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Review

THE LONG-TERM EFFICACY OF ACUTE-PHASE PSYCHOTHERAPY FOR DEPRESSION: A META-ANALYSIS OF RANDOMIZED TRIALS

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Background: *Understanding the effectiveness of treatment for depression in both the short term and long term is essential for clinical decision making. The present meta-analysis examined treatment effects on depression and quality of life in acute-phase psychotherapeutic interventions compared to no treatment control groups for adult depression at 6 months or longer postrandomization.* **Methods:** *A systematic literature search resulted in 44 randomized controlled trials with 6,096 participants. Acute-phase psychotherapy was compared to control groups at 6-month or longer postrandomization. Odds ratios of a positive outcome were calculated.* **Results:** *Psychotherapy outperformed control groups at 6 months or longer postrandomization (OR = 1.92, 95% CI: 1.60–2.31, P < .001). Heterogeneity was moderate (I^2: 65, 95% CI: 53–74, P < .001). However, effects significantly decreased with longer follow-up periods. Additionally, a small positive effect of psychotherapy was observed for quality of life, while similar effects were obtained in separate analyses of each type of psychotherapy, with the exception of nondirective supportive therapy. Studies that provided booster sessions had better treatment results compared with studies that did not provide any further sessions. Finally, we found that trials on psychotherapy aimed at major depressive disorder (MDD) had better outcomes than those that were aimed at elevated depressive symptoms.* **Conclusions:** *There is substantial evidence that acute-phase psychotherapy results in a better treatment effects on depression and quality of life in the long term for adult patients with depression. Depression and Anxiety 33:370–383, 2016.*

Key words: *depression; long-term; psychotherapy*

INTRODUCTION

Depression, a highly prevalent and disabling disorder, constitutes a major public health issue worldwide. Epidemiological studies have shown that 14.6% of individuals in developed countries have experienced a major

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depressive episode at some point throughout lifetime.[1] In addition to high prevalence rates, depression is currently ranked first among mental disorders with regard to disease burden, according to the World Health Organization.[2] This disease burden results from the large impact of depressive disorder on individuals' lives, as depression adversely affects quality of life. Depressive disorder is also associated with increased mortality rates and high economic and societal cost.[3–5] Additionally, depression has high relapse rates, which in turn increase the chance of depression developing into a chronic condition.[6,7] Keller[8] estimated that individuals who have experienced one episode of depression have 50% chance of experiencing a second episode, while those who have experienced a second episode have 90% chance of experiencing a third.[8]

The high adverse impact of depression on individuals' lives underscores the need for treatment. Maintenance pharmacotherapy is currently the most widely used treatment in preventing relapse of depressive episodes. Antidepressant medication reduces the risk of relapse, especially when used for long periods of time.[9] However, a notable number of patients have a preference for short-term use of antidepressants resulting in low adherence to medication and leading to recidivism. Moreover, research has shown that a considerable percentage of individuals with depression prefer psychotherapy to pharmacotherapy.[10] Psychotherapy aims at helping individuals to develop adaptive mechanisms in order to be more functional in their lives and to effectively cope with depression. Psychotherapy intends to alleviate symptoms of an active depression but also works to prevent future relapses and maintain the favourable treatment response over a lengthy time.

It is well known that acute-phase psychotherapy (psychotherapy targeted at an active depression) is effective in the treatment of depressive disorders in short term. For instance, a recent meta-analysis carried out by Cuijpers et al.[11] examined the effects of cognitive behavioral therapy (CBT) in treating adult depression. The authors found a large effect size in favour of CBT compared to control groups ($d = 0.71$) at the posttreatment assessment.[11] Similar results have been presented for several other major types of psychotherapy, such as interpersonal psychotherapy[12] and behavioral activation.[13] Despite these favourable short-term effects, there is little rigorous meta-analytic evidence regarding long-term outcomes of psychotherapy on depression.

Given the high risk of relapse, it is critical to examine whether psychotherapy results in an enduring effect on depression. Poor long-term outcomes lead to increased health care service utilization and consequently to higher costs for the public healthcare system.[14] Results derived from a meta-analysis by Piet et al.[15] showed that maintenance mindfulness-based cognitive therapy (MBCT) resulted in a better reduction of depressive symptoms in comparison with treatment as usual or pill placebo at 6 months follow-up. This corresponds to a relative risk reduction of 34% in favour of MBCT.[15] These results are in accordance with the meta-analysis of Biesheuvel-Leliefeld et al.[16] The authors examined the effectiveness of maintenance psychotherapy compared to treatment as usual (TAU) in reducing relapse or recurrence in patients with major depressive disorder (MDD). The results indicated that maintenance psychotherapeutic interventions reduced significantly the risk of relapse (RR = 0.64) in patients with MDD.[16]

To the best of our knowledge there is no systematic review that has examined the long-term effects of acute-phase psychotherapy compared to control groups. Such a systematic review would extend our knowledge from short-term to long-term outcomes and would assist us in guiding clinical decisions and planning processes regarding depression treatment strategies in primary and secondary mental health care. Moreover, it would give an indication of the number of patients that maintain treatment response in the long term, after receiving acute-phase psychotherapy. The aim of the present meta-analysis is to examine long-term treatment effects on depression and quality of life at 6 months or longer postrandomization to either acute-phase psychotherapy for depression or a control group. The hypothesis is that psychotherapeutic interventions will outperform the control groups on depression and quality of life at 6 months or longer postrandomization.

METHODS

DEFINITIONS

Psychotherapy was defined as an intervention in which either verbal communication between a therapist and a client is the core element, or in which a psychological treatment is contained in book (bibliotherapy) or electronic format (Internet-based treatment), which a patient works through more or less independently, but with some personal support from a therapist (guided by telephone, e-mail, or otherwise).[17] In the present meta-analysis, we used a definition of psychotherapy based on taxonomy of psychotherapy types for depression developed by a group of experts in the field.[17] The classification was based on a systematic search for studies on psychological treatments for depression, using broad definitions for psychotherapy. This process resulted in seven major types of psychotherapy for depression: behavioral activation (BA), cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), nondirective supportive therapy (SUP), psychodynamic psychotherapy (DYN), and social skills training (SST) (see Appendix A).

Acute-phase psychotherapy was defined as the short-term psychotherapy delivered during the occurrence of depressive symptoms, as opposed to maintenance psychotherapy that can be delivered during remission/recovery of depressive symptoms.

INCLUSION CRITERIA

We selected randomized controlled trials (RCTs) including adult patients with depression (based on a clinical interview or on elevated depressive symptoms ratings on symptom scales). The selected interventions were all main psychotherapeutic interventions (as described above), while the selected comparison groups were usual care, waiting list, no treatment (no pharmacotherapy), or pill placebo. Light therapy or other types of psychotherapy, not defined as a main type of psychotherapy according to the definition described above, were not

considered eligible as a comparison. We only included studies published and written in English.

SEARCH STRATEGY

We searched Medline (PubMed.com), PsycINFO (Ebsco), Embase (embase.com), and the Cochrane library (cochranelibrary.com) from database inception to January 1, 2015. We used index and text words indicating psychotherapy combined with key terms for depression. We used a filter for RCTs as recommended in the Cochrane Handbook.[18] The full search string for PubMed is given in Appendix B. Additionally, we searched an existing database on psychological treatments for depression in order to increase the probability of identifying eligible citations. This database has been developed and updated through literature searches in PubMed, PsycINFO, Embase, and the Cochrane Central Register of Control trials from January 2006 until January 2015.[19] Furthermore, references of selected studies were searched to identify additional relevant studies. Two reviewers (E.K. and Y.S. or D.B. or E.W.) independently examined abstracts for eligibility. Studies that met inclusion criteria were examined in full text. In the case of disagreement, the opinion of a third reviewer (P.C.) was sought.

DATA EXTRACTION

The following data were extracted: reference, years of inclusion, country, patient characteristics (e.g. target group: adults in general, specific target group, such as older adults, women with postpartum depression, etc.), therapy characteristics (type of psychotherapy, number of treatment sessions etc.), control characteristics (e.g. type of control), and type and length of follow-up period. Most studies in this field used a naturalistic follow-up. Therefore, for each study we reported how long the follow-up period lasted, but also whether there was regular contact with a therapist. In some studies, outcome data were only reported for patients who responded to treatment in the acute-phase treatment phase, while others reported outcomes for the full intention-to-treat sample. Two reviewers (E.K. and D.B.) extracted data independently; a third reviewer (P.C.) checked the data extraction.

QUALITY ASSESSMENT

The quality of the included RCTs was examined by two reviewers (E.K. and Y.S. or D.B.) independently, according to Cochrane Risk of Bias tool.[20] Any disagreement between the reviewers was solved through discussion.

STATISTICAL ANALYSIS

We focused on all positive dichotomous outcomes on depression. In the context of the present paper, this combination of all positive outcomes is defined as "all positive outcomes combined." For the examined comparison between psychotherapy and control conditions we calculated the odds ratio (OR) of all positive outcomes combined based on dichotomous results. The following outcomes were extracted from the studies and were entered into the analysis hierarchically (when the first outcome in the hierarchy was not available the next available outcome was used):

1. Recovery (absence of depressive symptoms for ≥4 months after remission)
2. Remission (no depressive symptoms; BDI I and II < 11; HAMD-17 and 21 < 8; MADRS < 7; PHQ-9 < 5)
3. Partial remission (no depressive symptoms or mild depressive symptoms; BDI I and II < 14; HAMD-17 and 21 < 14; MADRS < 20; PHQ-9 < 10)
4. Response (50% reduction from baseline severity on any depression measure)
5. If no dichotomous outcomes were reported, we calculated the standardized mean difference (SMD) as the difference in mean scores divided by the pooled standard deviation. Subsequently, the mean difference was transformed into the OR according to the procedures given by Borenstein et al.[21]

For dichotomous outcomes all randomized patients were taken as the denominator and reported outcomes in completers were taken as the numerator, thus simulating a last observation carried forward procedure. We also conducted meta-analyses for recovery, remission, partial remission, and response rates separately.

Regarding the outcome quality of life, we calculated the effect sizes (Hedges's *g*) for the global quality of life (social functioning, physical, and mental health). Hedge's *g* allows for small sample bias correction and is calculated by subtracting the average score (on global quality of life) of the psychotherapy group from the average score of the control group (at the follow-up) and dividing the results by the pooled standard deviation.[22]

We calculated pooled odds ratios using the Comprehensive Meta-Analysis (version 2.2.021) program. We expected considerable heterogeneity among the studies, so we used a random effects model to pool the results of the included RCTs.

The statistical heterogeneity was examined for all the outcomes of the present meta-analysis. This type of heterogeneity refers to the variability of the intervention effects between the included studies and indicates how much of the variability between studies can be explained by chance alone. Statistical heterogeneity can be caused by variability among the participants, interventions, outcomes, and design of the included studies.[23] The I^2-statistic, an indicator of heterogeneity in percentages, was calculated in order to examine the homogeneity of the effect sizes. Heterogeneity was not observed if the resulted value of $I^2 = 0\%$, as low when $I^2 = 1$–25%, as moderate when $I^2 = 26$–74% and as high when $I^2 \geq 75\%$. We calculated 95% confidence intervals (CI) around I^2[[24]] using the noncentral chi-squared based approach within the heterogi module for Stata.[25] The *Q*-statistic was calculated, and reported when significant.

We examined publication bias by examining the funnel plot on primary outcome measures and by using the Duval and Tweedie's trim and fill procedure.[26,27] This procedure provides an estimate of the effect size after adjusting for publication bias (as implemented in Comprehensive Meta-analysis, version 2.2.021). Finally, we used Egger's test of the intercept to test the asymmetry of the funnel plot and examine whether this possibility of publication bias was significant.[28]

RESULTS

STUDY SELECTION

The systematic literature search was performed on January 1, 2015. This search resulted in 15,057 citations. After removal of duplicates, 9,204 single citations were examined on title and abstract. This procedure led to 1,471 articles that were reviewed full text. Forty-four studies met the inclusion criteria and were included in the meta-analyses. Figure 1 presents the study selection process.

STUDY CHARACTERISTICS

Table 1 presents the characteristics of the included studies. Forty-four studies and five companion papers with a total number of 6,096 participants with depression evaluated the effects of psychotherapy compared to control groups at 6 months or longer postrandomization.

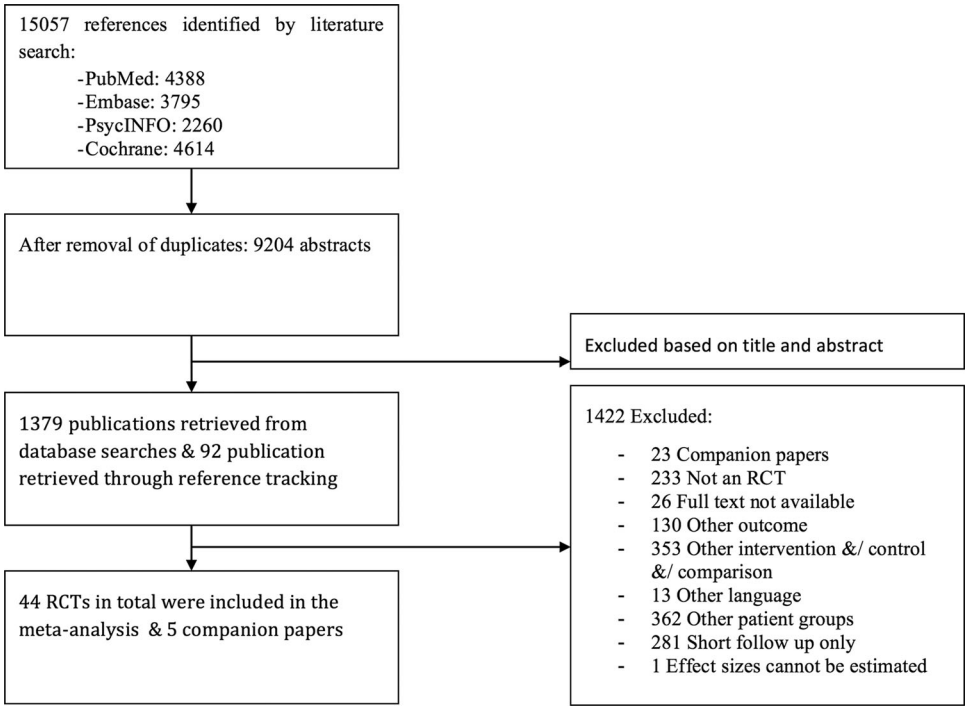

Figure 1. Flow chart of studies selection process.

Most of the included studies recruited their participants through clinical settings ($n = 33$) while nine studies recruited their participants through community samples and two studies used both clinical and community referrals. The included RCTs were conducted across 12 different countries: Australia, Brazil, China, Finland, Ireland, Norway, Spain, the Netherlands, the United Kingdom, the United States, Turkey, and Uganda. All studies used all of the initially randomized participants at the follow-up assessment. The follow-up duration varied from 6 to 18 months postrandomization. Most of the included studies did not report on the issue of out-of-protocol interval treatment during follow-up. Only four trials reported that participants were free to access treatment after the acute-phase therapy (naturalistic follow-up; Appendix C).

Among the examined types of psychotherapy were behavioral activation, cognitive behavioral therapy, interpersonal psychotherapy, nondirective supportive therapy, problem solving therapy, and psychodynamic therapy. We found no trials on long-term effects of social skills training. In the majority of the included studies, psychotherapy was administered face to face while six studies used web-based or telephone-based psychotherapy. The number of treatment sessions varied from four to 26 usually weekly sessions (more details on the duration of the therapy can be found in Appendix C). Most of the included studies used TAU as the control comparison condition. The definition of TAU varied across different studies and countries. In the included trials, TAU was mostly defined as therapy carried out by general practitioners (GPs), referrals to community mental health services and/or nonspecific antidepressant medications. Other types of control conditions were attention controls, life style interventions, no further assessment, nonspecific antidepressant medication, placebo alone or with clinical management, no treatment and waiting list (further details regarding the control conditions can be found in Appendix C).

RISK OF BIAS OF THE INCLUDED STUDIES

The quality of the included studies varied. Most of the studies presented adequate random sequence generation (31/44) while the allocation was adequate in 16 of the included RCTs. In the vast majority of the studies blinding of participants was not possible due to the nature of the psychotherapeutic interventions. However, one RCT used placebo psychotherapy. Finally, 26 studies used intention-to-treat analyses to handle incomplete outcome data and most of the studies were evaluated at a low risk for selective reporting (42/44) while all studies were free from other sources of bias (Fig. 2).

ACUTE PSYCHOTHERAPY VERSUS CONTROL CONDITIONS (AT ≥6 MONTHS POSTRANDOMIZATION)

All Positive Outcomes Combined and Quality of Life. The results of all the meta-analyses are presented in Table 2. Forty-four studies (55 comparisons) compared psychotherapy to control groups at 6 months or longer postrandomization. Psychotherapy significantly

TABLE 1. Characteristics of the included RCTs: psychotherapy (acute-phase) versus control groups in adults with depression

Studies	Diagnosis	Recruitment	Acute-phase PT	*N*	Number of sessions	Continuation phase PT	Control group	*N*	FU (m)	Outcome	Country
Allart-van Dam et al.[31]	BDI ≥ 10	Com.	CBT	62	12	1	No treatment	41	12	DS (BDI)	NL
Bass et al.[29]	MDD (DSM-IV)	Com.	IPT-G	107	16	No	TAU	117	6	DS (HSCL)	UG
Beeber et al.[32]	CESD ≥ 16	Com.	IPT	39	16	No	TAU	41	6	DS (CESD)	US
Burns et al.[33]	MDD (ICD-10)	Com.	CBT and TAU	18	12	No	TAU	18	8	DS (CISR), QoL (EQ-5D)	UK
Choi et al.[34]	HAMD ≥ 15	CS	T-PST	43	6	6	Attention control	36	6	DS (HAMD)	US
			In person PST	42							
Cooper et al.[35]	MDD (SCID)	Com.	CBT	43	NR	No	TAU–GPs	52	18	DS (EPDS); remission (SCID)	UK
			DYN	50							
			SUP	48							
Cramer et al.[36]	Clinical Depression (PHQ-9 ≥ 10 and <21)	CS	CBT-G	52	12	2	TAU–GPs	21	6	DS (PHQ-9); partial remission (PHQ-9 < 10); Response (50% PHQ-9)	UK
Dowrick et al.[37]	MDE, DYS (ICD-10)	Com.	PST	128	6	No	No treatment	189	6, 12	DS (BDI); QoL (SF-36)	FI, IE, NO, SP, UK
			CBT	108	12						
Duarte et al.[38]	MDD (DSM-IV)	CS	CBT	41	NR	6	TAU	44	9	DS (BDI)	BR
Dwight-Johnson et al.[39]	PHQ-9 > 10	CS	Tele-CBT	50	8	No	Enhanced TAU	51	6	DS (PHQ-9); Response (50% PHQ-9)	US
Elkin et al.[40,41]	MDD	CS	CBT	59	16	No	Placebo and CM	62	18	Recovery (DSM-IV, RDC)	US
			IPT	61							
Evans et al.[42]	CESD ≥ 16	CS	CBT-G	29	8	No	No treatment	26	6	DS (CES-D)	US
Freedland et al.[43]	MDD, Min DD (DSM-IV)	CS	CBT	41	12	No	TAU	40	6, 9	Remission (BDI< 7; HAMD < 7); recovery (sustain remission at FU); QoL (SF-36)	US
Gary et al.[44]	MDD, Min DD (DSM-IV)	CS	CBT	19	12	If needed	TAU	17	6	DS (HAMD)	US
			CBT and EX	18							
Geraedts et al.[45]	CESD ≥ 16	Com.	Web CBT	116	6	No	TAU	115	6, 12	DS (CESD)	NL
Hamamci et al.[46]	BDI ≥ 19	Com.	CBT-G	10	11	No	No treatment	11	6	DS (BDI)	TR
			CBT-G and PD	10	11						
Honey et al.[47]	EPD > 12	CS	SUP-G	23	8	No	TAU	22	6	DS (EPD); partial remission (EPD < 13)	UK
Kay-Lambkin et al.[48]	MDD (DSM-IV)	CS and com.	In person CBT	35	10	No	No treatment	30	6, 12	DS (BDI)	UK
			C-CBT	32	9						
Kessler et al.[49]	MDD (ICD-10)	CS	CBT	149	10	No	WL	148	8	Remission (BDI < 10); QoL (EQ-5D)	UK
King et al.[50]	BDI ≥ 14	CS	SUP	67	12	No	TAU	67	12	DS (BDI), QoL (EQ-5D)	UK
			CBT	63							

(*Continued*)

TABLE 1. Continued

Studies	Diagnosis	Recruitment	Acute-phase PT	*N*	Number of sessions	Continuation phase PT	Control group	*N*	FU (m)	Outcome	Country
Laidlaw et al.[51]	MDD (DSM-IV)	CS	CBT	21	17	No	TAU	23	6	DS (BDI, HAMD)	UK
Lamers et al.[52]	Min, mild, mod. DD (DSM-IV)	CS	CBT and self-management	183	10	No	TAU	178	9	DS (BDI); QoL (SF-36)	NL
Lustman et al.[53]	MDD (DSM-III)	CS	CBT	25	10	No	Nonspecific ADM	26	6	Response (50% BDI); remission (BDI < 10)	US
MacPherson et al.[54]	BDI-II ≥ 20	CS	SUP	302	12	No	TAU	151	12	DS (BDI-II, PHQ-9)	UK
Miranda et al.[55,56]	MDD (ICD-10)	CS	CBT	90	8	No	TAU	89	12	Remission (HAMD < 7)	US
Mohr et al.[57]	MDD (DSM-IV)	CS	Tele-CBT	41	16	No	TAU	44	6	DS (HAMD, PHQ-9)	US
Mossey et al.[58]	GDS > 10	CS	SUP	31	10	No	TAU	38	6	DS (GDS)	US
O'Mahen et al.[59]	MDD (DSM-IV)	CS	CBT	30	12	No	TAU	25	6	DS (BDI); Partial remission (BDI < 14)	US
Pagoto et al.[60]	MDD (DSM-IV)	CS and com.	BA	78	26	No	LI	83	6, 12	Remission (BDI < 10, HRSD < 7)	US
Poleshuck et al.[61]	HRSD>15	CS	IPT	34	8	No	TAU	28	6,9	DS (BDI, HRSD)	US
Power et al.[62]	MDD (DSM-IV)	CS	CBT IPT	39 22	16	No	TAU	10	6	DS (BDI)	UK
Prendergast et al.[63]	EPDS ≥ 12	CS	CBT	17	6	No	TAU	20	6	DS (EPDS)	AU
Qiu et al.[30]	MDD (DSM-IV)	CS	CBT-G	31	10	No	WL	31	6	DS (HRSD)	CN
Scott et al.[64]	MDD (DSM-III-R)	CS	CBT	24	6	No	TAU	24	8, 14	DS (BDI, HRSD)	UK
Serfaty et al.[65,66]	BDI-II ≥ 14	CS	CBT and TAU	70	12	No	TAU	67	10	DS (BDI-II); QoL (EQ-5D)	UK
Simpson et al.[67,68]	BDI ≥ 14	CS	DYN	92	6–12	No	TAU	89	6, 12	DS (BDI); partial remission (BDI < 14)	UK
Smit et al.[69,70]	MDD (DSM –IV)	CS	CBT and DRP	44	10–12	No	TAU	72	6	Remission (DSM-IV); recovery (DSM-IV)	NL
Swartz et al.[71]	MDD (DSM-IV)	CS	IPT	26	8	No	TAU	21	9	DS (BDI, HRDS)	US
Tandon et al.[72]	CESD ≥ 16	CS	CBT-G	61	6	No	TAU	59	6	DS (BDI-II)	US
Teasdale et al.[73]	MDD (RDC)	CS	CBT	17	20	2	TAU	17	6	DS (BDI)	US
Van Schaik et al.[74,75]	MDD (PRIME-MD)	CS	IPT	69	10	No	TAU	74	12	DS (GDS-15, MADRS); Partial remission (MADRS < 10); Response (50% MADRS); recovery (PRIME-MD); QoL (SF-36)	NL
Verduyn et al.[76]	BDI ≥ 15	Com.	CBT-G	47	16	No	No treatment Placebo PT	28 44	6, 12	DS (BDI, HAMD)	UK
Wiles et al.[77]	MDD (ICD-10)	CS	CBT and TAU	234	12	6	TAU	235	12	DS (BDI); response (50% BDI); remission (BDI < 10); QoL (SF-12)	UK
Williams et al.[78]	BDI-II ≥ 14	CS	Web CBT	141	3	No	TAU	140	12	DS (BDI-II)	UK

ADM, antidepressant medication; ACT, acceptance and commitment therapy; BA, behavioural activation therapy; BDI, Beck Depression Inventory; BR, Brazil; C-CT, computerized cognitive therapy; CBT and EX, combined exercise and cognitive behavioral therapy; CISR, Clinical Interview Schedule Revised; CM, clinical management; CN, China; Com, community sample; CS, clinical sample; CT, cognitive therapy; DRP, depression recurrence prevention; DS, depression severity; DSM, Diagnostic and Statistical Manual of Mental Disorders; DYN, psychodynamic therapy; DYS, dysthymia; EPDS, Edinburg Postnatal Depression Scale; EQ-5D, EuroQol- 5 Dimensions; FACT-B, functional assessment of cancer therapy-breast; FACT-B, functional assessment of cancer therapy-breast; FI, Finland; G, group therapy; GDS, Geriatric Depression Scale; HRSD, Hamilton Rating Scale for Depression; HSCL, Hopkins Symptoms Checklist; ICD-10, International Classification of Diseases; IE, Ireland; IPT, interpersonal psychotherapy; LI, lifestyle intervention; m, months; MADRS, Montgomery Asberg Depression Rating Scale; MBCT, mindfulness based cognitive therapy; MDD, major depressive disorder; MDE, major depressive episode; MinDD, minor depressive disorder; Mod. DD, moderate depressive disorder; N, number; NL, The Netherlands; NO, Norway; NR, not reported; PD, integrated psychodrama; PHQ-9, patient health questionnaire; PST, problem solving therapy; PT, psychotherapy; QoL, quality of life; RDC, Research Diagnostic Criteria; SCID, Structural Clinical Interview for DSM disorders; SCL-20, Symptom Checklist-20; SE, Sweden; SF, Short Form health survey; SP, Spain; SS-G, social support-group therapy; SSM, supportive stress management; SUP, non directive supportive therapy; TAU, treatment as usual; Tele, telephone; TR, Turkey; UG, Uganda; UK, the United Kingdom; US, the United States; WHOQOL, World Health Organization Quality of Life; WL, waiting list.

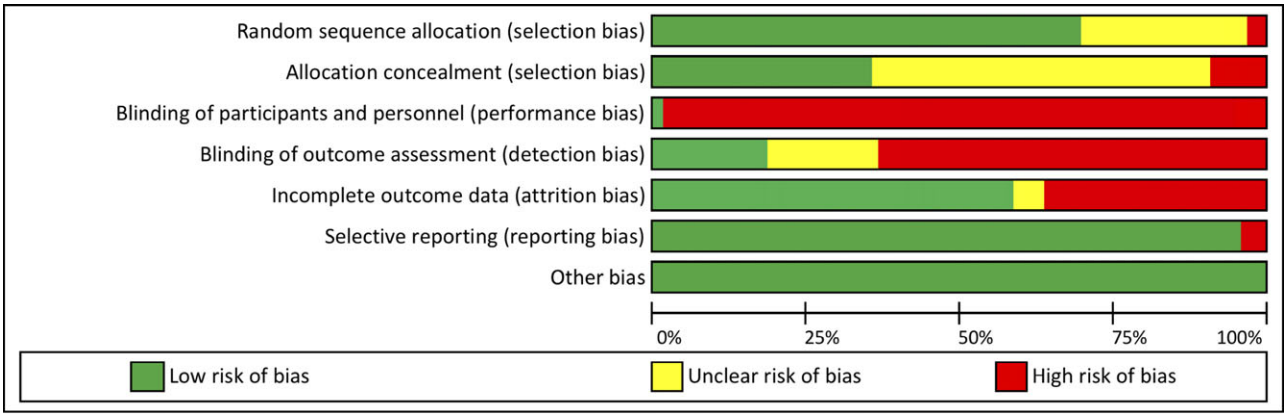

Figure 2. Risk of bias assessment.

outperformed control groups (OR = 1.92, $P < .001$). Heterogeneity was moderate (I^2: 65%, $P < .001$). The ORs and 95% CIs are presented in Fig. 3. Visual inspection of Fig. 3 suggested that two studies[29,30] were outliers because the 95% CIs around their effect sizes did not overlap with the 95% CIs around the overall pooled effect size. Thus, we decided to exclude these two studies to examine the impact on heterogeneity. The resulting effect remained significant in favour of psychotherapy (OR = 1.65, $P < .001$), while the heterogeneity was reduced considerably to $I^2 = 20\%$ ($P > .05$). Due to this important reduction in heterogeneity, we decided to exclude these two studies from all further analyses. However, after the removal of the outliers, there was an indication for publication bias (see funnel plot 1 in Appendix D). In Duval and Tweedie's Trim and fill procedure the imputed point estimate changed to OR = 1.45 (95% CI: 1.27–1.67) after adjustment for publication bias, while Egger's test was significant ($P < .05$).

In seven included studies, acute-phase psychotherapy was followed by booster sessions. These sessions were provided in the event that some patients needed further treatment. Considering that this type of continuation psychotherapy might have influenced the maintenance outcomes of psychotherapy, we decided to exclude these trials in a sensitivity analysis. The results of this analysis (44 comparisons) indicated that psychotherapy significantly outperformed control groups at 6 months or longer postrandomization (OR = 1.58, $P < .05$). However, Duval and Tweedie's Trim and fill procedure resulted in an adjusted OR of 1.39 (95% CI: 1.19–1.62) and Egger's test was significant ($P < .05$) (see also funnel plot 2 in Appendix D).

In order to examine possible sources of heterogeneity, we conducted a series of subgroup analyses (Table 2). We found significant differences between subgroup of studies that were specifically targeted at individuals with MDD (diagnosed by a clinical interview) and studies that recruited individuals who scored high on self-report outcome measures ($P < .05$). Subgroup analysis also revealed a significant difference between the studies that provided booster sessions after the completion of therapy, and studies that provided no additional sessions ($P < .05$). Other subgroup analyses did not result in significant differences. Moreover, we conducted meta-regression analyses to examine the associations between the dependent variable "all positive outcomes combined" and the independent variables "number of sessions" and "follow-up duration." Results indicated that the effect of psychotherapy significantly decreased as the follow-up duration increased (slope: −0.07, 95% CI: −0.10 to −0.04, $P < .001$; Fig. 4). No significant association was found between response to treatment and number of sessions (slope: 0.001, 95% CI: −0.02 to 0.03, $P > .05$).

With regard to quality of life, psychotherapy resulted in a significantly better quality of life compared to control groups at ≥ 6 months postrandomization across the eight studies that examined this outcome (Hedges's g = 0.22, 95% CI: 0.11–0.32, $P < .001$; Fig. 5). Heterogeneity was zero (95% CI: 0–68%, $P < .001$).

Recovery, Remission, Partial Remission, and Response. Separate meta-analyses were conducted for recovery, remission, partial remission, and response rates at 6 months or longer postrandomization. Recovery was reported in five comparisons between psychotherapy and control groups. Psychotherapy outperformed control conditions (OR = 1.77, $P < .05$). Similar long-term effects were observed for remission across ten comparisons. Psychotherapy resulted in higher remission rates compared to control groups (OR = 1.70, $P < .05$) Heterogeneity was moderate. Partial remission was examined across nine comparisons. Psychotherapy outperformed control groups on partial remission rates (OR = 1.61, $P < .05$). Heterogeneity was low. There was a small indication for publication bias (see funnel plot 3 in Appendix D). Using the trim and fill procedure, the imputed OR was 1.51 ($P < .05$), however, Egger's test was not significant. Finally, response rates were examined across five comparisons. Psychotherapy resulted in significantly higher response rates compared to controls (OR = 2.06, $P < .001$) and the heterogeneity was low.

TABLE 2. Long-term effects of psychotherapy in adults with depression compared to control groups (at ≥ 6 months postrandomization)

All types of psychotherapy vs. controls		*N*	OR	95% CI	I^2	95% CI	*P*
All positive outcomes combined		55	1.92	1.60–2.31	65	53–74	.000
All positive outcomes combined (two outliers excluded)		53	1.65	1.46–1.87	20	0–43	.000
All positive outcomes combined (psychotherapy with booster sessions excluded)		44	1.58	1.38–1.81	22	0–66	.000
Recovery		5	1.74	1.09–2.75	30	0–73	.025
Remission		10	1.70	1.20–2.45	57	14–79	.003
Partial remission		9	1.61	1.16–2.22	3	0–66	.004
Response		7	2.06	1.53–2.80	19	0–63	.000
CBT vs. controls							
All positive outcomes combined		36	1.70	1.45–1.98	18	0–46	.000
IPT vs. controls							
All positive outcomes combined		6	1.90	1.30–2.77	0	0–75	.001
SUP vs. controls							
All positive outcomes combined		5	1.39	0.86–2.24	52	0–83	.181
PST vs. controls							
All positive outcomes combined		3	1.91	1.16–3.15	34	0–78	.011
Subgroups—all positive outcomes combined							
CBT	CBT vs.	36	1.70	1.45–1.98	18	0–46	.60
	other PT	17	1.58	1.29–1.96	25	0–58	
IPT	IPT vs.	6	1.90	1.30–2.77	0	0–75	.46
	other PT	47	1.63	1.43–1.86	23	0–47	
SUP	SUP vs.	6	1.90	1.30–2.77	0	0–75	.44
	other PT	48	1.69	1.48–1.91	14	0–40	
PST	PST vs.	3	1.91	1.16–3.15	34	0–78	.56
	other PT	50	1.64	1.44–1.87	20	0–44	
Control group	TAU vs.	37	1.65	1.43–1.90	16	0–44	.84
	other	16	1.70	1.32–2.18	31	0–62	
Diagnosis	MDD vs.	25	1.88	1.53–2.31	26	0–55	.04
	other	28	1.45	1.27–1.66	0	0–42	
Quality of studies	High (defined as low scores in ≥4 items) vs.	32	1.56	1.33–1.82	31	0–56	.15
	low quality studies	21	1.88	1.53–2.32	0	0–47	
Recruitment	Community vs.	17	1.40	1.11–1.75	28	0–60	.07
	clinical sample	36	1.78	1.56–2.03	3	0–40	
Target group	Older adults vs.	7	1.99	1.42–2.78	0	0–71	.51
	postpartum vs.	8	1.53	0.96–2.43	41	0–74	
	other	38	1.63	1.42–1.87	21	0–47	
Therapy continuation	Booster sessions vs.	9	2.21	1.67–2.91	0	0–65	.03
	no further continuation of the therapy	44	1.58	1.38–1.81	22	0–46	
Treatment format	Individual vs.	44	1.63	1.43–1.87	25	0–49	.46
	group format	9	1.88	1.32–2.67	0	0–46	
Type of therapy	BA vs.	1	1.8	0.96–3.45	NA	NA	.73
	CBT vs.	36	1.70	1.45–1.98	18	0–46	
	DYN vs.	2	1.10	0.56–2.16	36	NA	
	IPT vs.	6	1.90	1.30–2.77	0	0–75	
	PST vs.	3	1.91	1.16–3.15	34	0–78	
	SUP	6	1.90	1.30–2.77	0	0–75	

BA, behavioral activation; CBT, cognitive behavioral therapy; CI, confidence intervals; DYN, psychodynamic psychotherapy; IPT, interpersonal psychotherapy; IPT, interpersonal psychotherapy; MDD, major depressive disorder; N, number of comparisons; OR, odds ratio; PST, problem solving therapy; PT, psychotherapy; SUP, nondirective supportive therapy; TAU, treatment as usual.

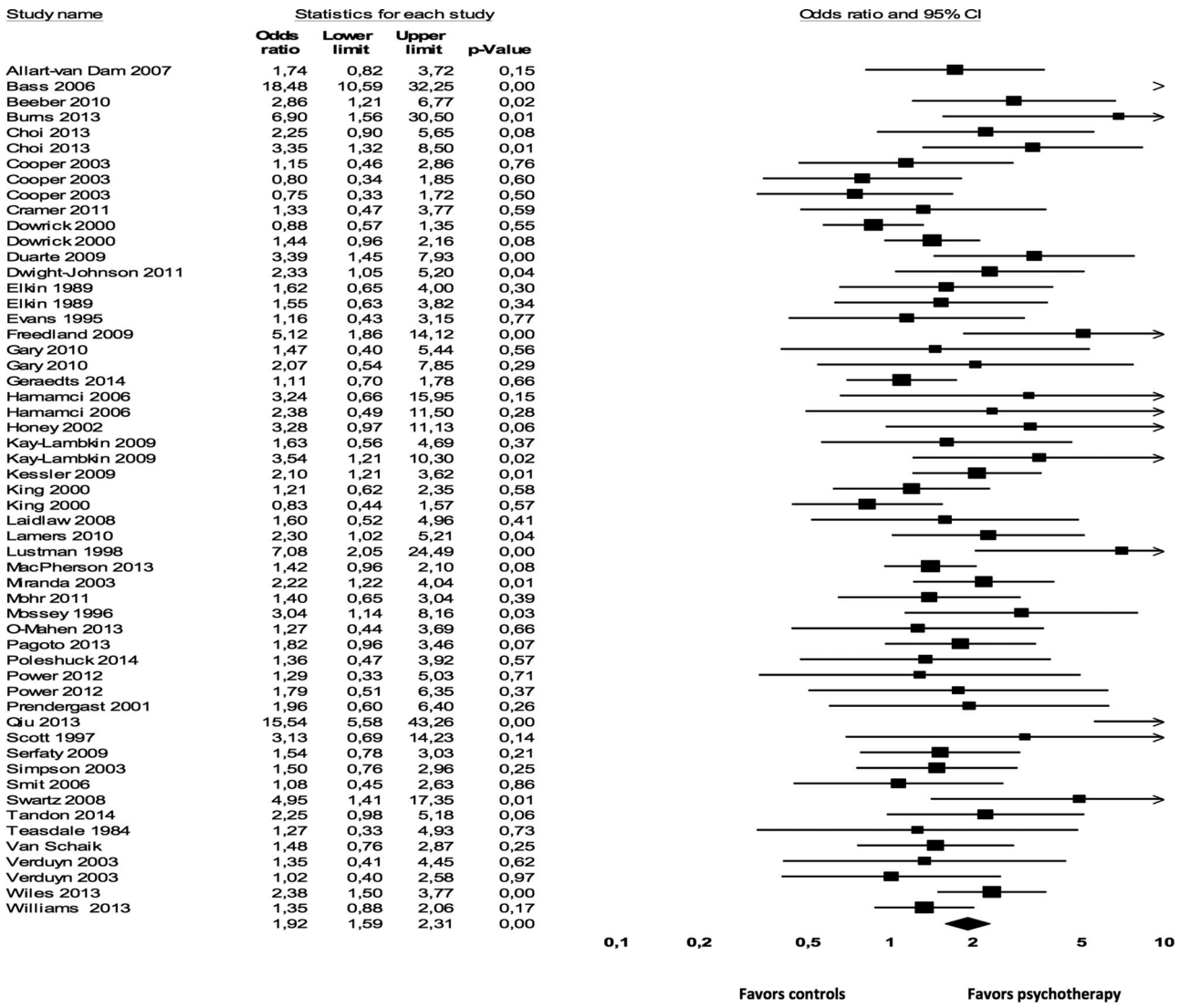

Figure 3. Forest plot of all positive outcomes combined.

Long-Term Effects of Individual Psychotherapies. We conducted separate meta-analyses for each type of psychotherapy when three or more studies were available. If less than three studies were available, results were described narratively. The outcomes of the individual comparisons are presented in Table 2. CBT resulted in a significantly higher positive therapy outcomes compared to control groups across 36 comparisons (OR = 1.70, $P < .001$). Heterogeneity was low. However, using Duval and Tweedie's Trim and fill procedure the values changed to OR = 1.51 (95% CI 1.27–1.79), while Egger's test was significant ($P < .05$) (see also funnel plot 4 in Appendix D). IPT outperformed control groups on all positive outcomes combined (OR = 1.90, $P < .05$) across six comparisons. Heterogeneity was zero. SUP did not result in significant long-term differences compared to control conditions in all positive outcomes combined (five comparisons). PST resulted in higher positive outcomes rates compared to controls at 6 months or longer postrandomization (OR = 1.91, $P < .05$) across three comparisons. Only one study was found on long-term effects of DYN therapy. Simpson et al. reported that DYN therapy significantly outperformed control groups in partial remission rates at 6 months follow up. Finally, we found one study examining the long-term effects of BA. Pagoto et al. found that BA resulted in higher remission and response rates compared to light intervention group at 6 months follow up.

DISCUSSION

To the best of our knowledge this is the first systematic review examining the long-term effects of acute-phase psychotherapy compared to control groups in adults with depression. Our hypothesis that psychotherapy would outperform the control groups on all-positive outcomes

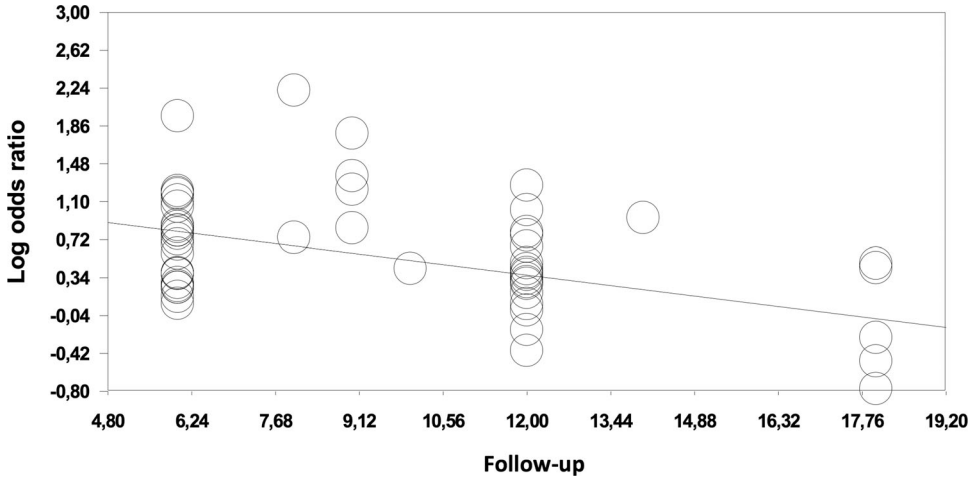

Figure 4. Meta-regression analysis of the association between follow-up duration and treatment outcome.

combined (recovery, remission, partial remission, response, and reduction in depression severity) and on quality of life was confirmed at a follow-up of 6 months or longer. This conclusion was replicated by analyzing each type of dichotomous outcome separately. Additionally, we examined the effects of different types of psychotherapy individually and the results showed that treatment gains were maintained through 6 months or longer postrandomization across all types of psychotherapy with the exception of nondirective supportive treatment, which was found to be less efficacious. We also found that in the long-term, psychotherapy resulted in higher effects compared to control groups when it was provided with additional booster sessions, or when it was exclusively targeted at adults with MDD. Finally, the results of this systematic review indicated that as the follow-up progressively increased the effects of psychotherapy versus control decreased.

Our findings are in line with previous work of Piet and Hougaard[15] and Biesheuvel-Leliefeld et al.[16] Piet and Hougaard[15] found a relative risk reduction of 34% in favour of maintenance mindfulness-based cognitive therapy compared to treatment as usual or pill placebo at 6 months or longer postrandomization in patients with MDD. Moreover, Biesheuvel-Leliefeld et al.[16] found that maintenance psychotherapy reduced significantly the risk of relapse in patients with MDD. To our knowledge there is no other systematic review on the long-term effects of acute-phase psychotherapy. Moreover, the finding that different types of psychotherapy, with the exception of nondirective supportive therapy, result in similar effects in treating depression is consistent with the meta-analyses of direct comparisons of different types of psychotherapy conducted by Cuijpers et al.[17] and Barth et al.[79] These meta-analyses showed no significant difference between the effects of seven major types of psychotherapy in treating depression and that nondirective supportive therapy is less efficacious compared to other types of psychotherapy. It should be noted at this point that although we analyzed and described different types of psychotherapy separately, the interpretation of the findings has to be done with caution as

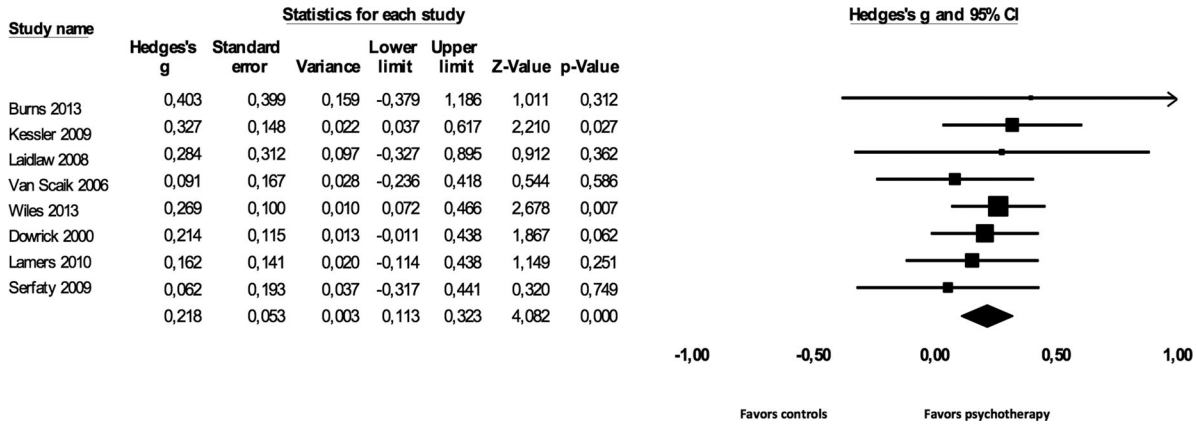

Figure 5. Forest plot of quality of life.

the majority of the included RCTs used CBT as a psychotherapy intervention.

We observed a decreasing difference between psychotherapy and control conditions over length of follow-up. The reasons for this reduction vary among the examined trials. In certain instances, this decrease in effects is due to greater relapse rates in the psychotherapy groups as the effects of acute treatment waned. However, in the majority of instances, this decrease in effects in the course of time can be attributed to spontaneous remission rates experienced by patients in the control groups. This is in line with research findings suggesting that approximately half of the untreated patients who are diagnosed with major depression will experience spontaneous remission within a year.[80]

The finding that studies required a diagnosis of major depression presented larger psychotherapy long-term differences compared to studies that used elevated depressive symptoms as inclusion criterion, is consistent with previous research findings regarding the moderating effects of depression severity in treatment outcome. The meta-analysis of Driessen et al. showed that psychotherapy might be more efficacious for more severely depressed individuals.[81] Furthermore, Bower et al.[82] conducted an individual patient data meta-analysis to examine the influence of baseline depression severity on the effects of low intensity psychotherapeutic intervention in outpatients with depression. The authors found that patients who had more severe depressive symptoms at baseline showed greater treatment effects in comparison with patients who had less severe symptoms of depression at the intake.[82]

The present study addresses, for the first time, the long-term effects of psychotherapy on quality of life. However, a recent systematic review by Kolovos et al. (under submission)[83] came to similar conclusions regarding the short-term effects of psychotherapy on quality of life. The authors meta-analyzed the effects of 44 RCTs on global quality of life, mental and physical components and found that psychotherapy has a positive impact on the quality of life at the posttreatment assessment.[83]

The present study has several limitations. First, treatment as usual was the most common control group used by the included studies. However, this condition had in some cases unclear definitions and generally presented important variations across countries. We also observed moderate heterogeneity between studies as a result of two outliers and thus, these studies were excluded in any further analyses. This difference, between the two studies and the rest studies of our sample, may have been caused by differences in populations or by differences in the control conditions. The study by Bass et al.[29] was conducted in Uganda and the study of Qiu et al.[30] was conducted in China, while the great majority of the rest-included studies were conducted in western countries. Thus, cultural differences may account for the observed differences between these two studies and the rest of the studies in our sample. Further, we observed some indications for publication bias in our main comparison between psychotherapy and control groups. However, the superior effects of psychotherapy remained significant after adjustment for publication bias. The lower effect size estimate of low quality studies was not significantly different from high quality studies. Finally, the external validity of the present meta-analysis might be limited due to the design of the included studies. A common difficulty of the RCT design is the limited duration of the provided treatment. For instance, the vast majority of the included trials did not provide booster sessions after acute-phase treatment. In contrast, therapists in clinical practice often provide continuation and maintenance therapy to recently improved patients. Thus the literature under examination represents a special case of a particular research design for psychotherapy.

Future research should examine ways to maintain the positive effects of psychotherapy during a more extensive follow-up period. Additionally, maintenance psychotherapy could be employed in order to sustain treatment response as the follow-up duration progressively increases. Studies should address the efficacy of different types of psychotherapy, in order to provide enough power to analyze the effects of each type of intervention separately. It is also important to address questions regarding predictors and moderators to treatment outcomes on long-term follow-up. This will provide us with essential information on who may benefit the most from psychotherapy over time. This need should drive new meta-analytic approaches such as individual patient data meta-analysis. Furthermore, more research is needed to address long-term effects of psychotherapy compared to pharmacotherapy, as well as the effects of combined psychotherapy and pharmacotherapy treatment. This would provide us with important information regarding the optimal therapeutic approach with respect to the long-term outcome of adult depression treatment.

In conclusion, acute-phase psychological interventions appear promising in treating depression in the long term. The improvement in depressive outcomes, while less apparent as the follow up duration increased, was considerable. Given the chronicity and disability associated with depression, these findings should be taken into account in clinical and policy decision making. Currently, pharmacotherapy is the predominant treatment for depression with more and more patients being prescribed with antidepressant medications in mental health care services worldwide. However, concerns have arisen about the side effects of antidepressants and about the durability of their effects after discontinuation. The results of the present meta-analysis recommend that psychological interventions may offer a viable approach to improve long-term outcomes of depression care. In light of these therapeutic gains, psychotherapy should be available in primary and secondary mental health care. Patients with depression should be able to discuss psychological treatment options with their doctors and decide based on their preferences. Alternative treatment modalities, such as maintenance psychotherapy or

the combination of psychotherapy and pharmacotherapy should also be considered to sustain long-term benefits.

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