.74	17.84–21.65	97	96–97		

BDI, Beck Depression Inventory; HAMD-17, Hamilton Depression Rating Scale; GAD, Generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; MDD, major depressive disorder; CI, Confidence interval; N_{cmp} , number of comparisons; NNT, number needed to treat.

^a According to the random-effects model.

^b The p values in this column indicate whether the difference between the different disorders is significant: MDD included.

^c The p values in this column indicate whether the difference between the different disorders is significant: MDD excluded.

^d None of the studies on panic disorder used the BDI-II as outcome measure.

a waiting-list control group was used, five used a pill placebo control group, 16 had a care-as-usual control group, and five another control condition. Forty-one studies were conducted in North America, 29 in Europe, and 11 in other countries.

Quality assessment

The quality of the studies varied. Thirty-two studies reported an adequate sequence generation, while the other 49 did not. Twenty-nine of the 81 studies reported allocation to conditions by an independent (third) party. Seventy-seven studies reported blinding of outcome assessors or used only self-report outcomes and 58 studies conducted intention-to-treat analyses. Twenty-five studies met all four quality criteria, 34 met two or three criteria, and the remaining 22 studies met one or none of the criteria.

Baseline differences among patients in treatment on GAD, SAD and PD

We first examined whether the baseline scores on BDI, BDI-II and HAMD-17 differed among patients with GAD, SAD, and PD. The pooled means are reported in Table 1. The difference between the three disorders was significant for the HAMD-17, indicating that baseline severity was lowest for SAD. There was also a

trend ($p < 0.1$) towards significance for the BDI suggesting that baseline depression was lower in SAD. However, the number of studies was very small in some subgroups for BDI-II and HAMD-17. Scores between 10 and 18 on BDI indicate mild to moderate (Beck *et al.* 1988), so on average patients with all three anxiety disorders fell into this category.

When we included the studies on MDD in these subgroup analyses, we found that all baseline severity scores were higher in studies in depression than in the anxiety disorders, and that was true for BDI, BDI-II and HAMD-17.

Heterogeneity was very high in most analyses with larger samples of studies, as is typically the case when pooling absolute numbers (Higgins & Green, 2011, sections 9.4.4. and 9.4.8). However, because of these significant baseline differences we decided to add baseline scores in the multivariate analyses examining whether the effect sizes of the therapies differed across disorders (see below).

Differential outcomes on depression of trials across GAD, SAD and PD

We tested whether the effects of therapies on depression differed across the three anxiety disorders (Table 2). A forest plot of the effects of the therapies is given in Fig. 2. When we pooled all three depression

Table 2. Relative effects of cognitive and behavioural therapies for GAD, SAD, PD and MDD on depression: Hedges' g^a

	N_{comp}	g	95% CI	MD	95% CI	I^2	95% CI	p^b	NNT
All depression measures				– ^c				0.13/0.35	
GAD	21	0.68	0.53–0.82			12	0–48		2.70
SAD	19	0.79	0.53–1.04			71	50–81		
PD	28	0.47	0.21–0.73			73	59–81		3.85
MDD	42	0.81	0.67–0.94			64	47–73		2.30
Only low risk of bias				– ^c				0.45/0.59	
GAD	6	0.53	0.31–0.76			25	0–70		3.42
SAD	4	0.59	0.20–0.98			65	0–86		3.09
PD	2	0.85	0.30–1.40			45	NA ^d		2.21
MDD	19	0.75	0.57–0.93			65	36–77		2.48
BDI								0.12/0.09	
GAD	16	0.83	0.66–1.00	6.14	4.88–7.39	0	0–45		2.26
SAD	11	0.69	0.42–0.97	5.12	3.63–6.61	48	0–73		2.67
PD	26	0.48	0.21–0.74	4.10	2.06–6.14	73	59–81		3.76
MDD	21	0.85	0.63–1.08	7.69	5.88–9.50	65	39–77		2.21
BDI, only between 19 and 29 ^e								0.19/0.09	
GAD	5	0.84	0.52–1.16	7.02	4.51–9.53	0	0–64		2.23
PD	7	0.28	–0.29 to 0.85	2.89	–3.13 to 8.90	74	27–86		6.41
MDD	20	0.84	0.60–1.07	7.52	5.66–9.38	66	40–78		2.23
BDI-II								0.001/0.07	
GAD	5	0.36	0.15–0.58	3.11	1.27–4.94	0	0–64		5.00
SAD	4	1.20	0.33–2.06	9.71	4.30–15.11	87	62–93		1.66
MDD	14	0.82	0.68–0.96	9.20	7.11–11.28	0	0–47		2.28
HAMD-17								0.02/0.07	
GAD	5	0.83	0.41–1.24	4.98	2.96–7.00	51	0–80		2.26
SAD	4	0.79	0.58–1.00	3.40	0.37–6.42	85	48–92		
PD	4	–0.09	–0.88 to 0.70	–0.39	–5.13 to 4.35	80	13–90		[20.00]
MDD	22	0.79	0.58–1.00	4.91	3.46–6.36	74	58–82		2.36

GAD, Generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; MDD, major depressive disorder; BDI, Beck Depression Inventory; HAMD-17, Hamilton Depression Rating Scale; CI, Confidence interval; MD, mean difference (not standardized); N_{comp} , number of comparisons; NNT, number needed to treat.

^a According to the random effects model.

^b The first p value in this column indicates whether the difference between the effect sizes among GAD, SAD, panic disorder and MDD is significant; in the second p value MDD is not included (comparison only among anxiety disorders).

^c The mean difference is only meaningful when one instrument is used (because it gives the exact points for this instrument).

^d The 95% CI of I^2 cannot be calculated when the number of studies is ≤ 2 .

^e No study on social anxiety disorder using the BDI as outcome instrument was available.

outcome measures, we found no significant difference across the three disorders ($p = 0.35$). This was also true when we limited the analyses to studies with a low risk of bias, although the number of studies was small. When we looked at the three depression instruments separately, we also found no significant differences across the anxiety disorders. There was a trend, however, suggesting that the effects of therapy in PD may be smaller than in the other anxiety disorders (BDI: $p = 0.09$; HAMD-17: $p = 0.07$). For BDI-II there was also a trend ($p = 0.07$) suggesting that the effects in SAD were larger than those in GAD.

Because baseline severity was lower in the anxiety disorders than in MDD, we selected the studies using

the BDI in which baseline severity was comparable to those in the MDD studies (a mean baseline BDI score between 19 and 29, suggesting moderate to severe depression (Beck *et al.* 1988). There was a trend ($p = 0.09$) suggesting that treatment of anxiety resulted in larger effects in GAD than in PD. Unfortunately, no studies in SAD were available in which the baseline BDI score was between 19 and 29.

Comparison of treatment of anxiety disorders with that of MDD

First, we compared the pooled effects on depression of the three anxiety disorders and compared these with

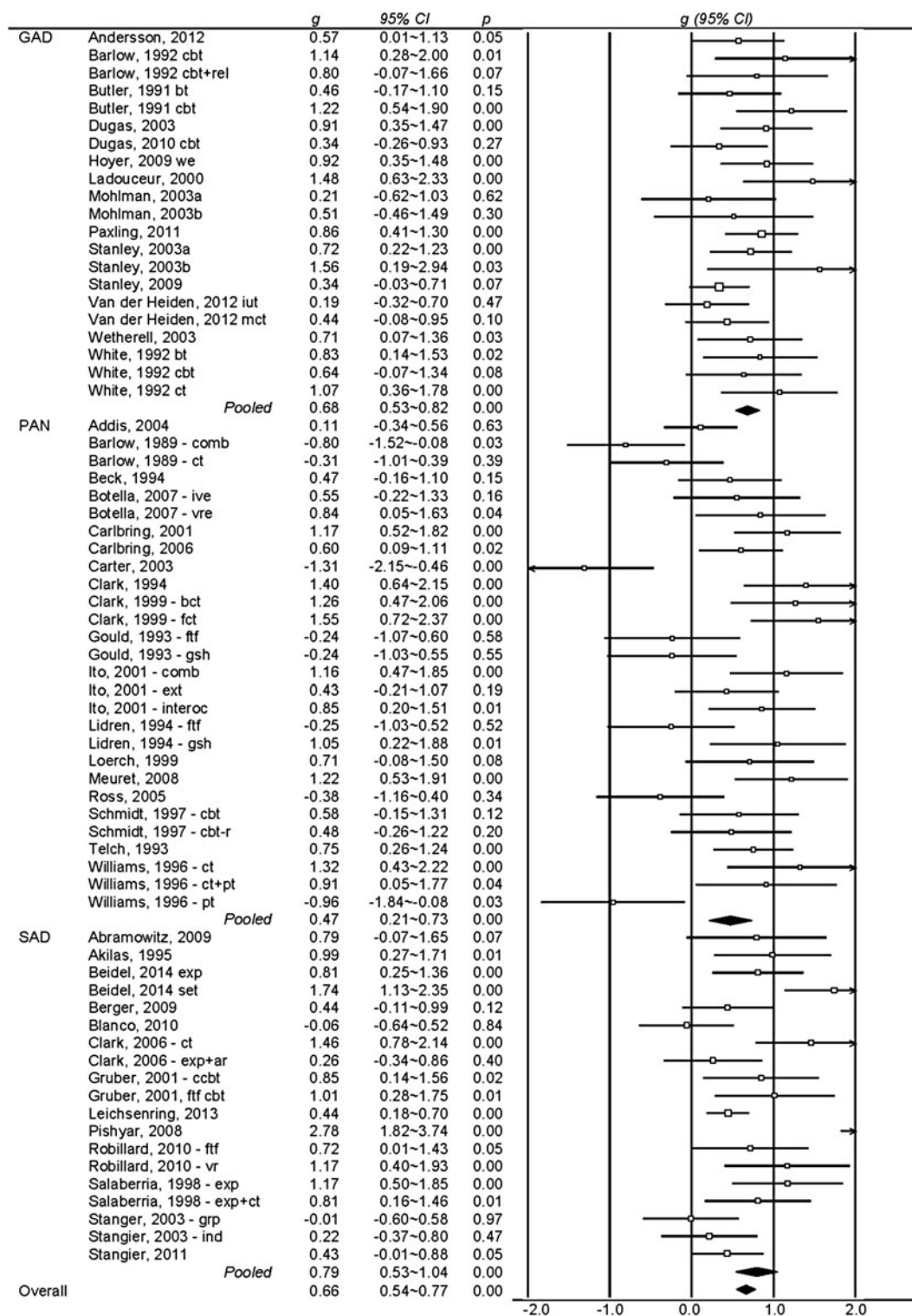


Fig. 2. Forest plot of effects of treatment of anxiety disorders on depression: Hedges' *g*.

the effects from the depression studies. The results are presented in Table 3. As can be seen, the difference between treatments of anxiety disorders and treatments of depression was small, but significant ($p=0.04$), with the effects of anxiety treatments on depression

being somewhat smaller ($g=0.61$, 95% CI 0.49-0.74) than depression treatments ($g=0.81$, 0.67-0.94). Heterogeneity was moderate to high in both groups of studies ($I^2=62$ and 64, respectively). This difference was not significant anymore, however, when we only

Table 3. Comparative effects of treatment of anxiety disorders on depression, compared with treatment of MDD: Hedges' g^a

	N_{cmp}	g	95% CI	MD	95% CI	I^2	95% CI	p^b	NNT
All depression measures									
All anxiety disorders	68	0.64	0.51–0.77	– ^c		62	49–70	0.09	2.86
MDD	42	0.81	0.67–0.94	– ^c		64	47–73		2.30
Only low risk of bias									
All anxiety disorders	12	0.59	0.40–0.77	– ^c		42	0–69	0.22	3.09
MDD	19	0.75	0.57–0.93	– ^c		65	36–77		2.48
BDI									
All anxiety disorders	53	0.64	0.49–0.80	4.95	3.69–6.22	62	47–71	0.13	2.86
MDD	21	0.85	0.63–1.08	7.69	5.88–9.50	65	39–77		2.21
BDI, only between 19 and 29									
All anxiety disorders	12	0.52	0.15–0.89	4.91	1.61–8.21	66	25–80	0.15	3.50
MDD	20	0.84	0.60–1.07	7.52	5.66–9.38	66	40–78		2.23
BDI-II									
All anxiety disorders	9	0.65	0.33–0.97	6.03	2.98–9.08	71	30–84	0.34	2.82
MDD	14	0.82	0.68–0.96	9.20	7.11–11.28	0	0–47		2.28
HAMD-17									
All anxiety disorders	13	0.52	0.14–0.90	2.81	0.75–4.87	80	64–87	0.22	3.50
MDD	22	0.79	0.58–1.00	4.91	3.46–6.36	74	58–82		2.36

MDD, Major depressive disorder; BDI, Beck Depression Inventory; HAMD-17, Hamilton Depression Rating Scale, CI, Confidence interval; MD, mean difference (not standardized); N_{cmp} , number of comparisons; NNT, number needed to treat.

^a According to the random effects model.

^b The p value in this column indicates whether the difference between the effect sizes across depression and anxiety disorders is significant.

^c The mean difference is only meaningful when one instrument is used (because it gives the exact points for this instrument).

looked at studies with low risk of bias ($p = 0.22$). When we looked at each of the three instruments separately, we found no significant difference between anxiety and depression treatments, except for the HAMD-17 ($p = 0.04$). When we limited the anxiety treatment studies to those in which patients had moderate to severe depression at baseline (BDI: 19–29), we also found no significant difference between anxiety and depression treatments.

Second, we conducted subgroup analyses in which we entered each of the anxiety disorders separately and compared them with MDD (results are presented in Table 2). When all depression measures were pooled there was no significant difference between the treatments for the four disorders, and that was also true when the analyses were limited to studies with low risk of bias. When we limited the analyses to each of the three specific depression measures, we found no significant difference for BDI, but we did find these for the BDI-II and HAMD-17. For the BDI-II the results suggested larger effects for SAD and smaller effects for GAD ($p = 0.001$). For HAMD-17 the results suggested that the effects for SAD were smaller and those for panic were not significantly different from zero. However, the number of studies in each of the groups

was small and heterogeneity was considerable in several of the subgroups. These results should, therefore, be considered with caution.

Within-group effect sizes

The within-group effect sizes of the treatments of anxiety disorders and MDD are given in Table 4. As can be seen the effect sizes did not differ between the three anxiety disorders, but they were highly significant when MDD was included ($p < 0.001$), with considerably larger effect sizes for MDD than for the anxiety disorders. The same pattern of no significant difference among the three anxiety disorders and the significant difference when MDD was added as a subgroup, was also found when we limited the studies to those with low risk of bias, and also when we looked at the BDI, BDI-II and HAMD-17 separately, as well as with the studies in which the patients with anxiety disorders scored between 19 and 29 on the BDI.

Multivariate meta-regression analyses

We conducted multivariate regression analyses with the effects of treatment on depression as the dependent

Table 4. Within group effect sizes of treatment of anxiety disorders on depression, compared with treatment of MDD: Hedges' g^a

	N_{cmp}	g	95% CI	MD	95% CI	I^2	95% CI	p^b	NNT
All depression measures				– ^c				<0.001/0.20	
GAD	21	0.87	0.76–0.98			55	16–71		2.16
SAD	19	0.73	0.57–0.89			78	65–85		2.54
PD	28	0.91	0.78–1.05			62	40–74		2.08
MDD	42	1.50	1.31–1.69			90	88–92		1.40
Only low risk of bias								<0.001/0.12	
GAD	6	0.93	0.76–1.10			56	0–80		2.04
SAD	4	0.65	0.38–0.93			77	0–90		2.82
PD	2	1.30	0.61–2.00			81	– ^d		1.56
MDD	19	1.52	1.21–1.83			94	93–95		1.39
BDI								<0.001/0.09	
GAD	16	0.81	0.65–0.98	7.01	5.42–8.60	66	35–79		2.30
SAD	11	0.70	0.53–0.87	5.99	4.38–7.54	53	0–75		2.63
PD	26	0.94	0.80–1.08	7.76	6.82–8.70	63	39–75		2.02
MDD	21	1.47	1.25–1.69	12.61	11.43–13.80	79	68–85		1.42
BDI, only between 19–29 ^e								<0.001/0.30	
GAD	5	0.97	0.65–1.30	8.74	6.16–11.33	69	0–86		1.97
PD	7	0.78	0.62–0.94	9.28	7.60–10.95	0	0–58		2.39
MDD	20	1.49	1.26–1.72	12.45	11.27–13.62	80	70–86		1.41
BDI-II								0.01/0.53	
GAD	5	0.94	0.75–1.13	9.00	6.29–11.71	64	0–84		2.02
SAD	4	0.79	0.37–1.21	8.55	3.89–13.22	83	40–92		2.36
MDD	14	1.31	1.14–1.47	13.81	10.64–16.98	59	11–76		1.55
HAMD-17								<0.001/0.68	
GAD	5	0.82	0.43–1.22	5.22	2.81–7.63	80	38–90		2.28
SAD	4	0.74	0.26–1.22	3.60	1.48–5.71	91	79–95		2.50
PD	4	0.61	0.32–0.90	4.26	2.01–6.51	51	0–82		2.99
MDD	22	1.72	1.39–2.04	9.92	7.62–12.22	94	92–95		1.29

GAD, Generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; MDD, major depressive disorder; BDI, Beck Depression Inventory; HAMD-17, Hamilton Depression Rating Scale; CI, Confidence interval; MD, mean difference (not standardized); N_{cmp} , number of comparisons; NNT, Number needed to treat.

^a According to the random effects model.

^b The first p value in this column indicates whether the difference between the effect sizes among GAD, SAD, panic disorder and MDD is significant; in the second p value MDD is not included (comparison only among anxiety disorders).

^c The mean difference is only meaningful when one instrument is used (because it gives the exact points for this instruments).

^d The 95% CI of I^2 cannot be calculated with less than three studies.

^e No study on social anxiety disorder using the BDI as outcome instrument was available.

variable. In the first model we pooled all trials on anxiety disorders and tested whether the effects on depression differed from the studies on MDD (dummy variable). In these analyses we adjusted for characteristics of the participants (mean baseline depression severity, type of recruitment, target group), the treatments (format, number of sessions) and the study (risk of bias, type of control group, and country where the study was conducted). The results of these analyses are presented in Table 5. As can be seen there was a non-significant trend suggesting that the effects of treatment of MDD on depression was larger than treatment of anxiety disorders ($p < 0.1$).

In the second multivariate meta-regression model we entered dummy variables for each of the anxiety disorders separately, while using MDD as the reference group, and we adjusted for the same variables as in the first model. As can be seen in Table 5, we found that the effects of treatment of PD on depression was significantly smaller than the effects of treatment of depression. The effects of treatment of GAD and SAD was not significantly smaller than treatment of depression.

In the third model, we did not include MDD and entered a dummy variable for each of the anxiety disorders (with GAD as reference). As can be seen, we found no significant difference for the three anxiety

Table 5. Standardized regression coefficients of characteristics of studies on cognitive and behavioural treatments of anxiety disorders on depression and of depression: Multivariate meta-regression analyses

	Model 1: All anxiety disorders <i>v.</i> MDD			Model 2: Separate anxiety disorders and MDD			Model 3: Separate anxiety disorders, no MDD		
	Coeff.	95% CI	<i>p</i>	Coeff.	95% CI	<i>p</i>	Coeff.	95% CI	<i>p</i>
Anxiety <i>v.</i> depressive disorder	2.61	-1.43 to 6.64	0.20						
Disorder				Ref.					
							Ref.		
				-1.64	-6.04 to 2.75	0.46			
				-1.51	-6.70 to 3.68	0.56	1.25	-3.96 to 6.45	0.63
				-3.83	-8.30 to 0.65	0.09	-1.59	-5.85 to 2.67	0.46
Risk of bias (continuous)	-0.50	-1.50 to 0.51	0.33	-0.76	-1.81 to 0.30	0.16	-1.25	-2.72 to 0.23	0.10
Baseline depression severity	0.21	-0.06 to 0.49	0.13	0.23	-0.06 to 0.51	0.12	0.19	-0.20 to 0.57	0.33
Recruitment				Ref.					
				-1.32	-4.84 to 2.20	0.46	0.27	-4.13 to 4.66	0.90
				2.21	-2.18 to 6.60	0.32	2.84	-3.64 to 9.32	0.38
Target group				Ref.					
				-2.91	-9.81 to 3.99	0.40	-2.72	-10.62 to 5.18	0.49
				-4.70	-9.86 to 0.47	0.07	-10.92	-19.66 to 2.18	0.02
Format				Ref.					
				-1.60	-4.50 to 1.29	0.27	-2.53	-6.08 to 1.03	0.16
				-1.87	-5.70 to 1.96	0.33	-0.69	-5.73 to 4.34	0.78
				-0.64	-5.61 to 4.34	0.80	2.05	-7.52 to 11.61	0.67
N sessions (continuous)	-0.13	-0.42 to 0.16	0.39	-0.15	-0.45 to 0.14	0.30	-0.15	-0.51 to 0.21	0.40
Control group				Ref.					
				-1.17	-4.97 to 2.63	0.54	0.07	-6.93 to 7.07	0.98
				-2.09	-7.90 to 3.71	0.47	-1.88	-9.15 to 5.39	0.61
				-0.89	-5.56 to 3.78	0.71	-1.83	-11.75 to 8.09	0.71
Country				Ref.					
				-0.51	-2.84 to 1.83	0.67	-0.69	-3.58 to 2.19	0.63
				-1.32	-5.09 to 2.46	0.49	-1.44	-7.15 to 4.26	0.61
Intercept	5.85	-1.17 to 12.87	0.10	8.95	-1.53 to 19.43	0.09	8.17	-2.55 to 18.89	0.13

MDD, Major depressive disorder; GAD, Generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; Coeff., regression coefficient; CI, confidence interval.

disorders on depression ($p > 0.1$), but that may be related to the small number of studies.

Discussion

In this meta-analysis we examined the effects of cognitive behavioural treatments of three major anxiety disorders, GAD, SAD and PD, on depression. We found that baseline severity of depression differed across the three anxiety disorders, with the highest levels of baseline depression for GAD, and the lowest for SAD, but this did not reach levels of significance for all depression measures. When compared with depression trials, baseline depression severity was significantly lower in all three anxiety disorders. However,

the average BDI score in the trials on anxiety disorders indicated that participants were mildly to moderately depressed, and there was a considerable number of studies in which patients had moderate to severe depression. These findings once more illustrate that comorbid depression is an important problem in anxiety disorders, which is in line with the well-established high levels of co-morbidity of anxiety disorders and depression.

We also found that the effects of treatments of anxiety disorders on depression were overall moderate to large, and limiting the analyses to studies with low risk of bias did not affect these overall outcomes very much. It could be possible that this is an indirect effect, in which a reduction of anxiety results in lower

levels of depression. It is also possible, however, that there is a direct effect of the treatments on depression, and that the same techniques that improve anxiety symptoms also improve depression. These findings are in line with earlier meta-analyses of each of the anxiety disorders, showing that these treatments also have considerable effects on depression (Mitte, 2005; Hunot *et al.* 2007; Acarturk *et al.* 2009; Sánchez-Meca *et al.* 2010; Cuijpers *et al.* 2014).

We found few indications that the effects of the treatments on depression differed consistently across the three anxiety disorders. The findings differed for each of the depression measures that were used, but these findings were obscured by high levels of heterogeneity and small numbers of studies in some categories. The overall analyses, bivariate and multivariate, suggested that no major differences existed between the effects on depression of the treatments for the three anxiety disorders. These findings should be considered with caution, because not finding a significant difference is no evidence for the absence of a difference, and the results could be related to the small number of trials in some comparisons and heterogeneity in the analyses.

However, the notion that there are no or only relatively small differences is interesting. It suggests that the effects of treatment of anxiety disorders on depression occur across disorders and can be seen as support for a transdiagnostic treatment approach in which the same treatment is given to patients with different disorders (Craske, 2012). If treatment of an anxiety disorder also improves depression, maybe a specific focus on this disorder may not be needed and the specific diagnosis may not be so relevant for the content of the treatment. A growing number of randomized trials find that transdiagnostic therapies are indeed effective in the treatment of depression and anxiety disorders (Newby *et al.* 2015). Our findings however cannot be seen as sufficient evidence for supporting transdiagnostic treatments, as these findings could also be seen as indirect effects and it would be needed to show that CBT interventions for anxiety reduce depression in a sample of only depressed individuals (and that CBT interventions for MDD work with PD, SAD, and GAD). Moreover, one could also argue that specific treatments aimed at specific disorders in specific ways may not be mandatory for the treatments to be effective, if any of these treatments results in effects similar to what we found in this meta-analysis. We also could challenge the idea of diagnoses in general because they are not only highly co-morbid, but also respond to the same treatments.

We also compared treatments for MDD with treatments for anxiety disorders, and found some indications that treatment of MDD has somewhat larger effects than treatments of anxiety disorders, especially

in the within-group effect sizes. However, the controlled effect sizes were relatively small and were no longer significant after adjusted for other characteristics. We found some indications that the effects of treatment of PD on depression are somewhat smaller than those of treatments of GAD, SAD and MDD. Overall these results can also be seen as support of transdiagnostic treatments.

There are several limitations of this meta-analysis. First, the number of trials was relatively small for several subgroup analyses, especially when considering the three depression outcome measures separately. Finding no difference while the number of studies is small cannot be considered as evidence that there is no difference. Furthermore, risk of bias was considerable in most of the included studies. Although we found no association between risk of bias and outcome, the results should be considered with caution because of this. Another limitation is that most of our results are based on subgroup and meta-regression analyses. The outcomes of these analyses are indirect and can only point at possible differences between studies, and new randomized trials are needed to confirm such findings. We also examined only short-term effects of treatments, because most studies did not report longer-term outcomes and the studies that did report them used many different follow-up periods, making comparisons impossible. We should also acknowledge that the treatments differed considerably across disorders. Although we limited this meta-analysis to studies on cognitive behaviour therapies, this is still a very broad category with many different types of treatment. Because of these limitations, the results of this meta-analysis should be considered with caution.

Despite these limitations we can conclude that patients participating in trials of treatments of anxiety disorders have high levels of depression, that these treatments have moderate to large effects on depression, that these effects are probably comparable across GAD, SAD and PD, and that they are comparable to those of direct treatments of depression.

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Supplementary material

The supplementary material for this article can be found at <http://dx.doi.org/10.1017/S0033291716002348>.

Declaration of Interest

None.

References

- Acarturk C, Cuijpers P, van Straten A, de Graaf R (2009). Psychological treatment of social anxiety disorder: a meta-analysis. *Psychological Medicine* **39**, 241–254.
- Beck AT, Steer RA, Brown GK (1996). *BDI-II, Beck Depression Inventory: Manual*. Psychological Corporation: San Antonio, TX.
- Beck AT, Steer RA, Carbin MG (1988). Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clinical Psychology Review* **8**, 77–100.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.
- Beutel ME, Scheurich V, Knebel A, Michal M, Wiltink J, Graf-Morgenstern M, Tschan R, Milrod B, Wellek S, Subic-Wrana C (2013). Implementing panic-focused psychodynamic psychotherapy into clinical practice. *Canadian Journal of Psychiatry* **58**, 326–334.
- Craske MG (2012). Transdiagnostic treatment for anxiety and depression. *Depression and Anxiety* **29**, 749–753.
- Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry* **58**, 376–385.
- Cuijpers P, Donker T, Weissman MM, Ravitz P, Cristea IA (2016). Interpersonal psychotherapy for mental health problems: a comprehensive meta-analysis. *American Journal of Psychiatry* **173**, 680–687.
- Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G (2014). Psychological treatment of generalized anxiety disorder: a meta-analysis. *Clinical Psychology Review* **34**, 130–140.
- Cuijpers P, van Straten A, Warmerdam L, Andersson G (2008). Psychological treatment of depression: a meta-analytic database of randomized studies. *BMC Psychiatry* **8**, 36.
- Duval S, Tweedie R (2000). Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455–463.
- Ekers D, Webster L, Van Straten A, Cuijpers P, Richards D, Gilbody S (2014). Behavioural activation for depression: an update of meta-analysis of effectiveness and sub group analysis. *PLoS ONE* **9**, e100100.
- Goldberg DP, Krueger RF, Andrews G, Hobbs MJ (2009). Emotional disorders: cluster 4 of the proposed meta-structure for DSM-V and ICD-11. *Psychological Medicine* **39**, 2043–2059.
- Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.
- Hedges LV, Olkin I (1985). *Statistical Methods for Meta-Analysis*. Academic Press: Orlando, FL.
- Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC, Cochrane Bias Methods Group, Cochrane Statistical Methods Group (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* **343**, d5928–d5928.
- Higgins JPT, Green S (eds) (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003). Measuring inconsistency in meta-analyses. *British Medical Journal (Clinical Research Edition)* **327**, 557–560.
- Hunot V, Churchill R, Silva de Lima M, Teixeira V (2007). Psychological therapies for generalised anxiety disorder. *Cochrane Database of Systematic Reviews* **1**, CD001848.
- Ioannidis JPA, Patsopoulos NA, Evangelou E (2007). Uncertainty in heterogeneity estimates in meta-analyses. *British Medical Journal (Clinical Research Edition)* **335**, 914–916.
- Kraemer HC, Kupfer DJ (2006). Size of treatment effects and their importance to clinical research and practice. *Biological Psychiatry* **59**, 990–996.
- Milrod B, Leon AC, Busch F, Rudden M, Schwalberg M, Clarkin J, Aronson A, Singer M, Turchin W, Klass ET, Graf E, Teres JJ, Shear MK (2007). A randomized controlled clinical trial of psychoanalytic psychotherapy for panic disorder. *American Journal of Psychiatry* **164**, 265–272.
- Mitte K (2005). Meta-analysis of cognitive-behavioral treatments for generalized anxiety disorder: a comparison with pharmacotherapy. *Psychological Bulletin* **131**, 785–795.
- Moher D, Liberati A, Tetzlaff A, Altman DG (2009). The PRISMA Group. Preferred Reporting Items for Systemic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Medicine* **6**, e1000097.
- Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalglish T (2015). Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. *Clinical Psychology Review* **40**, 91–110.
- NICE (2011). *Generalised Anxiety Disorder and Panic Disorder in Adults: Management, Guidance and Guidelines*. National Institute for Health and Clinical Excellence: London.
- Orsini N, Bottai M, Higgins J, Buchan I (2006). *HETEROGI: Stata Module to Quantify Heterogeneity in a Meta-Analysis*. Stata Statistical Software Components.
- Sánchez-Meca J, Rosa-Alcázar AI, Marín-Martínez F, Gómez-Conesa A (2010). Psychological treatment of panic disorder with or without agoraphobia: a meta-analysis. *Clinical Psychology Review* **30**, 37–50.
- Siev J, Chambless DL (2007). Specificity of treatment effects: cognitive therapy and relaxation for generalized anxiety and panic disorders. *Journal of Consulting and Clinical Psychology* **75**, 513–522.