

# Meta-Analysis of Efficacy of Interventions for Elevated Depressive Symptoms in Adults Diagnosed With Cancer

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**Background** Cancer patients are at increased risk for depression compared with individuals with no cancer diagnosis, yet few interventions target depressed cancer patients.

**Methods** Efficacy of psychotherapeutic and pharmacologic interventions for depression in cancer patients who met an entry threshold for depressive symptoms was examined by meta-analysis. Five electronic databases were systematically reviewed to identify randomized controlled trials meeting the selection criteria. Effect sizes were calculated using Hedges'  $g$  and were pooled to compare pre- and postrandomization depressive symptoms with a random effects model. Subgroup analyses tested moderators of effect sizes, such as comparison of different intervention modalities, with a mixed effects model. All statistical tests were two-sided.

**Results** Ten randomized controlled trials (six psychotherapeutic and four pharmacologic studies) met the selection criteria; 1362 participants with mixed cancer types and stages had been randomly assigned to treatment groups. One outlier trial was removed from analyses. The random effects model showed interventions to be superior to control conditions on reducing depressive symptoms postintervention (Hedges'  $g = 0.43$ , 95% confidence interval = 0.30 to 0.56,  $P < .001$ ). In the four psychotherapeutic trials with follow-up assessment, interventions were more effective than control conditions up to 12–18 months after patients were randomly assigned to treatment groups ( $P < .001$ ). Although each approach was more effective than the control conditions in improving depressive symptoms ( $P < .001$ ), subgroup analyses showed that cognitive behavioral therapy appeared more effective than problem-solving therapy ( $P = .01$ ), but not more effective than pharmacologic intervention ( $P = .07$ ).

**Conclusions** Our findings suggest that psychological and pharmacologic approaches can be targeted productively toward cancer patients with elevated depressive symptoms. Research is needed to maximize effectiveness, accessibility, and integration into clinical care of interventions for depressed cancer patients.

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By the year 2005, nearly 500 unique studies, 63% of which involved randomized designs, constituted the knowledge base on the efficacy of psychosocial interventions for individuals diagnosed with cancer (1). This literature often targets multiple outcomes, such as quality of life, distress, physical symptoms, and fatigue (1). Dramatically fewer trials assess depression as a primary outcome, although it is one of the most disabling psychological conditions experienced by cancer patients. Still fewer trials target the subgroup of individuals most in need of an intervention: those who have elevated depressive symptoms or are clinically depressed. The primary goal of this meta-analysis is to examine randomized controlled trials (RCTs) testing the efficacy of psychotherapeutic and pharmacologic interventions for depressive symptoms in individuals who are diagnosed with cancer and meet an entry threshold for elevated depressive symptoms.

Risk for depression among the population after a cancer diagnosis is higher compared with the population with no diagnosis (2), and prevalence of major depression diagnosed via standardized interview is estimated to be approximately 16% (3). Depression not only represents a psychological burden for adults with cancer but also carries negative health and behavioral consequences, including nonadherence to medical regimens (4), increased emergency and inpatient service use (5), delayed return to work (6), and possibly elevated rates of suicidal ideation or suicide (7–10) and mortality (10–17). In light of the pervasive impact of depression, it is essential to investigate whether published interventions are effective in reducing depression among cancer patients and to determine which approaches are most promising.

Reviewers of the literature on interventions designed to improve quality of life, including depression, in individuals diagnosed with

cancer have drawn inconsistent conclusions regarding the efficacy of interventions (18–30). However, most interventions include participants regardless of their baseline standing on the outcome of interest. For example, one review of 60 psychosocial interventions for depressive symptoms or anxiety in cancer patients revealed that only 5% of studies restricted eligibility to patients meeting a specified threshold for distress (24). Individuals with low depressive symptoms at baseline might not be likely to benefit from interventions (29,31,32), in that their outcome assessment contains little room for improvement (although prevention of future depressive symptoms and benefit on other outcomes are possible). Combining trials that do and do not use an eligibility criterion for depression may underestimate intervention efficacy for individuals in most need of an intervention. Specifically selecting trials for cancer patients with elevated depressive symptoms or diagnosed depression, Rodin et al. (33) conducted a systematic review of 11 interventions. They found “limited evidence for the effectiveness of pharmacological and psychosocial interventions in the treatment of cancer patients with depressive disorders” (33).

To our knowledge, no previously published review has included a quantitative analysis of the efficacy of psychosocial and pharmacologic approaches for individuals diagnosed with cancer who meet entry criteria for elevated depressive symptoms. Our review identifies existing interventions that can be productively directed toward depressed cancer patients, illuminates limitations in the current literature, and proposes directions for research and clinical practice. In addition to estimating the efficacy of extant interventions and the duration of the effects through a meta-analysis, we examined whether efficacy varies as a function of therapeutic approach (ie, specific psychotherapy and pharmacotherapy). We also considered other potential moderators including characteristics of the samples, cancer, interventions, and trial quality by pooling relevant data from the trials that met the eligibility criteria.

## Methods

### Literature Search Strategy

MEDLINE, PsycINFO, CINAHL, EMBASE, and Cochrane Library databases were systematically searched using appropriate controlled-vocabulary terms specific to each database (Supplementary methods, available online) and keyword searching for terms indicating depression and frequently used assessments of depressive symptoms (such as depression, depressive disorder, Beck Depression Inventory); cancer (including neoplasm, cancer, leukemia); and intervention trials (including random, placebo, treatment). The searches were inclusive of studies published in English from each database’s inception through October 31, 2011. We also examined the references of the articles identified through the searches and relevant reviews and meta-analyses. We did not include three of the studies included in the systematic review by Rodin et al. (33) because two studies (34,35) did not include an eligibility criterion for depressive symptoms and one (36) was not a randomized trial.

### Article Selection Strategy

Four pairs of raters (S. Hart, M. Hoyt, M. Diefenbach, D. Anderson, K. Kilbourn, L. Craft, J. Steel, A. Stanton) reviewed unique entries

from database searches. Each rater reviewed the abstract independently, and articles were obtained when the pairs agreed that the article required full-text examination; discrepancies were resolved by a third rater. Rater pairs conducted full-text review of the resulting articles for the following eligibility criteria: 1) adult participants (18 years or older) with a cancer diagnosis at the time of study entry; 2) inclusion criterion of elevated depressive symptoms at the time of study entry, as defined by each author, including specified threshold on a questionnaire or interview assessment; 3) random assignment to one or more interventions vs a usual care, placebo, attention control, or waiting-list control condition; and 4) depressive symptoms assessed as an outcome. Any RCT that included a psychosocial/behavioral intervention such as cognitive behavioral therapy (CBT), physical activity, and/or pharmacologic component qualified for inclusion, including collaborative care and complementary approaches such as mind–body approaches.

Five trials employing mixed eligibility thresholds in which presence of depressive symptoms was not required [eg, depressive symptoms and/or smoking and/or problem drinking (37); depressive symptoms and/or anxiety (38,39) and/or fatigue (40); depressive symptoms and pain (41)] did not qualify for inclusion. Also, eight trials that compared two interventions in the absence of a control condition were not included (42–49).

### Article Review Strategy

Using an online coding program designed for this project, the aforementioned four pairs of raters independently coded selected trials. Data regarding characteristics of the sample, intervention, and instrumentation were extracted, as were continuous data from assessments of depressive symptoms (percentage of participants meeting author-defined criteria for categorical “responder” or “remitted” were not extracted), to calculate effect sizes. The program produced a list of discrepancies, which were then systematically resolved by consensus, and final data were entered for each study. Studies were assessed for quality using a modified 14-item version of the PEDro scale (50), which was designed to identify studies that are generalizable, internally valid, and interpretable. The modified coding scheme was identical to the 11-item scale (50, <http://www.pedro.org.au/english/downloads/pedro-scale/>), with three additional items. Two items assessed quality of treatment fidelity (use of a treatment manual, monitoring of treatment implementation), as recommended by the Treatment Fidelity Workgroup of the National Institutes of Health Behavior Change Consortium (51). The third item assessed provision of loss to follow-up information, included as an important quality indicator in other reviews of interventions for cancer patients (26). When published articles did not present sufficient data to calculate the effect sizes, we contacted authors for the required information.

### Statistical Analysis

Comprehensive Meta-Analysis (version 2.2.055, Biostat, Englewood, NJ) was used to calculate effect sizes and analyze data (52). Hedges’ *g* was calculated for each trial and the overall pool of trials and was used as a measure of the effect size. Hedges’ *g* is calculated on the basis of the standardized mean difference effect size, which uses the pooled within-groups SD but corrects for bias from small sample sizes and therefore is considered to be more accurate

than the standardized effect size typically measured by Cohen's *d* (53). Hedges' *g* is a conservative estimate of effect size, which typically is interpreted by Cohen's *d* (54) guidelines (small effect = 0.20, medium effect = 0.50, large effect = 0.80). A positive effect size indicates that the intervention was superior to the control condition in reducing depressive symptoms, whereas a negative effect size indicates that the control condition outperformed the intervention. For example, a Hedges' *g* of 0.50 would indicate that the intervention condition produced a reduction in depressive symptoms of half a standard deviation more than did the control condition.

When outcome data for more than one measure of depressive symptoms were reported in a given study (a violation of outcome independence), we used the mean of the effect sizes (55). A variety of approaches exist to examine multiple assessments of the same construct, including multivariable approaches (56). We used the commonly employed method of combining effect sizes for multiple outcomes, which tends to yield a more conservative effect size estimate than do multivariable approaches (55,57). This was applicable for four studies (58–61). Two separate effect sizes were calculated for trials containing two intervention groups (59,62,63), in light of the observation that the two active treatments differed substantially in approach or content, such as two different medications or CBT vs social support.

Individual effect sizes were pooled in the Comprehensive Meta-Analysis program and were calculated separately for prerandomization compared with postintervention outcomes. The assessment closest in time to completion of the intervention was used for calculation of posttreatment effect size. Effect sizes were also calculated for prerandomization to longer-term follow-up assessment, when follow-up assessments were reported. Because none of the studies reported the correlation between baseline and postintervention outcomes, we used a fixed correlation of 0.90 for within-group comparison. This approach has a small chance of overestimating effect size and has been used in earlier psychological intervention research examining improvement rates (64).

Variability was assumed to be caused by both sampling error and random differences; therefore, the data were fit to a random effects model, which provides more conservative estimates than a fixed effects model (65). A random effects estimate assumes additional variance beyond the set of studies and facilitates generalizability of results. We examined the distribution of effect sizes to identify any extreme values for possible elimination from analyses (66).

We identified several *a priori* moderators, of which the primary one involved a comparison of specific psychotherapeutic and pharmacologic approaches. Others included PEDro trial quality criteria, sample and cancer characteristics (ie, sociodemographics, cancer type, cancer stage, time elapsed since diagnosis), questionnaire vs interview assessment approach, and intervention characteristics, such as length, group vs individual, and type of control group. Examination of any moderator required that it must be represented in a minimum of two trials, have sufficient variability across studies (note that the majority of PEDro criteria showed little variability across studies), and contain sufficient descriptive data for meaningful analysis. The subgroup analyses used a mixed effects model, which pools studies within subgroups with a random effects model, but tested for statistically significant between-groups differences with a fixed effects model. A Bonferroni correction was used to control for inflation of Type I error when multiple between-groups

comparisons were conducted. To test homogeneity of variance of the different effect sizes, we used the *Q* test statistic (66), which indicates whether the variability in effect sizes is within the range that would be expected if all studies shared a common population effect size. We also examined the *I*<sup>2</sup> statistic, which ranges between 0% and 100% and indicates the proportion of the total variance accounted for by heterogeneity (larger percentages reflect greater heterogeneity). We calculated 95% confidence intervals (CI) around *I*<sup>2</sup> (67), using the noncentral  $\chi^2$ -based approach within the heterogi module for Stata (68). For continuous moderators, such as mean age, we used meta-regression techniques in the Comprehensive Meta-Analysis program, using the method of moments estimator.

To evaluate sources of bias, we created and examined a funnel plot, which graphically displays the measure of study effect size against sample size. A funnel plot displaying absent publication bias should result in a symmetrical inverted funnel-shaped graph. We also used Duval and Tweedie's (69) trim and fill procedure, which "trims" off the asymmetric outlying part of the funnel plot, the remainder of which is used to estimate the true center of the plot. The procedure calculates the number of missing studies and provides an estimate of what the effect size would have been without bias, on the basis of "filling in" or imputing missing studies. Egger's test of the intercept, a linear regression method, was used to further capture the bias in the funnel plot (70). The fail-safe *N* also was calculated to determine the number of non-statistically significant trials missing from the analysis that would, if included, reduce the observed effect size to a non-statistically significant level.

## Results

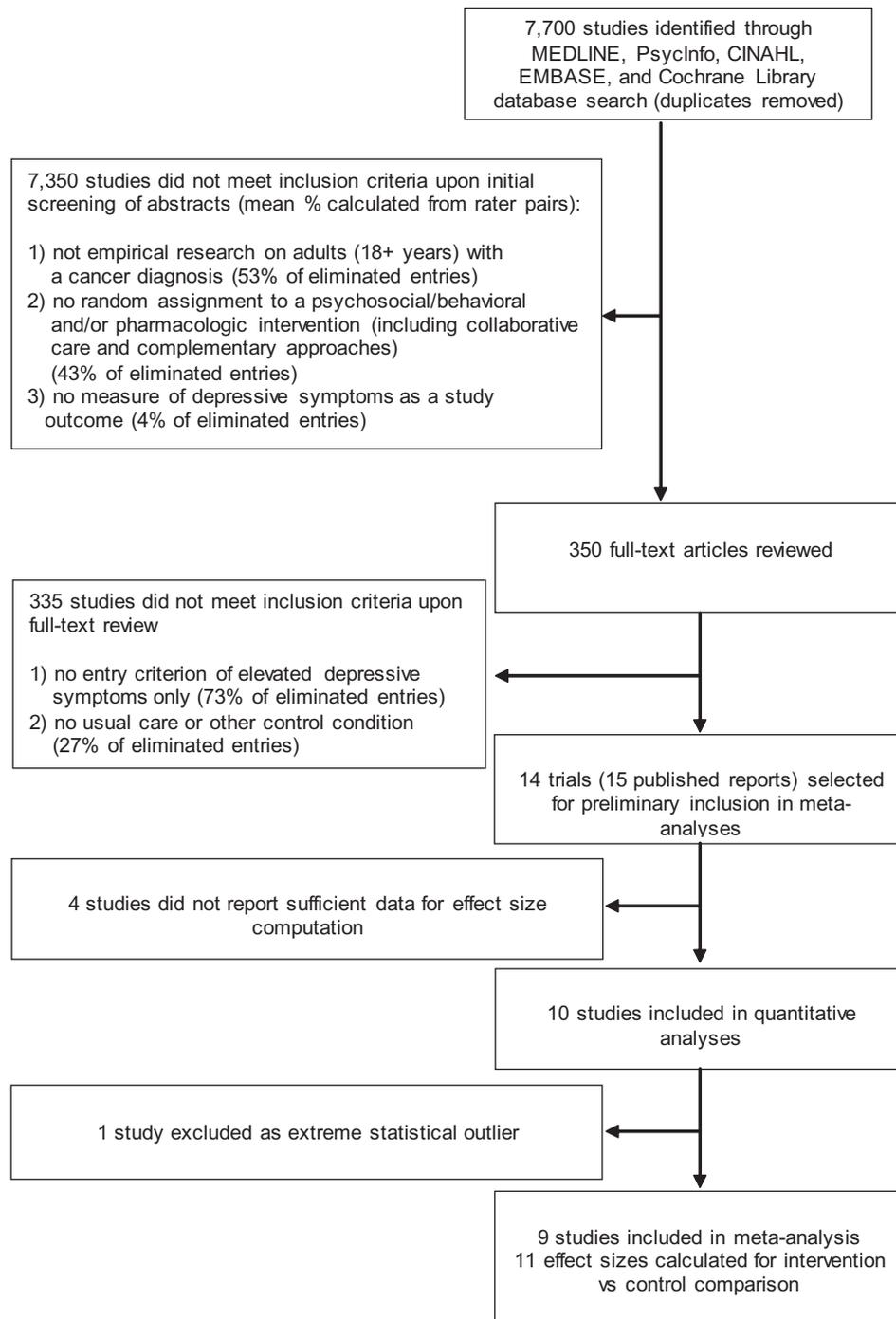
### Selection of RCTs

A search of the five databases identified 7,770 unique studies, of which the rater pairs conducted full-text review of 350 articles (Figure 1). Fourteen unique trials and one report of a follow-up analysis met all inclusion criteria. Five reports included sufficient data to calculate effect size (58–60,63,71), and five authors provided additional data that included pre- and all postintervention means, SDs, and sample sizes separated based on the treatment arm (61,62,72–75). Therefore, 10 unique trials (six psychotherapeutic and four pharmacologic) that included a total of 1362 participants with mixed cancer types and stages who had been randomly assigned to treatment groups were included in the meta-analysis (Figure 1). For the remaining four articles, including two publications from one trial, the authors were unable to provide essential data (76–79).

### Description of the Sample of RCTs

Table 1 provides demographic and cancer-related data for the 10 trials from which patient data were included in the meta-analysis. Of the 10 trials, seven enrolled outpatients with mixed cancer types and stages. The time elapsed after cancer diagnosis ranged widely from 6 or fewer weeks to 7 years.

Across the six psychotherapeutic trials, 1273 eligible adult cancer patients were invited to take part, of whom 1000 (78%) were randomly assigned to treatment arms and 725 (72.5%) completed the postintervention assessment (Table 1). Most participants were women (76%; not weighted by sample size) and on average were 51



**Figure 1.** Flow chart of study identification by systematic literature review.

years of age. The education level and racial/ethnic composition of the included patients varied widely.

Only one of the four pharmacologic trials reported the number of adults invited to participate (Table 1). A total of 362 participants were randomly assigned to treatment arms, and 224 (62%) completed the postintervention assessment. Participants were mostly women (83%) and had an average age of 55 years. These reports did not provide sufficient data on education level, and only two studies reported data on race/ethnicity (>80% of patients were white).

Table 2 displays recruitment and intervention characteristics. Five of the six psychotherapeutic trials used systematic screening,

which included screening of consecutive potentially eligible patients attending clinic to identify participants. Four trials evaluated a form of problem-solving therapy (PST, three of these within a collaborative care or multimodal approach that included antidepressant medication as an option), and two trials administered CBT. All studies except one used an individual intervention delivery approach (group delivery in 59), which ranged from 4 to 10 sessions, with the exception that participants in the study by Ell et al. (73,75) had access to up to 1 year of collaborative care. Interventionists were trained psychologists or psychology graduate students, social workers, nurses, oncologists, or psychiatrists. Usual

**Table 1.** Patients and cancer characteristics from studies included in the meta-analysis

Author, publication date (reference)	No. of individuals invited to participate	No. of participants assigned	No. of participants postintervention*	Mean age†, y	No. of female participants (%)‡	Educatio <sup>§</sup> s	No. of white participants (%)‡	Cancer type	Stage	Inpatient or outpatient	Point in medical treatment	Mean time after diagnosis	Funding source(s)
Psychotherapeutic trials													
Dwight-Johnson et al., 2005 (72)	81	55	30	47	55 (100.0)	84% less than high school	0 (0.0)¶	Breast or cervical	Mixed	Outpatient	NR	≥12 wk	National Cancer Institute (No. R21 CA93390-01); UCLA/National Institute of Mental Health Faculty Scholars Program (NIMH grant No. K-12-MH00990-01-01)
Elli et al., 2008 and 2011 (73,75)	571	472	258	49% ≥ 50 (73,75)	399 (84.5)	64% less than high school	21 (4.5)‡	Mixed	Mixed	Outpatient	Mixed	>12 wk	National Cancer Institute, Office of Cancer Survivorship (No. R01-CA105269)
Evans and Connis, 1995 (59)	78	78	72	54	25 (34.7)**	Mean = 11 y	43 (59.7)**	Mixed	Stage II	Outpatient	Active treatment	12 wk	VA Health Services Research and Development Program (investigator initiated research IIR, No. 90.045)
Nezu et al., 2003 (63)	150	150	132	47	89 (67.4)**, ††	Mean = 15 y	102 (77.2)**, ††	Mixed	Non-metastatic	NR	Active treatment	≤6 mo	National Cancer Institute (No. R01-CA61313)
Savard et al., 2006 (61)	59‡‡	45	37	51	45 (100.0)	30% high school or less	45 (100.0)	Breast	Metastatic	Outpatient	Mixed	78 wk	Canadian Breast Cancer Research Initiative (No. 010436); Canadian Institutes of Health Research
Strong et al., 2008 (74)	334	200	196	57	141 (70.5)	NR	NR	Mixed	Mixed	Outpatient	Mixed	66 wk	Cancer Research UK
Pharmacologic trials													
Costa et al., 1985 (58)	NR	73	51	52	73 (100.0)	NR	NR	Mixed	Mixed	96% inpatient	Active treatment	NR	None declared
Fisch et al., 2003 (71)	NR	163	83	60	81 (49.7)††	NR	146 (89.6)††	Mixed	Advanced, incurable	Outpatient	Mixed	NR	Mary Margaret Walther Program for Cancer Care Research, Indianapolis, IN; Eli Lilly Company, Indianapolis, IN
Musselman et al., 2006 (62)	NR	35	21	54	35 (100.0)	23% high school or less	29 (82.9)	Breast	Mixed	Outpatient	Mixed	Last cancer treatment within past 5 y	GlaxoSmithKline, King of Prussia, PA; Emory University Hospital General Clinical Research Center; National Institutes of Health (No. MO1-RR00039)
Razavi et al., 1996 (60)	103	91	69	53	73 (80.2)††	NR	NR	Mixed	Mixed	NR	NR	6 wk to 7 y	Lilly France and Lilly Benelux

\* Immediate postintervention assessment point or assessment point closest in time to intervention completion. The following studies used data imputation (including last observation carried forward) or multilevel modeling, so the number of participants used in our meta-analysis corresponds to the number of participants at the baseline assessment: Costa et al. (58), Dwight-Johnson et al. (72), and Musselman et al. (62). NR = not reported.

† Other statistics related to age are reported in the table if the mean age was not available.

‡ Percentages are based on number of participants randomly assigned, with exceptions noted.

§ When the percentage is displayed, the remainder of the sample had higher education than the descriptor displayed.

|| Mixed point in medical treatment describes any combination of pretreatment, active treatment, or posttreatment.

¶ All participants were Latina.

# Data provided directly from authors of studies.

\*\* Percentage based on number of participants postintervention.

†† Absolute numbers were extrapolated from reported percentages.

‡‡ Of the 59 individuals invited to participate, 45 were randomly assigned to treatment arms, seven declined to participate, and seven were not present for clinical interview.

**Table 2.** Recruitment and intervention characteristics of studies included in the meta-analysis

Author, publication date (reference)	Recruitment method	Intervention type	Delivery format	Intervention length	Total time or daily dose per intervention protocol*	Type of therapist	Control intervention
Psychotherapeutic trials							
Dwight-Johnson et al., 2005 (72)	Systematic screening	PST or medication in collaborative care	Individual	8 sessions	NR	Social worker and oncologist/psychiatrist	Usual care
Ell et al., 2008; 2011 (73,75)	Systematic screening	PST and/or medication in collaborative care	Individual	Access up to 12 mo	NR	Social worker and psychiatrist	Enhanced usual care
Evans and Connis, 1995 (59)	Systematic screening	CBT, social support	Group	8 sessions	480 min	Social worker	Offered crisis consultation and individual therapy (only 2 participants elected a single crisis consultation)
Nezu et al., 2003 (63)	Nonsystematic screening	PST, PST with significant other	Individual	10 sessions	900 min	Psychology graduate students and social workers	Wait-list
Savard et al., 2006 (61)	Systematic screening	CBT	Individual	8 sessions	480–720 min	Psychologist	Wait-list
Strong et al., 2008 (74)	Systematic screening	Education, problem solving, and medication	Individual	10 sessions	450 min	Nurse	Usual care
Pharmacologic trials							
Costa et al., 1985 (58)	NR	Mianserin	Individual	4 wk	60 mg	NR	Placebo pill
Fisch et al., 2003 (71)	Systematic screening	Fluoxetine	Individual, by mail delivery	12 wk	20 mg	NR	Placebo pill
Musselman et al., 2006 (62)	NR	Desipramine or paroxetine	Individual	6 wk	125–200 mg desipramine; 20–40 mg paroxetine	NR	Placebo pill
Razavi et al., 1996 (60)	NR	Fluoxetine	NR	5 wk (first wk was placebo)	20 mg	NR	Placebo pill

\* Medication dosage is daily goal dose after phase-in period; in some instances, goal dosages were modified according to therapeutic effect. CBT = cognitive behavioral therapy; NR = not reported; PST = problem-solving therapy.

care, enhanced usual care (eg, usual care plus written educational or resource information), or a waiting list for treatment constituted the control conditions.

The goal of the four pharmacologic trials was to evaluate the efficacy of various antidepressant medications against a pill placebo (Table 2). Only one trial reported that screening was systematic (71). Pharmacologic interventions ranged in duration from 4 to 12 weeks.

Table 3 summarizes how depression was defined and assessed. Studies most often employed validated questionnaire and/or interview assessments to assess both eligibility and outcomes. Postintervention assessments ranged from 8 weeks to 12 months after random assignment to treatment arms in psychotherapeutic

trials and 28 days to 12 weeks in pharmacologic trials. Of the 10 trials, only four psychotherapeutic trials included a follow-up assessment, which ranged from 6 to 24 months. Baseline levels of depressive symptoms typically ranged from mild to moderate for psychotherapeutic and pharmacologic trials, depending on the outcome measure used.

Table 4 displays coding of the PEDro criteria, including quality of randomization procedures, methods of blinding, reporting of data, data analysis, treatment fidelity, and adequacy of follow-up. Trials met 9–12 of the 14 quality criteria. One trial (63) did not meet the allocation concealment criterion. Two trials (62,71) did not have groups similar at baseline on prognostic indicators, such as cancer stage. As is standard in these trials, no psychotherapeutic

**Table 3.** Depression assessments and baseline depression severity

Author, publication date (reference)	Screening criterion	Timing of assessments	Report type	Assessment instrument	Mean depression score at baseline assessment (SD)
Psychotherapeutic trials					
Dwight-Johnson et al., 2005 (72)	From PHQ-9/PRIME-MD, major depressive disorder, dysthymia, or persistent (baseline and 1 mo later) depressive symptoms	Baseline, 4 mo, 8 mo	Self-report	PHQ-9	PST = 12.60 (7.00); control = 13.40 (7.20)
Ell et al., 2008; 2011 (73,75)	On PHQ-9, one of two cardinal symptoms of depression for more than half the days to nearly every day and score $\geq 10$ on PHQ-9 and/or two DSM-IV questions for dysthymia	Baseline, 12 mo, 18 mo, 24 mo*	Self-report	PHQ-9	PST = 13.17 (4.50); control = 12.79 (4.40)
Evans and Connis, 1995 (59)	$\geq 16$ on CES-D	Baseline, 8 wk, 6 mo	Self-report	CES-D	CBT = 27.20 (8.80); social support = 27.90 (8.40); control = 29.00 (7.00)
			Self-report	SCL-90-R Depression	CBT = 1.80 (0.50); social support = 1.40 (0.70); control = 1.30 (0.70)
Nezu et al., 2003 (63)	$\geq 14$ on HAM-D and T-score $\geq 63$ on Global Severity Index of Brief Symptom Inventory	Baseline, 10 wk†	Clinician-rated	HAM-D	PST = 20.40 (4.21); PST with significant other = 21.28 (3.66); control = 21.23 (3.33)
Savard et al., 2006 (61)	$\geq 7$ on HADS or $\geq 15$ on BDI	Baseline, 8 wk‡	Self-report	HADS	CBT = 9.42 (2.43); control = 8.87 (2.60)
			Self-report	BDI	CBT = 21.13 (5.41); control = 20.40 (5.76)
			Clinician-rated	HAM-D	CBT = 14.21 (4.26); control = 14.40 (4.52)
Strong et al., 2008 (74)	$\geq 15$ on HADS and SCID major depressive disorder of $\geq 1$ mo and $\geq 1.75$ on SCL-20 Depression	Baseline, 3 mo, 6 mo, 12 mo	Self-report	SCL-20 Depression	PST/education = 2.40 (0.45); control = 2.34 (0.45)
Pharmacologic trials					
Costa et al., 1985 (58)	1) Depression diagnosis according to Stewart et al. (1965) and Kathol and Petty (1981) criteria; 2) depression succeeding or paralleling development of cancer; 3) $\geq 41$ ZSRDS; and 4) $\geq 16$ HAM-D (first 17 items)	Baseline, 28 days§	Clinician-rated	CGI-S	Mianserin = 3.33 (1.19); control = 3.32 (1.09)
			Clinician-rated	HAM-D	Mianserin = 20.60 (3.62); control = 20.80 (3.85)
			Self-report	ZSRDS	Mianserin = 50.10 (6.31); control = 51.20 (6.56)
Fisch et al., 2003 (71)	$\geq 2$ on Two-Question Screening Survey (author-developed to assess depressed mood and anhedonia)	Baseline, 12 wk	Self-report	Brief ZSRDS	Fluoxetine = 24.44 (6.56); control = 23.09 (5.91)
Musselman et al., 2006 (62)	Clinical diagnosis of major depressive disorder for $\geq 1$ mo assessed by DSM-III-R criteria and $\geq 14$ HAM-D (1st 17 items)	Baseline, 6 wk	Clinician-rated	HAM-D¶	Desipramine = 23.00 (6.16); paroxetine = 21.00 (5.66); control = 23.91 (4.99)
Razavi et al., 1996 (60)	HADS $\geq 13$ before and after 1 wk on placebo; DSM-III-R major depressive disorder or adjustment disorder with depressed mood or mixed features	Baseline, 5 wk	Self-report	HADS	Fluoxetine = 22.70 (6.00); control = 23.50 (5.50)
			Clinician-rated	MADRS	Fluoxetine = 26.10 (7.10); control = 25.20 (7.70)
			Self-report	SCL-90-R Depression	Fluoxetine = 1.60 (0.70); control = 1.60 (0.80)

\* Assessments were also conducted at 6 months, which was before completion of the intervention. BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiologic Studies Depression Scale; CGI-S = Clinical Global Impression-Severity; DSM = Diagnostic and Statistical Manual; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Rating Scale for Depression (also abbreviated as HRSD); MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; PST = problem-solving therapy; SCID = Structured Clinical Interview for DSM Disorders; SCL = Symptom Checklist; ZSRDS = Zung Self-Rating Depression Scale.

† Assessments were also conducted at 6 and 12 months, but participants in the waitlist control were no longer assessed.

‡ Assessments were also conducted at 20 and 32 weeks, but participants in the treatment and wait-list groups were combined for analysis.

§ Assessments were also conducted at days 7, 14, and 21 after study enrollment, which was before completion of the intervention.

|| Assessments were also conducted at three other posttreatment points before 12 weeks.

¶ The CGI-S was also used to assess depression in this trial; however, data were not available from the author.

**Table 4.** Summary of quality of the studies included in the meta-analysis

Modified Physiotherapy Evidence Database (PEDro) criterion	Author, publication date (reference)*									
	Psychotherapeutic trials					Pharmacologic trials				
	Dwight-Johnson et al., 2005 (72)	Ell et al., 2008; 73,75	Evans & Connis, 1995 (59)	Nezu et al., 2003 (63)	Savard et al., 2006 (61)	Strong et al., 2008 (74)	Costa et al., 1985 (58)	Fisch et al., 2003 (71)	Musselman et al., 2006 (62)	Razavi et al., 1996 (60)
Eligibility criteria were specified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subjects were randomly assigned to treatment groups	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation was concealed	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
The groups were similar at baseline regarding most important prognostic indicators	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No†	No	Yes
All participants were blinded to treatment	No	No	No	No	No	No	Yes	Yes	Yes	Yes
There was blinding of all therapists who administered the therapy‡	No	No	No	No	No	No	Yes	Yes	Yes	Yes
All assessors who measured at least one key outcome were blinded to treatment information	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to treatment groups	No	No	Yes	Yes	No	Yes	No	No	No	No
All participants for whom outcome measures were available received the treatment or control intervention as allocated or, when this was not done, data for at least one key outcome was analyzed by “intention to treat” (including imputation)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The results of between-group statistical comparisons were reported for at least one key outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The study provided both point measures and measures of variability for at least one key outcome§	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The study had an adequate treatment fidelity protocol, including manualized treatment	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No
The study had an adequate treatment fidelity protocol, including monitoring of treatment implementation	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Loss to follow-up information was provided	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total no. of above criteria met	11	11	9	11	11	12	12	11	11	10

\* “Yes” indicates that the criterion was evidenced in the article, whereas “No” indicates that the criterion is not evidenced, not applicable, not coded, or could not be determined in the article.

† Baseline group differences were controlled statistically.

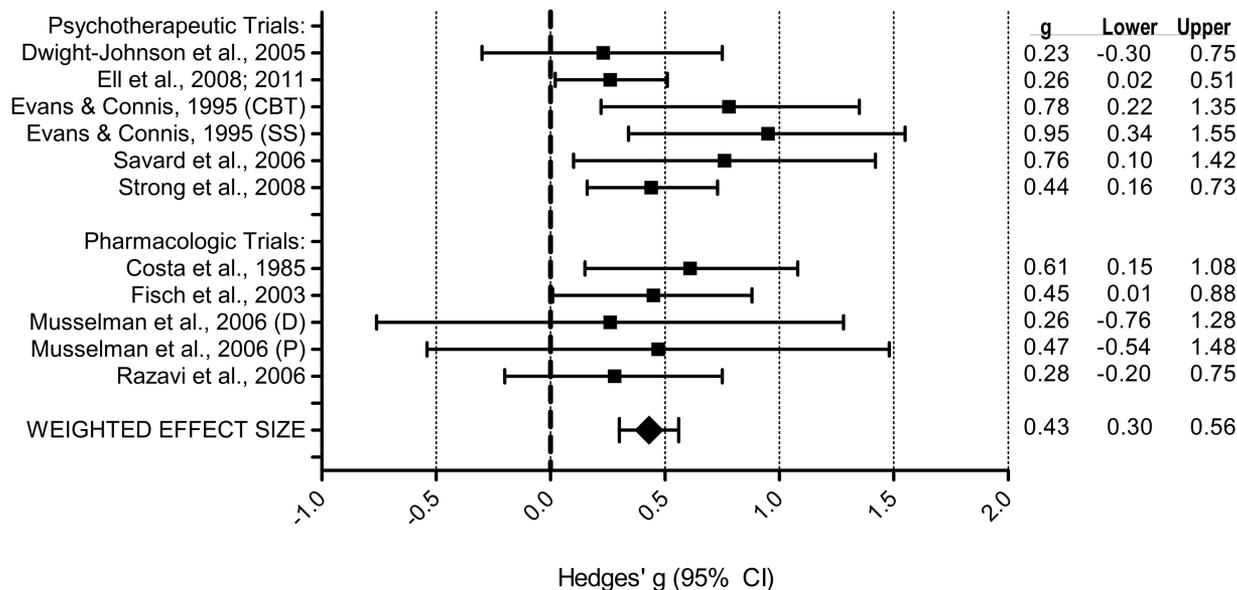
‡ This criterion typically is not applicable to psychotherapeutic and other behavioral interventions.

§ Data were provided in the article or obtained directly from the authors.

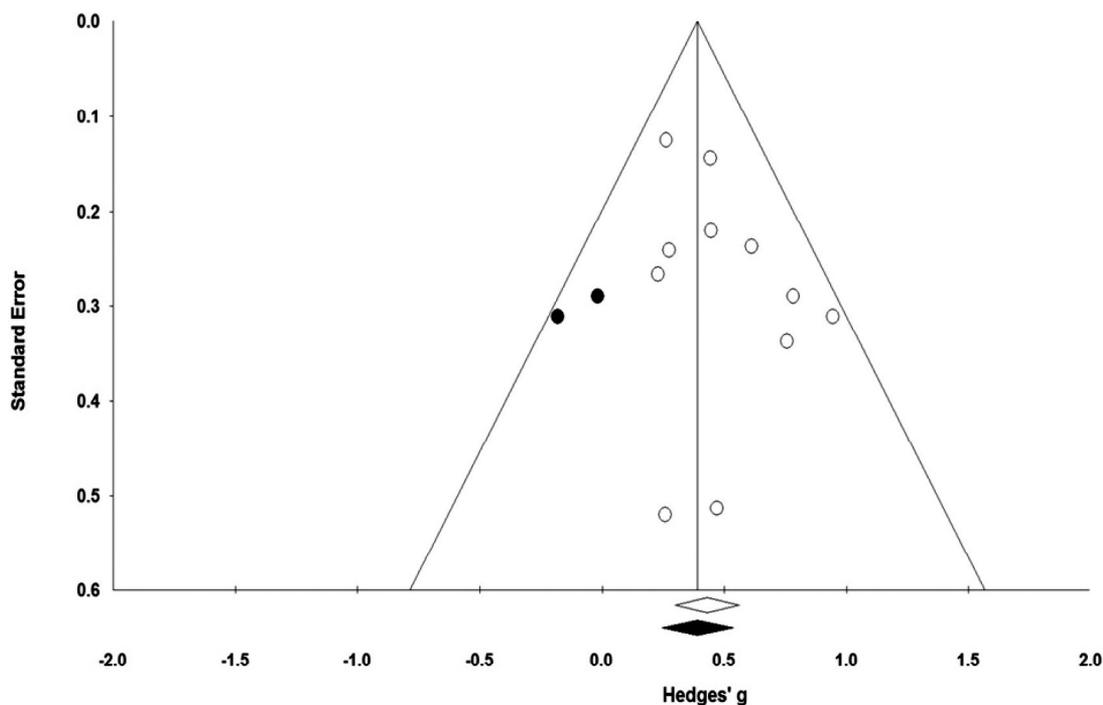
|| Data were not coded for pharmacologic interventions.

trial blinded treatment allocation for subjects or therapists. Two trials did not report blinding treatment allocation for assessors (59,60). Three studies had measures of key outcomes on more than

85% of participants (59,63,74). Five trials did not report having a treatment manual (58–60,62,71). Two trials did not report monitoring of treatment implementation (59,60).



**Figure 2.** Forest plot of effect sizes (Hedges' *g*, designated *g* in the figure) for trials included in the meta-analysis (58–62,72–75). The corresponding 95% CI (designated "Lower" and "Upper" and indicated graphically by whisker bars) are also given. Effect sizes for the trials containing two intervention groups are displayed separately (59,62). CBT = cognitive behavioral therapy; CI = confidence interval; D = desipramine; P = paroxetine; SS = social support.



**Figure 3.** Funnel plot of standard error by Hedges' *g* for trials included in the meta-analysis. The **open circles** represent observed studies and the **filled circles** represent imputed studies. The **open diamond** represents the observed effect size. The **closed diamond** represents the imputed effect size from Duval and Tweedie's (69) trim and fill procedure. Egger's test of the intercept indicated bias in the funnel plots was not statistically significant ( $P = .16$ ).

### Effect of Intervention Compared With Control Conditions

All 10 studies (with 13 comparisons of active treatment against the control condition after taking into account two intervention groups in three trials) reported posttest intervention effects against a control group. As displayed in Table 5, the random effects model showed that intervention conditions produced statistically significant reductions in depressive symptoms compared

with control conditions [Hedges'  $g = 1.01$ , 95% CI = 0.48 to 1.54,  $P < .001$ ]. Heterogeneity was very high ( $P = 93.4\%$ , 95% CI = 90.0 to 95.0;  $Q = 181.1$ , degrees of freedom [ $df$ ] = 12,  $P < .001$ ). Examination of the effect sizes for outliers indicated that the two comparisons by Nezu et al. (63) produced very large effects for PST (Hedges'  $g = 3.57$ , 95% CI = 2.90 to 4.23,  $P < .001$ ) and PST with involvement of a significant other (Hedges'  $g = 4.32$ ,

**Table 5.** Effects of intervention compared with control conditions and subgroup meta-analyses

Study or subgroup	Hedges' <i>g</i> * (95% CI)	<i>P</i>
Effect of intervention vs control conditions		
All included trials (58–63,71–75)†	1.01 (0.48 to 1.54)	<.001
Included trials (58–62,71–75)‡; outlier trial (63) removed§	0.43 (0.30 to 0.56)	<.001
Included trials (58–62,71–75) using lowest reported effect size	0.36 (0.22 to 0.49)	<.001
Included trials (58–62,71–75) using highest reported effect size	0.50 (0.31 to 0.70)	<.001
Effect of intervention compared with control conditions postintervention and at follow-up assessments		
Included trials with 6–8 mos postrandomization follow-up assessments (59,72,74)		
Postintervention	0.54 (0.27 to 0.82)	<.001
Follow-up	0.56 (0.34 to 0.78)	<.001
Included trials with 12–18 mos postrandomization follow-up assessments (73–75)		
Postintervention	0.34 (0.16 to 0.53)	<.001
Follow-up	0.37 (0.18 to 0.55)	<.001
Included trial with 24 mos postrandomization follow-up assessments (75)		
Postintervention	0.26 (0.02 to 0.51)	.040
Follow-up	0.19 (-0.08 to 0.46)	.173
Subgroup analyses		
Effect of CBT vs PST vs pharmacologic interventions		
CBT(59,61)	0.83 (0.48 to 1.18)	<.001
PST (72–75)	0.33 (0.15 to 0.50)	<.001
Pharmacologic (58,60,62,71)	0.44 (0.19 to 0.68)	<.001
Effect of intervention in psychotherapeutic trials meeting PEDro criterion: Whether at least 85% of study participants had postintervention data available for analysis		
Criterion met (59,74)	0.58 (0.34 to 0.81)	<.001
Criterion not met (61,72,73)	0.31 (0.10 to 0.52)	.004

\* Hedges' *g* was calculated on the basis of the standardized mean difference effect size which uses the pooled within-groups SD. Subgroup analyses used a mixed effects model, which pools studies within subgroups with a random effects model, but tested for statistically significant between-groups differences with a fixed effects model. All *P* values are two-tailed. CBT = cognitive behavioral therapy; PST = problem-solving therapy.

† Heterogeneity:  $I^2 = 93.4\%$ , 95% CI = 90.0 to 95.0;  $Q = 181.1$ , degrees of freedom (*df*) = 12,  $P < .001$ .

‡ Heterogeneity:  $I^2 = 0\%$ , 95% CI = 0.0 to 60.0;  $Q = 8.67$ , *df* = 10,  $P = .56$ .

§ Comparisons from Nezu et al. (63) included examination of effects of PST (Hedges' *g* = 3.57, 95% CI = 2.90 to 4.23,  $P < .001$ ) and PST with involvement of a significant other (Hedges' *g* = 4.32, 95% CI = 3.55 to 5.08,  $P < .001$ ).

95% CI = 3.55 to 5.08,  $P < .001$ ), both of which were dramatically larger than those of other studies (Table 5). A common recommendation for handling outliers is to remove them from the effect size distribution (66); eliminating that trial changed the overall effect size considerably, and the random effects model revealed a smaller effect. This model indicated that active treatments produced statistically significant reductions in depressive symptoms compared with control conditions; heterogeneity was not statistically significant (Hedges' *g* = 0.43, 95% CI = 0.30 to 0.56,  $P < 0.001$ ;  $I^2 = 0\%$ , 95% CI = 0.0 to 60.0;  $Q = 8.67$ , *df* = 10,

$P = .56$ ) (Table 5). Consequently, that trial was removed from further analyses. Figure 2 displays the forest plot for the remaining nine trials. As noted earlier, four studies used more than one outcome measure, and two studies had more than one intervention group (one of which also reported multiple outcomes). Table 5 shows that using only the lowest reported effect size for each of these studies did not substantially influence the statistically significant effect on depressive symptoms (Hedges' *g* = 0.36, 95% CI = 0.22 to 0.49,  $P < .001$ ), as was true when the analysis was limited to the highest reported effect size (Hedges' *g* = 0.50, 95% CI = 0.31 to 0.70,  $P < .001$ ).

### Postintervention Compared With Follow-up Assessments

Four trials (all psychotherapeutic) provided information on duration of the intervention effects (59,72–75). Three trials (59,72,74), provided follow-up data 6–8 months postrandomization, and Strong et al. (74) also included 12-month follow-up. The fourth trial (73,75) had follow-up at 18 and 24 months after random assignment to treatment arms. Because two trials had more than one follow-up and Ell et al. (73,75) conducted a longer follow-up, we performed analyses in three ways (Table 5).

First, the three trials with follow-up at 6–8 months (59,72,74) produced statistically significantly greater reductions in depressive symptoms than did the control conditions postintervention (Hedges' *g* = 0.54, 95% CI = 0.27 to 0.82,  $P < .001$ ) and at 6–8 months (Hedges' *g* = 0.56, 95% CI = 0.34 to 0.78,  $P < .001$ ). Second, the two trials that provided data at 12–18 months (73–75) demonstrated statistically significantly greater reductions in depressive symptoms favoring intervention vs control conditions (Hedges' *g* = 0.34, 95% CI = 0.16 to 0.53,  $P < .001$  at postintervention; Hedges' *g* = 0.37, 95% CI = 0.18 to 0.55,  $P < .001$  at 12–18 months). For the trial that had 24-month follow-up (75), the intervention was effective postintervention (Hedges' *g* = 0.26, 95% CI = 0.02 to 0.51,  $P = .04$ ), but not at 24 months after random assignment (Hedges' *g* = 0.19, 95% CI = -0.08 to 0.46,  $P = .17$ ).

### Subgroup Analyses

Effects of CBT vs PST vs pharmacologic interventions were assessed. For the psychotherapeutic studies, we created subgroups on the basis of the theoretical approach employed: CBT (59,61) vs PST (delivered within a collaborative care model or a multimodal intervention approach) (72–75). We then performed a subgroup comparison for CBT vs PST vs pharmacologic interventions (Table 5). CBT, PST, and pharmacologic interventions were more effective than control conditions in reducing depressive symptoms, as indicated by statistically significant effect sizes for each comparison (Hedges' *g* = 0.83, 95% CI = 0.48 to 1.18,  $P < .001$ ; Hedges' *g* = 0.33, 95% CI = 0.15 to 0.50,  $P < .001$ ; Hedges' *g* = 0.44, 95% CI = 0.19 to 0.68,  $P < .001$ , respectively). The difference among the three groups was statistically significant ( $P = .04$ ). Post hoc analyses revealed a statistically significant difference between CBT and PST ( $P = .01$ ), but the difference was not statistically significant between CBT and pharmacologic interventions ( $P = .07$ ) or between PST and pharmacologic interventions ( $P = .48$ ). The difference between CBT vs PST remained statistically significant after a Bonferroni correction for multiple tests ( $P = .02$ ).

The only PEDro criterion that had sufficient variability for analysis was whether at least 85% of study participants had postintervention outcome data available for analysis (Table 4). Of the psychotherapeutic studies, two met this criterion (59,74) and demonstrated a statistically significant reduction in depressive symptoms for active compared with control conditions (Hedges'  $g = 0.58$ , 95% CI = 0.34 to 0.81,  $P < .001$ ) (Table 5). The three studies that did not meet this criterion (61,72,73) also produced a statistically significant improvement in depressive symptoms (Hedges'  $g = 0.31$ , 95% CI = 0.10 to 0.52,  $P = .004$ ) (Table 5). The two effect sizes were similar ( $P = .10$ ). Note that none of the pharmacologic trials met this criterion.

None of the continuous variables examined through metaregression were statistically significantly associated with the observed overall effect size. Specifically, age ( $P = .91$ ), percentage of female participants ( $P = .13$ ), the number of psychotherapeutic sessions ( $P = .98$ ), and the number of weeks on medication ( $P = .93$ ) were not statistically significantly associated with the effect of active treatment on depressive symptoms as determined by the method of moments estimator (Supplementary Table 1, available online).

### Publication Bias

The funnel plot (Figure 3) shows a generally even distribution of effect sizes by standard errors, but the right side of the plot was populated by an additional two studies, compared with the left side. The slight skewness on the right side was confirmed by the fact that Duval and Tweedie's (69) trim and fill procedure imputed two studies on the left side of the plot, which indicates slight publication bias. As shown in Figure 3, the two studies that were imputed using the procedures described in the statistical analysis section slightly reduced the overall effect size (Hedges'  $g = 0.39$ ). However, the 95% CI of 0.24 to 0.54 for this effect size did not include 0. Egger's test of the intercept was not statistically significant ( $P = .16$ ) for bias in the funnel plot. The fail-safe  $N$  (the number of unpublished studies reporting statistically nonsignificant results needed to reduce the observed effect to statistical nonsignificance) of 106 confirms the relative stability of the observed effect size.

### Discussion

This meta-analysis of RCTs reveals that the set of five psychotherapeutic (after removal of one outlier) and four pharmacologic interventions were reliably superior in reducing depressive symptoms relative to control conditions for adults diagnosed with cancer who met an eligibility threshold for elevated depressive symptoms. The statistically significant effect size across trials was moderate and indicated that post-treatment, depressive symptoms were slightly less than a half SD lower for adults in intervention groups compared with those who were assigned to control treatment. In the four psychotherapeutic trials that included a longer-term follow-up (ie, 6–24 months postrandomization; note that the interventions were of variable length), the follow-up effect sizes remained statistically significant up to 12–18 months after randomization ( $P < .001$ ), indicating sustained effects.

The effect size obtained in this meta-analysis is somewhat lower than that found in a meta-analysis of interventions for adults who met an entry criterion for depression but were not selected

for diagnosis of a medical disorder (80) and is comparable to that of a meta-analysis (81) of 15 RCTs of psychological interventions in patients who had elevated depressive symptoms and had been diagnosed with one of 10 different medical disorders, including four oncology samples ( $d = .42$  after two outliers with very large effect sizes were removed). Previous meta-analyses (23,27,29) have documented the efficacy of psychotherapeutic interventions for cancer patients unselected at study entry for depression, particularly for individuals with relatively high baseline depressive symptoms (31,32,82). For example, Schneider et al. (31) conducted a meta-analysis of 27 psychosocial interventions (12 RCTs; 15 single-group designs) for cancer patients to examine whether preintervention depressive symptoms, as assessed by the Hospital Anxiety and Depression Scale (83), moderated intervention efficacy. Effects on HADS depressive symptoms were negligible when baseline depressive symptoms were low and pronounced when symptoms were relatively high. This finding did not vary by study design or intervention type, setting, or dose, and it held both immediately after treatment and 2–7 months later, although it weakened at longer follow-up. Baseline depressive symptoms explained 51.5% of the variance in treatment efficacy on depressive symptoms. Randomized and single-group interventions that specifically selected participants for elevated distress produced larger effect sizes than did nonselective interventions, but this factor was not a unique moderator of outcomes after statistical control for baseline depressive symptoms.

Our findings advance this literature by demonstrating that psychological and pharmacologic approaches, evaluated in RCTs, can be targeted productively toward cancer patients in need of intervention by virtue of clinical depression or elevated depressive symptoms. Whether tailoring or targeting of interventions to be responsive to specific characteristics of depression in the context of cancer, such as depression history or perceived cancer-related losses, produces more potent effects requires study.

In the current meta-analysis, heterogeneity of effect sizes was not marked across trials, and subgroup analyses suggest that effects did not vary systematically as a function of trial attrition rate, participant age and sex, or intervention length. However, a comparison of CBT, PST, and pharmacologic approaches revealed that CBT produced statistically significantly larger effects than did PST and a somewhat but statistically nonsignificantly larger effect than pharmacologic interventions; PST and pharmacologic interventions were similar. It is important to note that these comparisons are not equivalent to comparing the different interventions directly within an RCT. Thus, the finding of the superiority of CBT must be interpreted cautiously and within the context of the specific trials (Tables 1–4). In addition to their distinct intervention content, the CBT trials also differ from the other approaches in that the CBT trials on average included somewhat fewer participants, arguably employed less stringent eligibility criteria for depressive symptoms, and had less elapsed time from baseline to postintervention assessment compared with PST (but not with pharmacologic trials). In addition, CBT was the sole therapeutic approach of those trials, whereas PST was administered within a collaborative care (72,73,75) or multimodal approach (74), which included a pharmacologic option and did not invariably include PST (72,73,75). Furthermore, although interventionists received

systematic training in PST, they did not necessarily have a background in delivering psychological treatments (74), whereas interventionists in the CBT trials were experienced in that modality. These last two points also suggest the importance of continued research on the effectiveness of psychosocial interventions delivered within a specialized psycho-oncology context vs an approach imported from integrated primary care (84–86).

It is also important to note that the outlier removed from analysis was a PST trial that yielded very large effect sizes (63). We could not definitively identify why this trial yielded extremely large effects. However, it differed from the other RCTs in that it was conducted by founders of the treatment approach, provided intensive training of therapists on the manualized protocol, involved weekly supervision provided by the founders, used recruitment of interested patients rather than systematic screening of a clinic or other population, and required as an eligibility criterion that a significant other be willing to participate in the intervention, all of which may have contributed to the outlying large effect sizes. The advantage of CBT compared with other approaches to treat depression in the general population has been suggested in other reviews (87,88); however, randomized trials are required to test its advantage over other treatments in depressed cancer patients. Although head-to-head comparisons of intervention approaches are accruing, none of the 10 trials identified in our literature search compared the same two interventions (42–45,47–49,59,62,63). In the most relevant trial (47), a form of PST was compared with behavioral activation treatment in breast cancer patients with major depression. Both interventions were effective in decreasing depressive symptoms, with gains maintained or augmented throughout 12 months.

Several limitations of this meta-analysis and the current literature are apparent. First, three trials could not be included in the analysis because of incomplete data, and it is possible that some trials were missed, even in this comprehensive search. The finding that more than 100 trials—each demonstrating no statistically significant reduction in depression for the intervention (vs control condition)—would be needed to nullify the statistically significant effect of intervention, however, suggests the effect's stability. Nonetheless, the observation that only ten trials were available for analysis highlights the paucity of interventions targeted to cancer patients with elevated depressive symptoms and points to the importance of conducting additional RCTs. Second, differences among trials were pronounced on some features, including sample size, participants' education level, gender, race/ethnicity, cancer stage, and time elapsed after cancer diagnosis, interventionist type and expertise, intervention length, and entry criteria for and operationalization of depression. Although statistically significant heterogeneity in effect sizes was not evident once the one outlier was removed, a larger pool of trials might yield important moderators of intervention effects. Third, relatively few intervention approaches were represented in this review; approaches receiving current attention in cancer populations, such as physical activity interventions, require study for their impact on depression. Finally, generalizability of the findings to other groups (eg, adolescents/young adults) awaits additional research.

Limitations in the individual trials also suggest that additional research is essential. Specifically, five trials relied on questionnaire

assessment of depressive symptoms rather than interview-based assessment for depressive disorder, medication protocols were no longer than 12 weeks in duration, attrition from the point of random assignment to the postintervention assessment exceeded 33% in four of 10 trials (62,71–73), and six trials did not include follow-up assessment beyond the postintervention point.

The current meta-analysis revealed reliable positive effects of psychotherapeutic and pharmacologic interventions, with some advantage for CBT, for adults diagnosed with cancer who had comorbid elevated depressive symptoms or a depression diagnosis. These data are consonant with findings from the literature on depression in the general adult population showing that bona-fide psychotherapies and second-generation antidepressants are effective at reducing depression in the short term (89). Our findings inform two crucial clinical questions, the first of which regards the advisability of screening for depression in cancer patients and subsequent provision of interventions specifically targeted toward individuals with elevated symptoms. A recent meta-analysis (31) suggests that preintervention assessment of distress may be an efficient way to identify those who are most likely to benefit from therapeutic intervention. Further, the National Comprehensive Cancer Network guidelines (90) and an Institute of Medicine report (91) emphasize the importance of screening cancer patients for distress. Reviews indicate that screening for depression has not yet become a standard part of oncology care (92,93), however, and controversy exists regarding the utility of psychosocial screening in oncology settings (94–97). Our findings demonstrate that when assessment is performed with psychometrically sound questionnaires or interviews and intervention is targeted toward cancer patients meeting criteria for elevated depressive symptoms, reliable improvement in depression occurs, at least within a research context. The available evidence suggests that patients who demonstrate elevated symptoms of depression should be referred for treatment. However, two caveats are important. First, because screening itself was not randomized in these trials, we can conclude that only the combination of depression assessment and intervention (not screening by itself) is effective. Indeed, authors of a recent review reported that no RCTs have examined whether screening for depression in cancer patients improves depression outcomes and outweighs the potential harms of such screening (98). Second, dissemination research on the effectiveness of interventions for depressed cancer patients in clinical settings is lacking.

In light of the efficacy of existing interventions demonstrated in this meta-analysis, a second question is whether additional interventions require development and investigation for individuals with cancer who are depressed. Burgeoning awareness of the importance of depression in individuals with cancer is evidenced by on-going trials of interventions targeted at this group (99,100). We would argue that such intervention development and evaluation in RCTs remains essential for several reasons. First, conclusions regarding intervention efficacy are limited by the small number of existing trials and their lack of efficacy assessment beyond 3 months for pharmacologic trials and 24 months after randomization for psychotherapeutic trials. Second, examination of important moderators of efficacy was limited by the small number of available trials. For example, insufficient data were available to examine whether interventions are differentially effective for depressed

individuals with advanced cancers vs early-stage disease. A particularly interesting question is whether interventions require tailoring to individuals who have a premorbid history of depression (101) and to individuals who develop depression at particular points in the cancer trajectory (eg, at diagnosis and medical treatment, after treatment completion, at cancer recurrence; 102,103). Third, the obtained moderate effect size leaves room for improvement in the power of interventions to ameliorate depression. Finally, interventions that are maximally accessible to diverse groups require study. Most interventions in the present review were delivered in person in individual sessions, which requires substantial resources on the part of both recipients and professionals. In light of the psychological, behavioral, and economic toll of depression, as well as its health burden on adults with cancer, intensive attention to the development and dissemination of maximally effective, efficient, and accessible interventions for heterogeneous cancer patients is warranted.

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