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Is it Beneficial to Add Pharmacotherapy to Cognitive-Behavioral Therapy when Treating Anxiety Disorders? A Meta-Analytic Review

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Abstract

In order to examine the benefit of adding pharmacotherapy to cognitive-behavioral therapy (CBT) for anxiety disorders, we searched for studies comparing CBT plus pharmacotherapy and CBT plus pill placebo for adults meeting DSM-III-R or DSM-IV diagnostic criteria for an anxiety disorder between the 1st available year and July 1, 2008. Of 874 studies that were initially considered, 11 studies were identified, representing 471 patients with post-acute completer data and 236 participants with follow-up completer data. CBT plus pharmacotherapy was generally more effective than CBT plus placebo at post-treatment for measures of anxiety disorder severity (Hedges' $g = 0.59$, 95% confidence interval: 0.29–0.90) and treatment response ($OR: 1.95$, 95% confidence interval: 1.25–3.03), but not at 6-month follow-up. Despite the relatively small number of studies, the fail-safe N suggested that the results are reliable. The largest effect sizes at post-treatment were found for panic disorder and generalized anxiety disorder. No differences were observed between self-report and clinician-administered measures. The reported effect sizes linearly decreased with publication year. In sum, there is preliminary evidence to suggest that adding pharmacotherapy to CBT is a useful short-term treatment strategy at least for some of the anxiety disorders.

Keywords

Psychotherapy; Pharmacotherapy; Combination Therapy; Treatment outcome; Placebo; Anxiety disorders; Meta-analysis

A large body of work indicates that cognitive-behavioral therapy (CBT) and pharmacological treatments are both effective interventions for anxiety disorders (Hofmann & Smits, 2008; Roy-Byrne & Cowley, 2002). CBT is an exposure-based approach aimed at helping patients reacquire a sense of safety around cues associated with anxiety disorders. To achieve this type of learning, CBT protocols, usually 12 to 15 weeks in length, emphasize education about anxiety psychopathology as well as repeated exposure to fear-eliciting cues, often in

combination with restructuring of false threat appraisals (Westra & Stewart, 1998). In contrast to CBT, pharmacological interventions aim to directly target biochemical pathways underlying the anxiety elicited by disorder-specific cues (Bourine & Lambert, 2002). Pharmacological agents that have demonstrated efficacy for a variety of anxiety disorders include selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants and benzodiazepines (Baldwin et al., 2005).

Although both treatment modalities are efficacious, there is clearly room for improvement (Hofmann & Smits, 2008; Roy-Byrne & Cowley, 2002). For example, a completer analysis of placebo-controlled trials showed an average effect size of 0.73 for continuous anxiety severity measures (Hofmann & Smits, 2008). One, perhaps natural, response to this reality has been the idea to add medication to CBT to improve its outcomes. It is generally believed that two effective treatment modalities that target different mechanisms of treatment change should be more effective than either modality alone (e.g., Barlow, Gorman, Shear, & Woods, 2000). In fact, between 55% and 95% of patients presenting for psychotherapy are on some type of anxiolytic medication (Wardle, 1990). However, there is little direct empirical evidence for this contention (Westra & Stewart, 1998). A direct comparison between CBT alone, pharmacotherapy alone, and combined treatment is complicated by placebo effects, attribution effects, and differences in therapist contact time. These complications can be avoided or minimized by conducting a comparison between CBT plus pharmacotherapy and CBT plus placebo for the treatment of anxiety disorders. Limiting the study selection to only randomized placebo-controlled studies further ensured that only high quality trials were included in the analyses.

Assuming that psychotherapy and pharmacotherapy have additive and synergistic effects, we predicted that combined CBT plus pharmacotherapy would be associated with greater effect-sizes at post-test and follow-up relative to CBT plus pill placebo for the anxiety disorders. We further examined publication year, assessment procedure (clinician-administered vs. self-report), number of treatment sessions, diagnosis, and medication class as possible moderator variables.

Methods

Data Sources

A variety of data sources were utilized to identify the studies used in the analyses. First, literature searches were conducted in PubMed, PsycInfo, and Cochrane databases between the 1st available year and July 1, 2008. The search terms *random*, *randomized*, *randomised*, and *clinical trial*, were used to identify randomized controlled studies. The following search terms were used to identify the CBT condition in each study: *cognitive-behavioral therapy*, *cognitive*, *behavioral*, *behavioural*, and *exposure*. The search was not limited to a strict CBT condition, but also included any studies with an exposure, behavioral, or cognitive component, given the common therapeutic mechanisms of change in these forms of therapy. The pharmacotherapy condition was identified through the terms *drug*, *medication*, *psychotropic*, or *pharmacotherapy*. The condition of combined CBT and pharmacotherapy was identified with the search terms *combination* or *combined*.

To identify studies of specific anxiety disorders, the following search terms were used: *Panic Disorder*, *Agoraphobia*, *PD*, *PDA*, *Social Phobia*, *Social Anxiety Disorder*, *SAD*, *Generalized Anxiety Disorder*, *GAD*, *Obsessive Compulsive Disorder*, *OCD*, *Specific Phobia*, *Simple Phobia*, *Post-traumatic Stress Disorder*, *PTSD*, *Acute Stress Disorder*, *ASD*, and *anxiety*. The search terms for the criterion were used for each independent search. For example, *drug** or *medication** and *anxiety** and *cognitive** or *behavioral** and *combined**, or *randomized**, was used as the initial search in each database. All subsequent searches followed the same format

using all possible sequencing of the search terms. Second, we conducted an extensive review of the reference lists in the relevant studies extracted from the database searches and existing review papers and chapters on combination therapy for anxiety disorders.

Selection Criteria

Studies were selected based on the following criteria: (1) included adult samples (ages 18–65) meeting DSM-III-R or DSM-IV diagnostic criteria for an anxiety disorder; (2) diagnoses must have been assessed through the use of a structured diagnostic instrument known to possess valid and reliable psychometric properties; (3) provided sufficient data to perform effect size analyses (i.e., means and standard deviations, *t* or *F* values, change scores, frequencies, or probability levels); (4) involved random assignment; and (5) employed psychometrically sound clinician administered measures or self-report questionnaires for clinical severity. Samples with children or geriatric individuals were excluded due to differences in CBT approaches for these groups.

Data Extraction

For each study, two of the authors (SGH, ATS) independently selected psychometrically sound measures of anxiety disorder severity (e.g., symptom severity, symptom frequency, and degree to which the symptoms interfere with daily functioning) and treatment response. In case of disagreement, the authors reached consensus through discussion. Two other individuals independently extracted the numerical data. Because the number of studies reporting on intent-to-treat analyses was small ($n = 2$; and insufficient for pooled analyses), we only extracted data from completer samples.

Effect Size Estimates

For continuous measures, we calculated the Hedges' *g* effect size and its 95% confidence interval. This effect size is a variation on Cohen's *d* that corrects for biases due to small sample sizes and is calculated using the following formula (Hedges & Olkin, 1985):

$$g = \frac{\bar{\Delta}_{CBT+Medication} - \bar{\Delta}_{CBT+Placebo}}{\sqrt{\frac{(n_{CBT+Medication}-1)S_{CBT+Medication}^2 + (n_{CBT+Placebo}-1)S_{CBT+Placebo}^2}{(n_{total}-2)}}} \times \left(1 - \frac{3}{4(n_{CBT+Medication} + n_{CBT+Placebo}) - 9}\right),$$

where $\bar{\Delta}$ is the mean pre- to posttreatment change, *SD* is the standard deviation of posttreatment scores, and *n* is the sample size. These controlled effect sizes may be conservatively interpreted with Cohen's (1988) convention of small (0.2), medium (0.5), and large (0.8) effects. For dichotomous measures, we calculated the odds ratio (OR) and its 95% confidence interval using the Cox Hinkley Miettinen Nurminen method (Miettinen & Nurminen, 1985). The odds ratio is a measure of the effect size that is defined as the ratio of the odds of treatment response occurring in the experimental condition to the odds of that event in the control condition,

$OR = \frac{p/(1-p)}{q/(1-q)}$, where *p* refers to the percent responders in the CBT plus pharmacotherapy condition and *q* to the percent responders in the CBT plus placebo condition. The effect size estimates (Hedges' *g* and *OR*, separately) were combined across studies to obtain a summary statistic. These were calculated with random effects models, which estimate the overall effect size assuming the studies included are only a sample of the entire population of studies (Hedges & Vevea, 1998).

Evaluation of Publication Bias

We computed the “fail-safe N ” (Rosenthal, 1991; Rosenthal & Rubin, 1988) for addressing the publication bias. The fail-safe N can be computed using the formula,

$$X = \frac{K(\bar{Z}^2 - 2.706)}{2.706}$$
, where K is the number of studies in the meta-analysis and $\bar{Z}$ is the mean Z obtained from the K studies. According to Rosenthal (Rosenthal, 1991), effect sizes may be considered robust if the required number of studies (X) to reduce the overall effect size to a non-significant level exceeds $5K + 10$.

Moderator Analyses

We examined whether the effect sizes varied as a function of study characteristics (study year, assessment procedure [self-report vs. clinician-rated], number of treatment sessions) or clinical characteristics (disorder, medication class). To examine differences in effect sizes as a function of categorical moderator variables we considered 95% confidence intervals. The effects of continuous moderator variables were examined using meta-regression analyses. All analyses were completed with the software program Comprehensive Meta-Analysis, Version 2 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

Results

Study Selection

Figure 1 illustrates our study selection process. Out of the 874 potential studies identified through our searches, 11 met our inclusion criteria and were included in this meta-analysis. Of the 11 studies, the most commonly studied disorder was panic disorder (PD; $n = 4$) followed by social anxiety disorder (SAD; $n = 3$), obsessive-compulsive disorder (OCD; $n = 2$), and generalized anxiety disorder (GAD; $n = 2$). No studies were identified that met our inclusion criteria for specific phobia, acute stress disorder, or post-traumatic stress disorder. Table 1 describes the characteristics of the studies included. Ten studies ($n = 485$) provided data for continuous measures of anxiety disorder severity at posttreatment, and three studies ($n = 127$) provided these data for the 6-month follow-up assessment. Eight studies ($n = 471$) provided data for response rate after the acute treatment phase, and 6 studies ($n = 236$) provided these data for 6-month follow-up assessment.

Evaluation of Study Criteria

Two authors (SGH, KJK) judged each trial on its quality using the following modified Jadad criteria (Jadad, Moore, Carroll, Jenkinson, Reynolds, Gavaghan, & McQuay, 1996): (1) the study was described as randomized; (2) participants were adequately randomized; (3) the study was described as double blind; (4) the method of double blinding was appropriate; and (5) a description of drop-outs and withdrawals was provided. One point was assigned for each criterion met. As can be seen in Table 1, the total scores for the study sample ranged from 2 to 4 with a median of 3 ($M = 2.91$; $SD = 0.51$) on the 0 to 5 scale. There was high inter-rater agreement ($\kappa = 1$).

Effects at Posttreatment

As can be seen in Figures 2 and 3, the random effects meta-analysis yielded an overall mean Hedges' g of .59 (95% CI : 0.29–0.90, $z = 3.79$, $p < .001$) for continuous measures of severity and an odds ratio of 1.95 (95% CI : 1.25–3.03, $z = 2.95$, $p < .05$) for treatment response.

Publication Bias

The effect size observed for measures of anxiety disorder severity corresponded to a z -value of 5.92 ($p < .001$), indicating 82 unpublished studies with a mean effect of zero would be necessary in order to nullify the observed effect (i.e. for the combined 2-tailed p -value to exceed 0.05), which is greater than the robust cut-off of 60. The fail-safe N for response rates was 14 ($z = 3.21$, $p < .05$), which is not larger than the robust cut-off of 50. These findings suggest that the effect sizes observed may only be robust for the continuous measures.

Moderators

Given the low sample size of studies that included response rates and follow-up data, we limited the moderator-analyses to acute-phase effect sizes (Hedges' g) for continuous measures of anxiety disorder severity.

Self-report vs. clinician-administered measures—We compared effect sizes for self-report measures of anxiety disorder severity with clinician-administered measures. Nine studies reported data from self-report measures of anxiety. The mean effect size for this pooled self-report data was Hedges' $g = .80$ (95% CI : 0.23–1.36, $z = 2.77$, $p < .05$). Eight studies reported clinician-administered measures of anxiety severity, and the effect size for this clinician-administered pooled data was Hedges' $g = .39$ (95% CI : 0.20–0.58, $z = 4.04$, $p < .001$). Again, both effect sizes showed a significant advantage of CBT plus pharmacotherapy over CBT plus placebo, and there were no significant differences between the effect sizes for self-report measures and those observed for clinician-administered measures.

Diagnostic group—We compared effect sizes for continuous measures of anxiety disorder severity across disorders. The largest effect size was observed for PD (Hedges' $g = .99$, 95% CI : 0.26–1.71, $z = 2.67$, $p < .05$), followed by GAD (Hedges' $g = .81$, 95% CI : 0.18–1.44, $z = 2.52$, $p < .05$). Non-significant effect sizes were observed for OCD (Hedges' $g = .36$, 95% CI : -0.08 – 0.79 , $z = 1.62$, $p = .11$), and SAD (Hedges' $g = .16$, 95% CI : -0.16 – 0.48 , $z = 1.00$, $p = .32$). The differences across diagnostic groups were not significant.

Medication class—Of the 11 studies included in the analyses, 3 administered benzodiazepines, 4 SSRIs, 2 buspirone (a serotonin receptor agonist) and 2 other medications (a tricyclic and a reversible MAOI). The effect size for CBT combined with benzodiazepines (Hedges' $g = 1.28$, 95% CI : 0.90–1.66, $z = 6.59$, $p < .0001$) was not significantly different from the effect size observed for buspirone (Hedges' $g = 0.52$, 95% CI : -0.10 – 1.14 , $z = 1.64$, $p = .10$), but was significantly more effective than CBT plus SSRIs (Hedges' $g = .20$, 95% CI : -0.10 – 0.50 , $z = 1.32$, $p = .19$), and tricyclics or rMAOIs (Hedges' $g = .32$, 95% CI : -0.01 – 0.65 , $z = 1.91$, $p = .057$).

Treatment length—The number of treatment sessions did not moderate the Hedges' g for anxiety disorder severity ($B = -0.01$, $SE = 0.01$, $p = 0.14$).

Publication year—Hedges' g was moderated by publication year ($B = -0.05$, $SE = 0.02$, $p = 0.003$) indicating that the effect size decreased linearly with time. This relationship is illustrated in Figure 5.

Effects at Follow-up

Only 3 studies included no-treatment follow-up data for continuous anxiety measures, therefore all follow-up analyses were conducted using data from the 6 studies that reported response rate follow-up data. The follow-up periods included in the analyses ranged from 5.75 months to 6 months (Median = 6; $M = 5.96$; $SD = 0.09$) and included data both from patients who received

post-study treatment and those who did not. For those studies that conducted more than one follow-up, data from the follow-up conducted closest to 6 months was included. The pooled odds ratio for treatment response at follow-up was .66 (95% *CI*: 0.26–1.67, $z = -0.87$, $p < .38$; see Figure 4).

Discussion

Combining pharmacotherapy and CBT is a popular strategy for treating anxiety disorders; between 55% and 95% of patients are estimated to receive such combination treatment (Wardle, 1990; Westra & Stewart, 1998). In order to examine whether CBT plus pharmacotherapy is more effective than CBT plus placebo for adult anxiety disorders, we performed a comprehensive literature review of randomized controlled trials. Our comprehensive search yielded 11 studies, including trials on panic disorder ($n = 4$), social anxiety disorder ($n = 3$), obsessive-compulsive disorder ($n = 2$), and generalized anxiety disorder ($n = 2$). The total number of patients for the analyses ranged between 236 (response rate analyses at follow-up) and 471 (response rate analyses at post-acute) participants. Our analyses had to be limited to completer data due to the very small sample of studies ($n = 2$) that reported intent-to-treat data.

Despite the relatively small total number of studies with completer data, the fail-safe *N* for the post-treatment completer analysis was 82, suggesting that the results are reliable. Furthermore, the majority of studies were of high quality as suggested by the Jadad scores. However, the lack of intent-to-treat data calls for an urgent need for more high-quality trials examining combination strategies.

Based on the available evidence, combined therapy appears to be effective among completers in the short term. The pooled effect size for the main outcome measures at the post-acute assessment for anxiety disorder severity was Hedges' $g = .59$, and the pooled OR was 1.95, indicating that CBT plus pharmacotherapy is more effective than CBT plus placebo in the short-term. However, a publication bias analysis suggests that the effect size may only be considered robust for continuous measures. No difference was observed in the effect sizes of the self-report measures and the clinician-administered measures. Finally, we detected a significant publication year bias, suggesting that more recent studies reported smaller effects than older studies. This latter finding might be due to more rigorous assessment methods in more recent studies.

Although the overall effect of combined CBT and pharmacotherapy over CBT and placebo was medium at post-acute treatment, no difference between these two treatment modalities was found at 6-month follow-up. Moreover, combined therapy was not equally effective for all anxiety disorders. Large average effects were found for panic disorder (Hedges' $g = .99$) and medium to large effects were found for generalized anxiety disorder (Hedges' $g = .81$), but only small and non-significant effect-sizes were found for obsessive-compulsive disorder and social anxiety disorder. Finally, we observed that the effect size for CBT combined with benzodiazepines was significantly greater than CBT combined with SSRIs, tricyclics, or rMAOIs. However, the number of trials included in these analyses is too small to draw any firm conclusions.

Previous meta-analyses have either been limited to only one disorder or have generally employed more liberal inclusion criteria (Furukawa, Watanabe, & Churchill, 2006; Mitte, Noack, & Hautzinger, 2005; Abramowitz, 1997; Rodebaugh, Holaway, & Heimberg, 2004; Bandelow, Seidler-Brandler, Becker, Wedekind, & Ruther, 2007). Accordingly, it is difficult to compare our findings to those reported in these previous studies. A recent meta-analytic review of randomized placebo controlled studies of CBT for adult anxiety disorders indicated that CBT was the least effective for treating generalized anxiety disorder and panic disorder

with average effect sizes of Hedges' $g = 0.51$ and Hedges' $g = 0.35$, respectively (Hofmann & Smits, 2008). Therefore, it is perhaps not surprising to see that the greatest efficacy for combination interventions was observed for these two anxiety disorders.

Several additional limitations deserve mention. First, the sample of studies included in this meta-analysis was of high quality, but relatively small. The fail-safe analysis suggests that the results are reliable for the continuous measures. Nevertheless, the data have to be interpreted with caution. Second, most of the studies included in the analyses failed to report intent-to-treat analyses. We consider this to be the most puzzling result, given the long tradition of randomized controlled trials with CBT. Consequently, the findings had to be limited to completer data. It is certainly possible that the intent-to-treat effect sizes are significantly smaller. Third, few studies reported follow-up data for patients who had not received post-study treatment. Therefore, the follow-up responder rate analyses included data both from patients who received subsequent treatment as well as from those who did not. Given the confounding influence that treatment after the acute study phase may have on follow-up results, the results of this analysis should be interpreted with caution.

In sum, we conclude that medication may be a useful strategy for enhancing acute-phase CBT outcomes, especially for panic disorder and generalized anxiety disorder. Less support exists for combination therapy for obsessive-compulsive disorder and social anxiety disorder. Furthermore, the findings to date do not support the use of this strategy for maximizing long-term CBT outcomes. In addition to a need for more clinical trials examining the efficacy of combination strategies across the different anxiety disorders, our study supports the examination of novel combination strategies that specifically target the mechanisms underlying the effects of CBT which may be more likely to improve long-term outcomes (Hofmann, 2007; Hofmann, Pollack, & Otto, 2006).

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References

- Abramowitz JS. Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. *Journal of Consulting and Clinical Psychology* 1997;65:44–52. [PubMed: 9103733]
- Appel S. Modifying solo performance anxiety in adult pianists. *Journal of Music Therapy* 1976;30:2–16.
- Bandelow B, Seidler-Brandler U, Becker A, Wedekind D, Rther E. Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. *World Journal of Biological Psychiatry* 2007;8:175–187. [PubMed: 17654408]
- Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bon A, Davidson JR, denBoer JA, Fineberg NA, Knapp M, Scott J, Wittchen HU. British Association for Psychopharmacology: Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2005;19:567–596. [PubMed: 16272179]
- Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine or their combination for panic disorder: a randomized controlled trial. *Journal of the American Medical Association* 2000;283:2529–2536. [PubMed: 10815116]
- Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* 1988;56:893–897. [PubMed: 3204199]

- Bond AJ, Winegrove J, Curran HV, Lader MH. Treatment of generalized anxiety disorder with a short course of psychological therapy, combined with buspirone or placebo. *Journal of Affective Disorder* 2002;72:267–271.
- Borenstein, M.; Hedges, L.; Higgins, J.; Rothstein, H. *Comprehensive meta-analysis*, version 2. Englewood, NJ: Biostat Inc.; 2005.
- Bourine M, Lambert O. Pharmacotherapy of anxiety disorder. *Human Psychopharmacology* 2002;17:383–400. [PubMed: 12457374]
- Clark DB, Agras WS. The assessment and treatment of performance anxiety in musicians. *American Journal of Psychiatry* 1991;148:598–605. [PubMed: 2018160]
- Cohen, J. *Statistical power analysis for the behavioral sciences*. Vol. 2. Hillsdale, NJ: Erlbaum; 1988.
- Cottraux J, Bouvard M, Defayolle M, Messy P. Validity and factorial structure of the compulsive activity checklist. *Behavior Therapy* 1988;19:45–53.
- Cottraux J, Mollard E, Bouvard M, Marks I, Sluys M, Nury AM, Douge R, Cialdella P. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. *International Clinical Psychopharmacology* 1990;5:17–30. [PubMed: 2110206]
- Davidson JRT, Foa EB, Huppert JD, Keefe FJ, Franklin ME, Compton JS, Zhao N, Connor KM, Lynch TR, Gadde KM. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Archives of General Psychiatry* 2004;61:1005–1013. [PubMed: 15466674]
- Davidson JRT, Miner CM, de Veauh Geiss J, Tupler LA, Colket JT, Potts NLS. The brief social phobia scale: a psychometric evaluation. *Psychological Medicine* 1997;27:161–166. [PubMed: 9122296]
- Derogatis, LR. *SCL-90 Administration, Scoring, and Procedures Manual for the Revised Version*. Baltimore, MD: John's Hopkins University Press.; 1997.
- Furukawa TA, Watanabe N, Churchill R. Psychotherapy plus antidepressant for panic disorder with or without agoraphobia. *British Journal of Psychiatry* 2006;188:305–312. [PubMed: 16582055]
- Gelder MG, Marks IM. Severe agoraphobia: a controlled trial. *British Journal of Psychiatry* 1966;112:309–319. [PubMed: 5939892]
- Gladso JA, Rapaport MH, McKinney R, Auerbach M, Hahn T, Rabin A, Oliver T, Hazen A, Judd LL. Absence of neuropsychologic deficits in patients receiving long-term treatment with alprazolam-XR for panic disorder. *Journal of Clinical Psychopharmacology* 2001;21:131–138. [PubMed: 11270908]
- Goldberg, DP. *Maudsley Monograph 21*. London: Oxford University Press; 1972. *The Detection of Psychiatric Illness by Questionnaire*.
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleishmann RL, Hill CL, Heninger GR, Carney DS. Yale-Brown Obsessive Compulsive Scale: Part 1. Development, use, and reliability. *Archives of General Psychiatry* 1989;46:1006–1011. [PubMed: 2684084]
- Hamilton M. The measurement of anxiety states. *British Journal of Medical Psychology* 1959;32:50–55. [PubMed: 13638508]
- Hedges, LV.; Olkin, I. *Statistical methods for meta-analysis*. New York, NY: Academic Press; 1985.
- Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. *Psychological Methods* 1998;3:486–504.
- Hohagen F, Winkelmann G, Rasche-Räuchle H, Hand I, König A, Münchau N, Hiss H, Geiger-Kabisch C, Käppler C, Schramm P, Rey E, Aldenhoff J, Berger M. Combination of behaviour therapy with fluvoxamine in comparison with behaviour therapy and placebo: results of a multicentre study. *British Journal of Psychiatry* 1998;35(suppl):71–80.
- Hofmann SG, Smits JAJ. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *Journal of Clinical Psychiatry* 2008;69:621–632. [PubMed: 18363421]
- Hofmann SG. Enhancing exposure-based therapy from a translational research perspective. *Behaviour Research and Therapy* 2007;45:1987–2001. [PubMed: 17659253]
- Hofmann SG, Pollack MH, Otto MW. Augmentation treatment of psychotherapy for anxiety disorders with d-cycloserine. *CNS Drug Rev* 2006;12:208–217. [PubMed: 17227287]
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clinical Trials* 1996;17:1–12.

- Kellner R, Sheffield BF. A self-rating scale of distress. *Psychological Medicine* 1973;3:88–100. [PubMed: 4692494]
- Liebowitz MR. Social Phobia. *Modern Problems in Pharmacopsychiatry* 1987;22:141–173.
- Marks, IM. *Maudsley Pocketbook of Management*. London: Institute of Psychiatry; 1986. Behavioural Psychotherapy.
- Marks, IM.; Hallam, R.; Connolly, J.; Philpott, R. *Nursing in behavioral psychotherapy. An advanced clinical role for nurses*. London and Tonbridge: Whitefriars Press; 1977.
- Marks IM, Mathews AM. Brief standard self-rating for phobic patients. *Behaviour Research and Therapy* 1979;17:263–267. [PubMed: 526242]
- Marks IM, Swinson RP, Başoğlu M, Kuch K, Noshirvani H, O'Sullivan G, Lelliott PT, Kirby M, McNamee G, Sengun S, Wickwire K. Alprazolam and exposure alone and combined in panic disorder with agoraphobia: a controlled study in London and Toronto. *British Journal of Psychiatry* 1993;162:776–787. [PubMed: 8101126]
- Miettinen OS, Nurminen M. Comparative analysis of two rates. *Statistical Medicine* 1985;4:213–226.
- Mitte K, Noack P, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *Journal of Clinical Psychopharmacology* 2005;25:141–150. [PubMed: 15738745]
- Guy, W.; Bonato, RR., editors. *National Institute of Mental Health. 028 CGI; Clinical Global Impressions, in Manual for the EDCEU Assessment Battery. Vol. 2. Chevy Chase, MD: 1976. p. 12-6.*
- Power KG, Simpson RJ, Swanson V, Wallace LA, Feistner ATC, Sharp DM. A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo alone and in combination, for treatment of generalized anxiety disorder. *Journal of Anxiety Disorders* 1990;4:267–292.
- Praško J, Dockery C, Horáček J, Houbová P, Kosová J, Klaschka J, Pašková B, Prašková H, Seifertová D, Záleský R, Höschl C. Moclobemide and cognitive behavioral therapy in the treatment of social phobia: a six-month controlled study and 24 months follow up. *Neuroendocrinology Letters* 2006;27:473–481. [PubMed: 16891998]
- Reiss S, Peterson RA, Gursky M, McNally RJ. Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. *Behaviour Research and Therapy* 1986;24:1–8. [PubMed: 3947307]
- Rodebaugh TL, Holaway RM, Heimberg RG. The treatment of social anxiety disorder. *Clinical Psychology Review* 2004;24:883–908. [PubMed: 15501560]
- Rosenthal, R. *Meta-analytic procedures for social research (rev. ed.)*. Thousand Oaks, CA: Sage Publications Inc.; 1991.
- Rosenthal R, Rubin DB. Comment: Assumptions and procedures in the file drawer problem. *Statistical Science* 1988;3:120–125.
- Roy-Byrne, PP.; Cowley, DS. Pharmacological treatments for panic disorder, generalized anxiety disorder, specific phobia, and social anxiety disorder. In: Nathan, PE.; Gorman, JM., editors. *A Guide To Treatments That Work. Vol. 2. New York, NY: Oxford University Press; 2002. p. 337-365.*
- Sharp DM, Power KG, Simpson RJ, Swanson V, Moodie E, Anstee JA, Ashfold JJ. Fluvoxamine, placebo, and cognitive behaviour therapy used alone and in combination in the treatment of panic disorder and agoraphobia. *Journal of Anxiety Disorders* 1996;10:219–242.
- Shear MK, Brown TA, Barlow DH, Money R, Gorman JM, Woods SW. Multicenter collaborative Panic Disorder Severity Scale. *American Journal of Psychiatry* 1997;154:1571–1575. [PubMed: 9356566]
- Snaith RP, Baugh SJ, Clayden AD, Husain A, Supple MA. The clinical anxiety scale: an instrument derived from the Hamilton Anxiety Scale. *British Journal of Psychiatry* 1982;141:518–523. [PubMed: 7150890]
- Spielberger, CD.; Gorsuch, RL.; Lushene, RE. *State-Trait Anxiety Inventory, Manual*. Palo Alto, CA: Consulting Psychologists Press; 1970.
- Spitzer, RL.; Williams, JB.; Gibbons, M. *The Structured Clinical Interview for the DSM-III-R*. Biometric Research Department. New York, NY: New York State Psychiatric Institute; 1984.
- Steptoe A, Fidler H. Stage fright in orchestral musicians: a study of cognitive and behavioral strategies in performance anxiety. *British Journal of Psychology* 1987;78:241–249. [PubMed: 3594093]
- Turner SM, Beidel DC, Dancu CV, Stanley MA. An empirically derived inventory to measure social fears and anxiety: the social phobia and anxiety inventory. *Psychological Assessment* 1989;1:35–40.

- Wardle J. Behaviour therapy and benzodiazepines: Allies or antagonists? *British Journal of Psychiatry* 1990;156:163–168. [PubMed: 1969321]
- Westra HA, Stewart SH. Cognitive behavioural therapy and pharmacotherapy: complementary or contradictory approaches to the treatment of anxiety? *Clinical Psychology Review* 1998;18:307–340. [PubMed: 9564583]
- Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavia* 1983;67:361–70.

Figure 1.
Study selection and reasons for exclusions.

Figure 2. Effect size estimates (Hedges' g) for primary continuous anxiety measures

Note: OCD = Obsessive-Compulsive Disorder; GAD = Generalized Anxiety Disorder; PDA = Panic Disorder with Agoraphobia; PD = Panic Disorder; SAD = Social Anxiety Disorder; PDSS = Panic Disorder Severity Scale (Shear et al., 1997).

Figure 3. Odds ratios for treatment response after acute treatment phase

Note: OCD = Obsessive-Compulsive Disorder; GAD = Generalized Anxiety Disorder; PDA = Panic Disorder with Agoraphobia; PD = Panic Disorder; SAD = Social Anxiety Disorder; Y-BOCS = Yale Brown Obsessive-Compulsive Scale (Goodman et al., 1989); CGI-I = Clinical Global Impressions Scale – Improvement (National Institute of Mental Health, 1976); CGI-S = Clinical Global Impressions Scale – Severity (National Institute of Mental Health, 1976).

Figure 4. Odds ratios for treatment response at follow-up

Note: OCD = Obsessive-Compulsive Disorder; GAD = Generalized Anxiety Disorder; PDA = Panic Disorder with Agoraphobia; PD = Panic Disorder; SAD = Social Anxiety Disorder; CGI-I = Clinical Global Impressions Scale Improvement (National Institute of Mental Health, 1976); CGI-S = Clinical Global Impressions Scale Severity (National Institute of Mental Health, 1976).

Figure 5.
Regression of Study Year on Hedges' g

Table 1

Characteristics of included studies

Study	Year	Disorder	Number of Tx Sessions	Medication	Total Sample Size	Anxiety Measures	Jadad Score
Bond et al.	2002	GAD	8	Buspirone	23	HADS - Anxiety HAM-A	2
Power et al.	1990	GAD	7	Diazepam	39	HAM-A SRT	3
Cottraux et al.	1990	OCD	24	Fluvoxamine	31	GHQ Target Rituals (self) Discomfort Duration per day Target Rituals (assessor) Discomfort Duration per day BAT CAC	3
Hohagen et al.	1998	OCD	48	Fluvoxamine	49	Y-BOCS CAS GAS CGIS-T CGIS-P SCL-90-R	3
Barlow et al.	2000	PD	12	Imipramine	92	PDSS CGI	3
Gladysjo et al.	2001	PD	12	Alprazolam-XR	38	STAI-state STAI-trait ASI	3
Marks et al.	1993	PDA	8	Alprazolam	64	Panic Attacks (per week) PQ Major Panic Attacks (per week) Spontaneous Panic Attacks (per week) Four phobic targets---avoidance level	3

Study	Year	Disorder	Number of Tx Sessions	Medication	Total Sample Size	Anxiety Measures	Jadad Score
Sharp et al.	1996	PDA	9	Fluvoxamine	62	CGI Disability--(work/social) HAM-A SRT FQ	2
Clark et al.	1991	SAD	5	Buspirone	15	Self-Statement Questionnaire PRCP	3
Davidson et al.	2004	SAD	14	Fluoxetine	88	BSPS CGI-S SPAI	4
Prasko et al.	2006	SAD	12	Moclobemide	46	LSAS CGI-S BAI	3

Note: GAD = Generalized Anxiety Disorder; OCD = Obsessive Compulsive Disorder; PD = Panic Disorder; PDA = Panic Disorder with Agoraphobia; SAD = Social Anxiety Disorder; ASI = Anxiety Sensitivity Index (Reiss et al., 1986); BAI = Beck Anxiety Inventory (Beck et al., 1988); BAT = Behavioural Avoidance Test (Marks et al., 1990); BSPS = Brief Social Phobia Scale (Davidson et al., 1997); CAC = Compulsive Activity Checklist (Marks et al., 1977; Cottraux et al., 1988); CAS = Clinical Anxiety Scale (Snaith et al., 1982); CGI = Clinician Global Improvement; CGI - S = Clinical Global Impressions Scale Severity; CGIS-T = Clinical Global Improvement Scale-Therapist assessed (NIMH, 1976); CGIS-P = Clinical Global Improvement Scale-Self assessed (NIMH, 1976); FQ = Fear Questionnaire (Marks & Mathews, 1979); GAS = Global Assessment Scale (Spitzer et al., 1984); GHQ = The Global Health Questionnaire (Goldberg, 1972); HADS Anxiety = Hospital Anxiety and Depression Scale Anxiety subscale (Zigmond & Snaith, 1983); HAM-A = Hamilton Anxiety Rating Scale (Hamilton, 1959); LSAS = Liebowitz Social Anxiety Scale (Liebowitz, 1987); PDSS = Panic Disorder Severity Scale (Shear et al., 1997); PRCP = Personal Report of Confidence as a Performer (Appel, 1976); PQ = Phobia Questionnaire (Marks & Mathews, 1979); SCL 90-R = Symptom Checklist 90 Revised (Derogatis, 1977); Self-Statement Questionnaire (Stephens & Fidler, 1987); SRT = Symptom Rating Test (Kellner & Sheffield, 1973); SPAI = Social Phobia Anxiety Inventory (Turner et al., 1989); STAI-trait = State Trait Anxiety Inventory Trait subscale (Spielberger et al., 1970); STAI-state = State Trait Anxiety Inventory State subscale (Spielberger et al., 1970); Y-BOCS = Yale Brown Obsessive Compulsive Scale (Goodman et al. 1989).