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Psychological and pharmacological treatments for generalized anxiety disorder (GAD): a meta-analysis of randomized controlled trials

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ABSTRACT

The purpose of this meta-analysis was to provide updated pooled effect sizes of evidence-based psychotherapies and medications for generalized anxiety disorder (GAD) and to investigate potential moderators of outcomes. Seventy-nine randomized controlled trials (RCT) including 11,002 participants with a diagnosis of GAD were included in a meta-analysis that tested the efficacy of psychotherapies or medications for GAD. Psychotherapy showed a medium to large effect size (g = 0.76) and medication showed a small effect size (g = 0.38) on GAD outcomes. Psychotherapy also showed a medium effect on depression outcomes (g = 0.64) as did medications (g = 0.59). Younger age was associated with a larger effect size for psychotherapy ($p < 0.05$). There was evidence of publication bias in psychotherapy studies. This analysis found a medium to large effect for empirically supported psychotherapy interventions on GAD outcomes and a small effect for medications on GAD outcomes. Both groups showed a medium effect on depression outcomes. Because medication studies had more placebo control conditions than inactive conditions compared to psychotherapy studies, effect sizes between the domains should not be compared directly. Patient age should be further investigated as a potential moderator in psychotherapy outcomes in GAD.

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GAD; meta-analysis: randomized controlled trial; generalized anxiety disorder; medication; therapy

Introduction

Generalized anxiety disorder (GAD) is characterized by worry about a number of events or activities that is excessive and difficult to control (American Psychiatric Association,

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2013). GAD is relatively common, with an estimated lifetime prevalence of 4.3% in the general population (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), and associated with marked impairment in role functioning and social life to a degree equivalent to major depression (Kessler, DuPont, Berglund, & Wittchen, 1999), as well as impairments in psychosocial functioning, role functioning, work productivity, and health-related quality of life (Revicki et al., 2012). GAD is also associated with increased health care utilization and medical costs. Marciniak et al. (2005) found that the total lifetime medical cost for individuals with any anxiety disorder was US$6475, and that a diagnosis of GAD was associated with an additional US$2138 total cost. Furthermore, there is evidence that GAD is associated with utilizing emergency departments as much as twice as often as patients with another Axis I diagnosis (Jones, Ames, Jeffries, Scarinci, & Brantley, 2001). Given the high cost and adverse outcomes associated with GAD, an updated critical comparison of the numerous available treatments is necessary.

Evidence-based psychotherapies have shown large effect sizes on GAD outcomes (Hedges' g = 0.80; Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016). Research has also supported the utility of pharmacological interventions for GAD. Specifically, a meta-analysis of 21 placebo-controlled studies yielded a small effect size (d = 0.39; Hidalgo, Tupler, & Davidson, 2007). Since these dates, new randomized controlled trials (RCT) are available for both psychotherapies and pharmacological interventions. Thus, there is a need to update the pooled effect sizes to reflect the addition of these trials to better understand the effects of these interventions on GAD.

Moreover, there are several candidates for moderators of GAD treatment outcomes. For example, there is some evidence that older age might lead to worse GAD treatment outcomes (Gonçalves & Byrne, 2012; Gould, Coulson, & Howard, 2012; Hendriks, Oude Voshaar, Keijsers, Hoogduin, & Van Balkom, 2008; Pinquart & Duberstein, 2007; Wetherell et al., 2013). Next, the prognostic effect of comorbid disorders on GAD outcomes is unclear, with some evidence that comorbidity is indicative of worse prognosis (Bruce et al., 2005) and some evidence that comorbidity in GAD is associated with larger treatment gains (Newman, Przeworski, Fisher, & Borkovec, 2010). A recent systematic review investigated a large number of potential treatment moderators of treatment for anxiety disorders and found little evidence for demographic variables, baseline symptom severity, or comorbidity as moderators (Schneider, Arch, & Wolitzky-Taylor, 2015). However, this study was not specific to GAD, only included 24 studies that compared at least two active treatments, and did not employ meta-analytic techniques.

The present investigation employed a meta-analytic approach to compare the effect of evidence-based psychotherapies and pharmacotherapy to control conditions. Both primary GAD outcomes and secondary depression outcomes were compared, and follow-up data were examined when available. We also explored a number of plausible moderators, including demographic variables (e.g. age, percent female), clinical variables (e.g. pretreatment severity, percent comorbid), and study variables (e.g. control type). Based on the extant literature, we hypothesized that psychotherapy would show a large effect size compared to waitlist and pill placebo conditions and a small effect size compared to treatment as usual or psychological control conditions (Cuijpers et al., 2016). We also hypothesized that medication would show a small effect size compared to controls (Hidalgo et al., 2007).

Method

Study selection

We selected RCT of both psychological and pharmacological treatment for GAD using a comprehensive search strategy. We searched the following databases: PsycINFO, PubMed, EBSCO, Web of Science, and Cochrane database of systematic reviews. We searched for articles on psychotherapy and pharmacotherapy for GAD from up until June 2017. The searches included the following terms: "cognitive behavioral, " "cognitive behavioral therapy," "acceptance and commitment therapy," "worry exposure," "psychotherapy," "pharmacotherapy," "pharmacology," "SSRIs," OR "benzodiazepines," in addition to "clinical trial" or "trial" alone; and in combination with "generalized anxiety disorder," or "GAD." These words were searched as key words, title, abstract, and Medical Subject Headings. We also examined citation maps and used the "cited by" search tools. These findings were cross-referenced with references from reviews. We included articles found in two existing meta-analyses examining CBT for GAD (Cuijpers et al., 2016) and pharmacotherapy for GAD (Hidalgo et al., 2007). Lastly, we asked colleagues from the United States of America and the Netherlands to identify any RCT for GAD that we had left out. These initial search strategies produced 846 potential articles. Examination of the abstracts identified 79 articles that met all inclusion criteria. The study selection process is depicted in Figure 1.

Inclusion criteria were as follows: (a) participants who met full DSM-III-R, DSM-IV, DSM-IV-TR, or DSM-5 criteria for GAD; (b) empirically supported psychotherapy, including cognitive-behavioral therapy, acceptance-based behavior therapy, applied relaxation, worry exposure, etc.; or empirically supported pharmacotherapy, including SSRIs, benzodiazepines, and other anxiolytics; (c) included a waitlist, treatment as usual, or pill placebo or psychological placebo control condition; and (d) studies that used validated measures of generalized anxiety. Studies meeting the following exclusion criteria were not selected for the current meta-analysis: (a) single case studies; (b) treatment conditions based on augmentation of psychological treatment; (c) studies of relapse prevention; (d) studies only treating patients who showed a response to the treatment; (e) studies with insufficient data unless study authors were able to provide such data; (f) studies with redundant data; and (g) studies on children. Studies were also imported from the extant meta-analyses (Cuijpers et al., 2016; Hidalgo et al., 2007). Of the 234 studies screened, 155 were excluded. Seventy-seven did not report on a GAD group specifically and four did not diagnose GAD according to the DSM-III-R, DSM-IV, DSM-IV-TR, or DSM-V. Sixty-one were not RCT. Thirty-eight had missing data; we attempted to contact the authors of these studies but were unable to either receive a response or obtain the relevant data. Twenty-eight studies did not provide a sufficient control condition. Twenty-two studies recruited nonresponders to treatment or relapse prevention. Four studies were excluded for a child population. In total, 79 studies with 11,002 participants met the final inclusion criteria and were included in the meta-analysis. Study characteristics are presented in Table 1.

Software

Analyses were completed with Comprehensive Meta-Analysis version 3.3070 (CMA; Biostat, 2014).

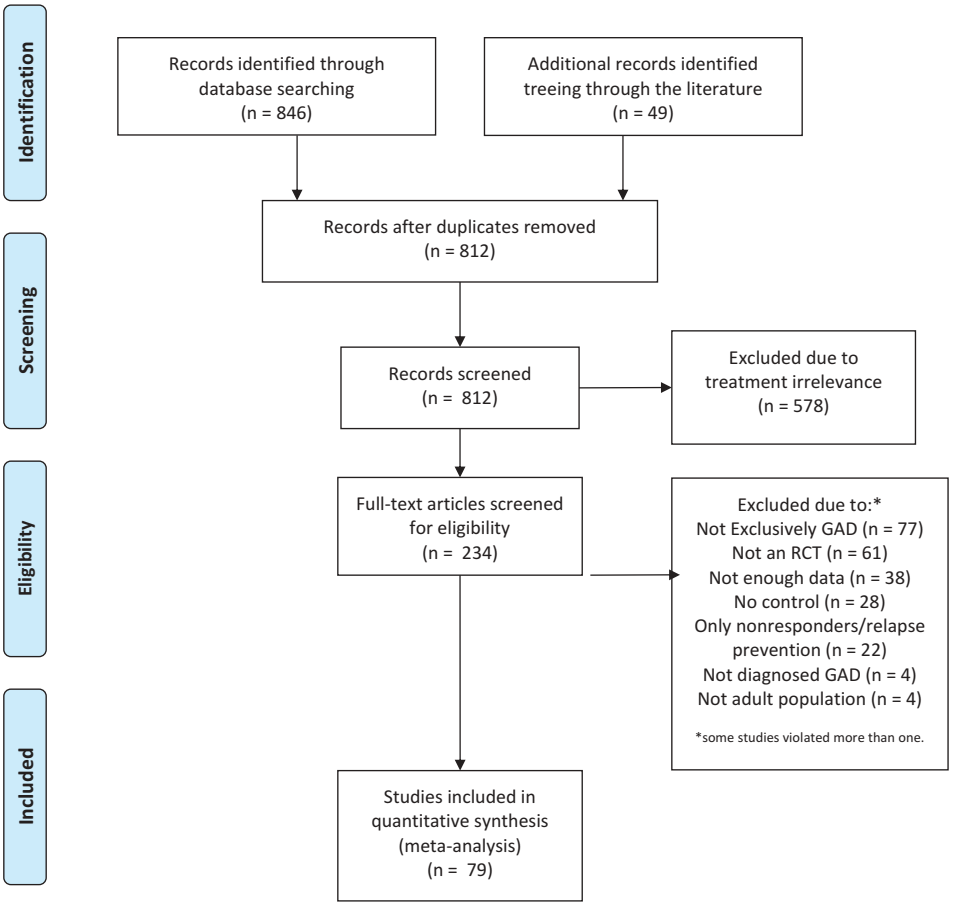

Figure 1. Flowchart of inclusion of studies.

Procedure

The primary outcome was reduction of GAD symptoms. The Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959), Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) and Penn State Worry Questionnaire—Abbreviated version (PSWQ-A; Hopko et al., 2003), Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988), and State-Trait Anxiety Inventory—Trait (STAI-T; Spielberger, Gorsuch, & Lushene, 1970) captured generalized anxiety outcome in all studies. Outcome data from the above measures were combined from each study using every measure available. The secondary outcome of this analysis was depression symptoms. Studies with multiple primary or secondary outcome measures had outcomes combined in the respective domain. Combined measures were given equal weight. Table 2 provides a complete list of included outcome measures.

Data on the following variables were also collected: treatment protocol (e.g. CBT, sertraline), treatment dose (i.e. number of sessions and/or medication dosage), year of publication, study quality (allocation sequence, concealment of allocation to conditions,

Table 1. Study characteristics.

Authors	Year	N[1]	Primary measure(s)	Secondary measure (s)	Primary outcome[2]
Alaka et al.	2014	291	HAM-A		Duloxetine > PP
Aliyev et al.	2008	74	HAM-A		Depakine-chrono > PP
Allgulander et al.	2001	268	HAM-A		Venlafaxine (37.5 mg) > PP
		260			Venlafaxine (75 mg) > PP
		261			Venlafaxine (150 mg) > PP
Allgulander et al.	2004	370	HAM-A	MADRS	Sertraline > PP
Bakhsani et al.	2007	13	BAI, HAM-A		Diazepam + tricyclic antidepressant > PP
		13			CBT > PP
Ball et al.	2015	226	HAM-A		Duloxetine > PP
Barlow et al.	1992	23	HAM-A, STAI-T	BDI, HAM-D	CT > WL
		20			Relaxation > WL
		21			CT + relaxation > WL
Bidzan et al.	2012	254	HAM-A		Vortioxetine > PP
Bonne et al.	2003	44	HAM-A, STAI-T	BDI, HAM-D	Homeopathic > PP
Borkovec et al.	1987	30	HAM-A, STAI-T	HAM-D	CT > Psych PL
Borkovec et al.	1993	36	HAM-A, PSWQ, STAI-T	BDI, HAM-D	AR > Psych PL
		38			CBT > Psych PL
Bowman et al.	1997	35	HAM-A, STAI-T		Self-examination therapy > WL
Brawman-Mintzer et al.	2006	326	HAM-A	MADRS	Sertraline > PP
Brenes et al.	2015	118	HAM-A, PSWQ	BDI	Telephone CBT > Psych PL
Butler et al.	1991	37	BAI, HAM-A, STAI-T	BDI	BT > WL
		38			CBT > WL
Connor et al.	2002	35	HAM-A		Kava kava < PP
Dahlin et al.	2016	85	BAI, PSWQ	MADRS, PHQ-9	Internet acceptance BT > WL
Darcis et al.	1995	110	HAM-A		Hydroxyzine > PP
Davidson et al.	1999	191	HAM-A		Buspirone > PP
		185			Venlafaxine (75 mg) > PP
		185			Venlafaxine(150 mg) > PP
Davidson et al.	2004	307	HAM-A	HAM-D	Escitalopram > PP
Davidson et al.	2008	70	HAM-A		Duloxetine > PP
Dugas et al.	2003	52	BAI, PSWQ	BDI	Group CBT > WL
Dugas et al.	2010	42	PSWQ, STAI-T	BDI-II	AR > WL
		43			CBT > WL
Durham et al.	1994	30	BAI, HAM-A, STAI-T	BDI	Analytic therapy high contact < Psych PL
		31			Analytic therapy low contact < Psych PL
		31			CT high contact > Psych PL
		36			CT low contact > Psych PL
Feltner et al.	2003	130	HAM-A	HAM-D	Lorazepam > PP
		135			Pregbalin (150 mg) > PP
		127			Pregbalin (600 mg) > PP
Gelenberg et al.	2000	238	HAM-A		Venlafaxine > PP
Gommoll et al.	2015	444	HAM-A	HAM-D	Vilazodone (20 mg) > PP
		444			Vilazodone (40 mg) > PP
Hackett et al.	2003	186	HAM-A		Diazepam > PP
		288			Venlafaxine (75 mg) > PP
		276			Venlafaxine (150 mg) > PP
Hartford et al.	2007	323	HAM-A		Duloxetine > PP
		325			Venlafaxine > PP
Hoge et al.	2013	89	BAI, HAM-A		MBSR > Psych PL
Hoyer et al.	2009	57	HAM-A, PSWQ, STAI-T	BDI, HAM-D	AR > WL
		58			Worry exposure > WL
Johnston et al.	2011	85	PSWQ	PHQ-9	Clinician-guided iCBT > WL
		88			Coach-guided iCBT > WL
Jones et al.	2016	41	PSWQ-A	PHQ-9	iCBT > WL
Kasper et al.	2009	249	HAM-A	HAM-D	Pregbalin > PP
		253			Venlafaxine > PP
Koszycki et al.	2010	22	BAI, HAM-A, PSWQ	BDI	CBT > Psych PL

(*Continued*)

Table 1. (Continued).

Authors	Year	N^1	Primary measure(s)	Secondary measure (s)	Primary outcome[2]
Lader et al.	1998	163	HAM-A	MADRS	Buspirone > PP
		162			Hydroxyzine > PP
Ladoucer et al.	2000	26	BAI, PSWQ	BDI	CBT > WL
Leichsenring et al.	2009	57	BAI, HAM-A, PSWQ, STAI-T	BDI	CBT > Psych PL
Lenze et al.	2009	177	HAM-A, PSWQ	HAM-D	Escitalopram > PP
Levy Berg et al.	2009	61	BAI		Affect-Focused Psychotherapy > TAU
Linden et al.	2005	72	HAM-A, STAI-T		CBT Group A > Psych PL
		72			CBT Group B > Psych PL
Llorca et al.	2002	196	HAM-A		Hydroxyzine > PP
Mahableshwarkar et al.	2014	303	HAM-A		Duloxetine > PP
		308			Vortioxetine (2.5 mg) > PP
		302			Vortioxetine (5 mg) > PP
		308			Vortioxetine (10 mg) > PP
Mohlman et al. a	2003	15	STAI-T	BDI	Enhanced CBT > WL
Mohlman et al. b	2003	21	BAI	BDI	Standard CBT > WL
Moller et al.	2001	207	HAM-A	HAM-D	Alprazolam > PP
		205			Opipramol > PP
Montgomery et al.	2006	266	HAM-A	HAM-D	Pregbalin > PP
Pande et al.	2003	126	HAM-A	HAM-D	Lorazepam > PP
		132			Pregbalin (150 mg) > PP
		132			Pregbalin (600 mg) > PP
Park et al.	2014	94	HAM-A, PSWQ, STAI-T	BDI	Gamisoyo-San (Individual) > PP
		95			Gamisoyo-San (Multi-Compound) > PP
Paxling et al.	2011	82	BAI, PSWQ, STAI-T	BDI, MADRS	iCBT > WL
Pollack et al.	2001	324	HAM-A		Paroxetine > PP
Pollack et al. a	2008	425	HAM-A		Tiagbine (4 mg) > PP
		420			Tiagbine (8 mg) > PP
		421			Tiagbine (12 mg) > PP
Pollack et al. b	2008	441	HAM-A		Tiagbine > PP
Pollack et al. c	2008	438	HAM-A		Tiagbine > PP
Power et al.	1990	21	HAM-A		CBT > PP
		21			Diazepam > PP
Power et al.	1990	40	HAM-A		CBT > PP
		40			Diazepam > PP
Rezvan et al.	2008	24	PSWQ		CBT > WL
		24			CBT + IPT > WL
Rickels et al.	2000	182	HAM-A		Venlafaxine (75 mg) > PP
		177			Venlafaxine (150 mg) > PP
		182			Venlafaxine (225 mg) > PP
Rickels et al.	2003	368	HAM-A		Paroxetine (20 mg) > PP
		377			Paroxetine (40 mg) > PP
Rickels et al.	2005	173	HAM-A	HAM-D	Alprazolam > PP
		174			Pregbalin (300 mg) > PP
		172			Pregbalin (450 mg) > PP
		170			Pregbalin (600 mg) > PP
Robinson et al.	2010	95	PSWQ	PHQ-9	Clinician-guided iCBT > WL
		98			Technician-guided iCBT > WL
Roemer et al.	2008	31	PSWQ	BDI	ACT > WL
Rothschild et al.	2012	289	HAM-A		Vortioxetine < PP
Sarris et al.	2013	58	BAI, HAM-A		Kava kava > PP
Stanley et al.	1996	31	HAM-A, PSWQ, STAI-T	HAM-D	CBT < Psych PL
Stanley et al. a	2003	64	HAM-A, PSWQ, STAI-T	BDI, HAM-D	CBT > Psych PL
Stanley et al. b	2003	9	BAI, PSWQ	BDI	CBT > TAU
Stanley et al.	2009	134	HAM-A, PSWQ	BDI-II	CBT > TAU
Stein et al.	2008	121	HAM-A		Agomelatine > PP
Stein et al.	2014	233	HAM-A		Agomelatine > PP
		234			Escitalopram > PP

(*Continued*)

Table 1. (Continued).

Authors	Year	N[1]	Primary measure(s)	Secondary measure (s)	Primary outcome[2]
Stein et al.	2017	270	HAM-A		Agomelatine (10 mg) > PP
		278			Agomelatine (25 mg) > PP
Titov et al.	2009	35	PSWQ	PHQ-9	iCBT > WL
Titov et al.	2010	34	PSWQ		iCBT > WL
Van der Heiden et al.	2012	56	PSWQ, STAI-T	BDI-II	Intolerance of uncertainty therapy > WL
		57			Metacognitive therapy > WL
Wetherell et al.	2003	39	BAI, HAM-A, PSWQ	BDI, HAM-D	CBT > WL
		36			CBT > Psych PL
Wetherell et al.	2009	31	HAM-A, PSWQ	BDI-II	Modular psychotherapy > TAU
White et al.	1992	42	STAI-T	BDI	BT > WL
		37			CBT > WL
		42			CT > WL
		21			Subconscious retraining > WL
Wu et al.	2011	210	HAM-A		Duloxetine > PP
Zinbarg et al.	2007	18	BAI, PSWQ		CBT > WL

Abbreviations: ACT: acceptance and commitment therapy; AR: applied relaxation; BDI: Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); BDI-II: Beck Depression Inventory-II (Beck, Steer, & Brown, 1996); BT: behavior therapy; CBT: cognitive behavior therapy; CT: cognitive therapy; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale (Hamilton, 1960); iCBT: internet cognitive behavior therapy; IPT: interpersonal therapy; MADRS: Montgomery Asberg Depression Rating Scale (Montgomery & Asberg, 1979); MBSR: mindfulness-based stress reduction; PP: pill placebo; PHQ-9 Patient Health Questionnaire—9 (Kroenke, Spitzer, & Williams, 2001); PSWQ: Penn State Worry Questionnaire; PSWQ-A: Penn State Worry Questionnaire—Abbreviated; Psych PL: psychological placebo; STAI-T: State-Trait Anxiety Inventory—Trait; TAU: treatment as usual; WL: waitlist.

Table 2. Primary and secondary outcome measures.

Outcome	Measure
Primary	Beck Anxiety Inventory
	Hamilton Anxiety Rating Scale
	Penn State Worry Questionnaire
	Penn State Worry Questionnaire—Abbreviated
	State-Trait Anxiety Inventory—Trait
Secondary	Beck Depression Inventory
	Beck Depression Inventory-II
	Hamilton Depression Rating Scale
	Montgomery-Asberg Depression Rating Scale
	Patient Health Questionnaire—9

blind assessors, dealing with incomplete outcome data), treatment quality (use of a treatment manual, therapist training, check of treatment integrity), flexible versus fixed dosage, mean age, percent female of total sample, percent comorbidity, and follow-up length (if applicable). Dependent variables were classified as either primary (measures of generalized anxiety) or secondary (measures of depression).

Control conditions were categorized as pill placebo (n = 43), waitlist (WL; n = 22), psychological placebo (n = 10), or treatment as usual (TAU; n = 5), with one study (Wetherell, Gatz, & Craske, 2003) including both a WL and psychological placebo group. Psychological control conditions that were categorized as psychological placebo included supportive therapy, affect-focused body psychotherapy, clinician-supported therapy, nondirective therapy, nondirective supportive therapy, spiritually based intervention, stress management education, discussion group, minimal contact (providing

assessments/brief support), and short-term psychodynamic psychotherapy. Control conditions that study authors termed TAU were considered TAU for the analysis. Control conditions in which participants did not receive any treatment for GAD symptoms for a specified amount of time were considered WL.

Quantitative data analysis

The effect size for each study was computed using Hedges' *g* (Rosenthal, 1991) in CMA. Hedges' *g* allows for correction for small sample sizes (Hedges & Olkin, 1985). When the necessary data were available, Hedges' *g* was calculated using means and standard deviations. If means and standard deviations were not reported, we contacted the authors to obtain these data. In cases that these values were not obtainable, Hedges' *g* was calculated using available data (least squares means, standard errors). If there were not sufficient data to calculate Hedges' *g* and authors could not be reached, the data were not included in the final analyses. These controlled effect sizes may be interpreted conservatively with Cohen's convention of small (0.2), medium (0.5), and large (0.8) effect sizes (Cohen, 1988). When there were multiple outcomes per domain, they were combined according to Borenstein, Hedges, and Rothstein (2007).

The I^2 statistic was used to measure heterogeneity. The I^2 statistic describes the percentage of variation due to heterogeneity, with 0% indicating no observed heterogeneity, 25% low, 50% moderate, and 75% high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). In addition, a test for significance of heterogeneity and the *Q* value are reported. Because we expected considerable heterogeneity due to patient and treatment variability, we used the random effects model in all analyses. For categorical moderators, we reported *p*-values and between-group heterogeneity (*Q*) as recommended by Hedges and Olkin (1985) and for continuous variables we used meta-regression analyses, which is indicated by a slope and a *p*-value.

Study quality ratings

The quality of the studies that were included was rated using four items from the Cochrane Risk of Bias Tool (Higgins & Green, 2011): (1) adequately random sequence generation for group assignment, (2) concealment of allocation to conditions, (3) blind assessors, and (4) dealing with incomplete outcome data.

Results

Characteristics and quality of included trials

Seventy-nine RCT including 11,002 participants met criteria for inclusion. Of the 79 included studies, 30 had low bias for sequence generation, 22 qualified for low bias for allocation concealment, 66 qualified for low bias for blind assessors, and 39 qualified for low bias for incomplete outcome data. Six studies met 0 study quality criteria, 27 studies met one criterion, 21 studies met two criteria, 10 studies met three criteria, and 15 studies met all four criteria.

Heterogeneity

A heterogeneity analysis was conducted to test the assumption that the effect sizes were from a homogeneous sample (Hedges & Olkin, 1985). An analysis of all primary outcomes on pretreatment to posttreatment time points revealed significant moderate heterogeneity (I^2 = 72.56, p < 0.001). This was also true when psychotherapy (I^2 = 54.90, Q = 84.25, p < 0.001) and medication studies (I^2 = 54.26, Q = 163.72, p < 0.001) were considered separately. Therefore, random effects analyses were most appropriate and moderator analyses were justified. Studies and their effect sizes are presented in a forest plot (Figure 2).

Outliers were defined as studies whose effect size 95% confidence interval (CI) did not overlap with the 95% CI of the pooled effect size of its psychotherapy or pharmacotherapy domain. When outliers were excluded, heterogeneity decreased in psychotherapy (I^2 = 37.84, p = 0.01) and pharmacotherapy (I^2 = 40.14, p < 0.01) domains. Excluding outliers did not significantly change primary outcomes for either psychotherapy or medication domains, and therefore results excluding outliers are not reported. The following analyses were conducted on all studies including outliers.

Efficacy on primary and secondary outcomes

Efficacy of psychotherapy versus control conditions on primary outcome measures

This analysis included 39 comparisons. Consistent with prediction, evidence-based psychotherapies outperformed control conditions on primary outcome measures at posttreatment with a medium to large effect size (g = 0.76, 95% CI: 0.61–0.91, p < 0.001). At follow-ups, 12 comparisons showed that evidence-based psychotherapies outperformed control conditions on primary outcome measures at follow-ups with a small effect size (g = 0.27, 95% CI: 0.00–0.53, p = 0.05).

Within psychotherapy comparisons, pill placebo-controlled studies had the highest effect size (n = 3, g = 1.44, 95% CI: 0.94–1.94, p < 0.001), followed by WL controls (n = 22, g = 0.90, 95% CI: 0.73–1.08, p < 0.001), psychological placebo (n = 10, g = 0.47, 95% CI: 0.25–0.69, p < 0.001), and TAU (n = 5, g = 0.38, 95% CI: 0.05–0.71, p < 0.05; in Wetherell et al., 2003, the psychological placebo and waitlist control group comparisons were each included in this analysis).

Efficacy of psychotherapy versus control conditions on secondary outcome measures

This analysis included 29 comparisons. Evidence-based psychotherapies outperformed control conditions on secondary outcome measures at posttreatment with a medium effect size (g = 0.64, 95% CI: 0.49–0.79, p < 0.001). At follow-ups, 8 comparisons showed that evidence-based psychotherapies outperformed control conditions on secondary outcome measures at follow-ups with a small effect size (g = 0.27, 95% CI: 0.06–0.49, p = 0.01).

Efficacy of pharmacotherapy versus control conditions on primary outcome measures

This analysis included 43 comparisons. Consistent with prediction, pharmacotherapy outperformed control conditions on primary outcome measures at posttreatment with a small effect size (g = 0.38, 95% CI: 0.30–0.47, p < 0.001). There were no pharmacotherapy

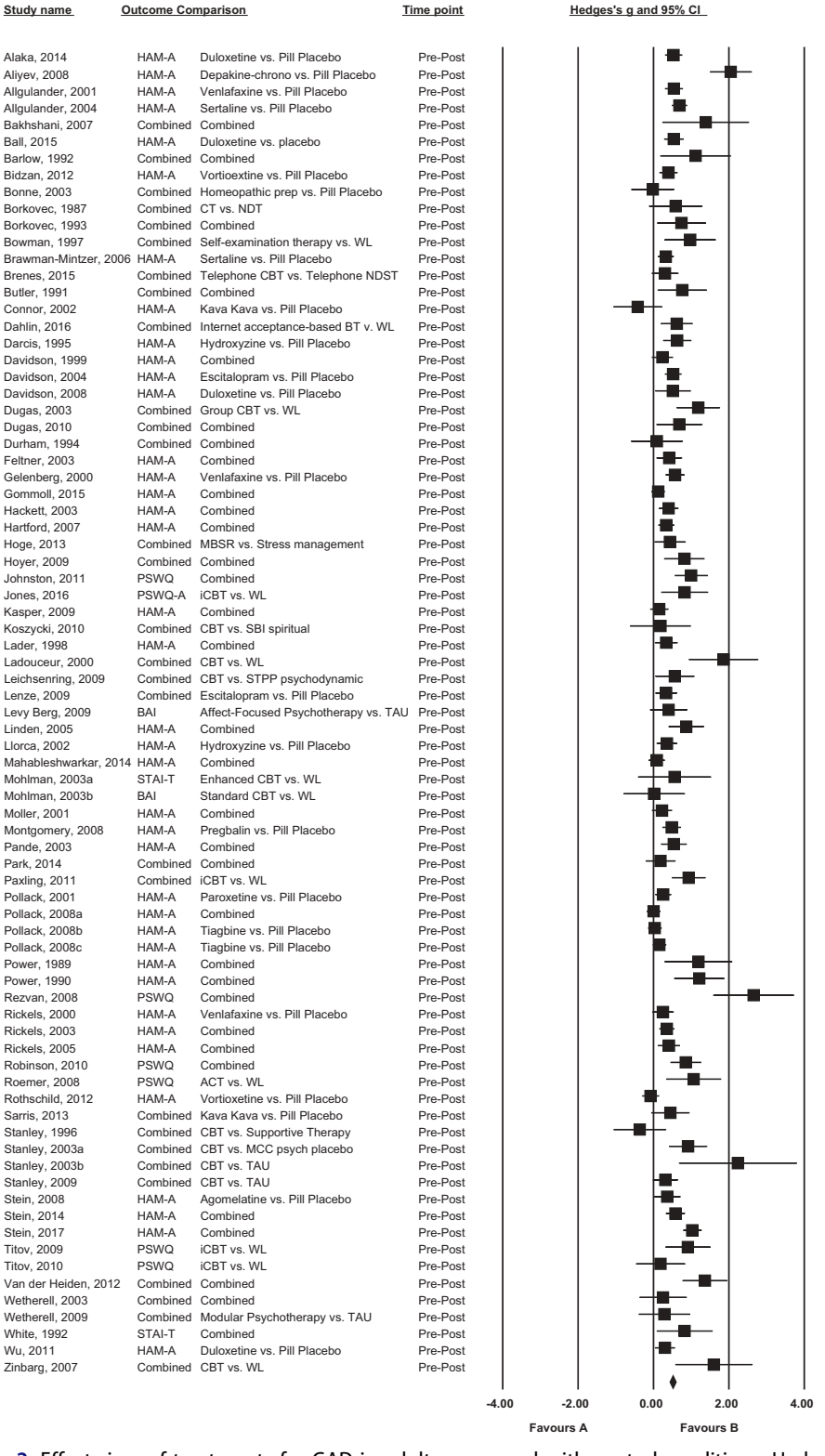

Figure 2. Effect sizes of treatments for GAD in adults compared with control conditions: Hedges' g.

studies with data on follow-up measures of the primary outcome available. All included medication comparisons used pill placebos as a control.

Efficacy of pharmacotherapy versus control conditions on secondary outcome measures

This analysis included 11 comparisons. Pharmacotherapy outperformed control conditions on secondary outcome measures at posttreatment with a medium effect size (g = 0.59, 95% CI: 0.21–0.97, $p < 0.01$). There were no pharmacotherapy studies with follow-up data of depression measures available.

Moderators

Moderator analyses were conducted on psychotherapy and pharmacotherapy separately. Although outliers had minor effect on pooled effect size estimates, they were removed from moderator analyses due to their substantial leverage and influence on regression results.

Mean age of the sample was a significant moderator of psychotherapy outcomes. A lower mean age predicted a larger treatment effect size in psychotherapy ($\beta = -0.013$, $p < 0.05$). This difference was also demonstrated when comparing psychotherapeutic outcomes for adult and elderly populations categorically (Q = 5.16, df = 1, $p < 0.05$), with studies involving non-elderly adult participants showing a larger effect size (g = 0.87) than studies involving older adult participants (g = 0.47). Mean age was not associated with outcome in medication studies ($p > 0.05$).

There was no significant relationship between effect size and treatment dose (number of sessions or medication dosage), treatment quality, year of publication, fixed versus flexible dose, percent comorbidity, percent female, or pretreatment severity (all $p > 0.10$).

Publication bias: "the file drawer problem"

Because nonsignificant studies tend not to be published, there may be a discrepancy in results between the studies that are retrievable and all studies that have been conducted. Unavailable negative results may lead to overestimate the true effect size. Rosenthal and colleagues have termed this phenomenon "the file drawer problem" (Rosenthal, 1991).

Because pooled effect sizes in pharmacotherapy and psychotherapy domains differed substantially, publication bias was examined separately in each. A funnel plot revealed asymmetry in psychotherapy studies (Egger's intercept = 1.93, $p < 0.01$; Figure 3), and the Duval and Tweedie (2000) trim and fill procedure imputed 5 studies for an adjusted effect size estimate of 0.66. A funnel plot in pharmacotherapy studies did not reveal asymmetry according to Egger's intercept and a trim and fill procedure did not impute any studies or adjust the effect size estimate.

Discussion

Main findings

The current study provides an updated meta-analysis including 79 studies that showed similar effect sizes to previous meta-analyses. The overall effect size of evidence-based

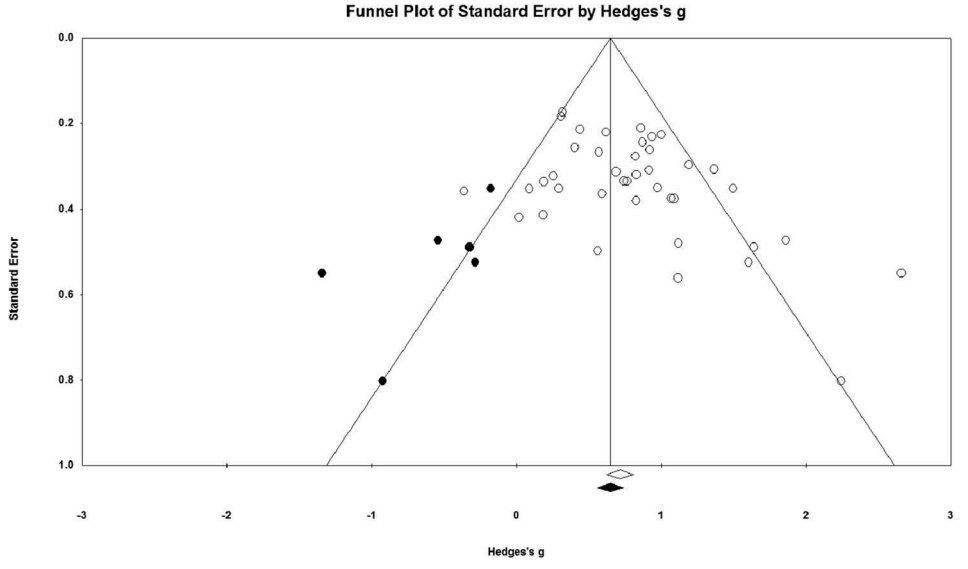

Figure 3. Funnel plot for psychotherapy studies with imputed studies and adjusted effect size.

psychotherapy for GAD on primary GAD outcomes (g = 0.76, n = 39) was comparable to the previous meta-analysis on psychotherapy (g = 0.80, n = 31; Cuijpers et al., 2016). Additionally, the effect size for medication for GAD (g = 0.38, n = 43) was comparable to a previous meta-analysis for medication (d = 0.39, n = 21; Hidalgo et al., 2007).

While it may seem possible to draw the conclusion that psychotherapy has a larger effect on GAD symptoms than pharmacotherapy, this is not supported for more than one reason. First, the two treatment modalities use different control types. In the current study, all pharmacotherapy trials used a pill placebo as a comparison, while psychotherapy studies often had a waitlist control. Although in this analysis the three pill placebo controlled psychotherapy studies had a higher effect size than waitlist controlled studies, this is likely a fluke and underpowered, as a larger meta-analysis of CBT for anxiety disorders showed that effects were large for waitlist conditions and small to medium for pill placebo comparisons (n = 144 trials; Cuijpers et al., 2016). If a pill placebo is a much more stringent control condition than WL, this would have contributed to this apparent difference in effect size. Next, psychotherapy studies showed evidence of publication bias. Finally, a network meta-analysis including head-to-head treatment comparisons in addition to treatments versus control conditions would provide a more comprehensive dataset for comparing treatments.

Most moderators did not show evidence of influence. This corroborates previous conclusions (Schneider et al., 2015). However, younger age of the study sample was associated with higher effect size in psychotherapy studies.

Implications

Some evidence suggests that patients strongly prefer psychological treatment to medication, with one meta-analytic review showing a three-fold preference (McHugh,

Whitton, Peckham, Welge, & Otto, 2013). Because the efficacy appears to be at least comparable, increased access to psychological treatment is necessary to provide sufficient treatment to individuals with GAD.

Next, moderator analyses showed that mean age of the sample was a significant moderator in the psychotherapy studies, such that younger mean age of the sample was associated with more symptom improvement in psychotherapy. This difference was also evident when comparing adult populations and elderly populations categorically. Although this is not direct evidence that younger age was the cause of receptiveness to psychotherapy, this is consistent with findings from a number of investigators that treatments for anxiety disorders are not as effective for older people relative to younger people (Gonçalves & Byrne, 2012; Gould et al., 2012; Hendriks et al., 2008; Pinquart & Duberstein, 2007; Wetherell et al., 2013).

Limitations

Notably, although psychotherapy yielded larger effect sizes than medication, this meta-analysis suggests that control type may contribute to this apparent difference. Publication bias in psychotherapy studies might also contribute to the difference in psychotherapy and medication effect sizes. Therefore, this meta-analysis indicates that although controlled psychotherapy studies may have larger effect sizes than medication studies for GAD, the methodologies in these studies are not equivalent enough to draw firm conclusions. Studies that compare medication and psychotherapy side-by-side would be more informative to this end. Lastly, given the relatively small number of studies incorporating follow-up measures of GAD symptoms (12 total included), as well as the variability of follow-up times (2 weeks to 3 years), more evidence is necessary to draw conclusions about psychotherapy and medication long-term outcomes following treatment.

Summary

This meta-analysis drew from 79 RCT with 11,002 participants to examine effects of psychotherapy and pharmacological treatments for GAD. Both types of interventions significantly improved both primary GAD outcomes and secondary depression outcomes. The mean effect size for psychotherapy was $g = 0.76$ and for pharmacotherapy was $g = 0.38$. However, control type (placebo v. TAU and WL) and publication bias cast doubt on the validity of the comparison of the effect sizes. Age moderated the primary GAD outcomes in psychotherapy, with younger age predicting better treatment response.

Notes

1. *N* refers to the total number of participants included in each primary comparison (single treatment group + single placebo), respectively, from pretreatment to posttreatment.
2. Direction of comparison refers to the group with the superior primary outcome at posttreatment.

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*Studies included in the meta-analysis are denoted with an asterisk.

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