



Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation medication? A meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002542
Article Type:	Research
Date Submitted by the Author:	30-Dec-2012
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	MENTAL HEALTH, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

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Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation medication?

A meta-analysis

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Abstract

Objectives: Although cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of adult depression, it is not known how they compare across the longer term. In this meta-analysis we compared the effects of acute phase CBT without any additional treatment with the effects of pharmacotherapy that either was continued or discontinued across a subsequent one-year follow-up.

Design: We conducted systematic searches in bibliographical databases to identify relevant studies, and conducted a meta-analysis of studies meeting inclusion criteria.

Setting: mental health care

Participants: patients with depressive disorders.

Interventions: CBT and pharmacotherapy for depression.

Outcomes measures: Relapse rates at longer-term follow-up.

Results: Nine studies with 506 patients were included. The quality was relatively high. Prior CBT was compared with continued pharmacotherapy during follow-up in five studies. There was a trend ($p < 0.1$) indicating that patients who received prior CBT were less likely to relapse following treatment termination than patients who were continued on medication (OR=1.62; 95% CI: 0.97~2.72; NNT = 10). Prior CBT was compared with medication discontinuation during follow-up in eight studies. Patients who received prior CBT were significantly less likely to relapse than patients who were withdrawn from medication treatment (OR=2.61; 95% CI: 1.58~4.31; $p < 0.001$; NNT = 5). Short-term outcomes of CBT and pharmacotherapy were comparable, although drop-out from treatment was significantly lower in CBT.

Conclusions: We found a trend that prior exposure to CBT was more effective than pharmacotherapy at preventing relapse across a one-year follow-up whether medication treatment was continued or withdrawn. CBT not only seems to have an enduring effect following treatment termination but the magnitude of this effect may even be somewhat greater than keeping patients on continuation medication. Given the small number of studies this finding should be interpreted with caution pending replication.

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4 Article summary
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7 Article focus
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- 9 • Cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective
10 in the treatment of depression
- 11 • Longer term differential effects are not well-known
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16 Key messages
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- 18 • There were indications that patients who received CBT without continuation
19 therapy may be less likely to relapse during follow-up than patients who were
20 continued on medication
- 21 • When pharmacotherapy was discontinued during follow-up, relapse rates in
22 CBT without continuation therapy were significantly lower than in
23 pharmacotherapy
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29 Strengths and limitations of this study
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- 31 • Too few studies have examined the long-term effects of treatments for
32 depressive disorders
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Introduction

It is well-established that cognitive behaviour therapy (CBT) is efficacious in the treatment of adult depression. Dozens of randomized trials have shown that CBT is superior to no treatment, nonspecific controls and care-as-usual in the acute treatment of adult depression [1,2], and that the effects of CBT are comparable to those of antidepressant medication (ADM) with lower rates of attrition [3].

What is not clear, however, is how acute CBT compares to pharmacotherapy over the longer term. It has long been claimed that psychotherapy leads to lasting change because patients learn skills that can be implemented after the treatment has ended and because they are instructed on specific techniques on how to handle relapse. CBT has been found to have an enduring effect that lasts beyond the end of treatment [4]. No such claim has ever been made for medication treatment [5]. Nonetheless, it is well established that keeping patients on medications even after they are better can reduce the risk of subsequent symptom return and it is standard practice to keep patients with chronic or recurrent depressions on medications indefinitely [6].

If CBT has an enduring effect that extends beyond the end of treatment it is important to know how that compares to simply keeping patients on medication. This is important from a clinical point of view, since clinicians and patients have to decide which modality to choose at the outset of treatment and will want to consider information about the relative long-term effects of each in their initial decision.

Improvement during acute treatment is called *response* and the full normalization of symptoms is called *remission* [7]. Recently remitted patients typically are kept on *continuation medication* for another six to twelve months in order to reduce the risk of *relapse*, the return of symptoms associated with the treated episode, and patients who have gone that long without relapse are said to be *recovered*, with the presumption that the underlying episode has run its course. Keeping recovered patients on *maintenance medication* beyond that point is intended to reduce risk for *recurrence*, the onset of a wholly new episode, and is standard for chronic or recurrent patients [7].

Although several studies have compared the long-term effects of acute CBT with those of continuation medication, no meta-analysis of these studies has been conducted. One earlier review examined whether prior CBT had an enduring effect relative to

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4 medication withdrawal, but no direct comparison was made to continuation medication
5 [8]. Since that is now the current standard of treatment and the key decision that
6 clinicians need to make, we decided to conduct such a meta-analysis.
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10 11 12 Methods

13 14 15 Identification and selection of studies

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17 We used a database of 1,344 papers on the psychological treatment of depression
18 described in detail elsewhere [9] that has been used to conduct a series of published
19 meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously
20 updated through comprehensive literature searches (from 1966 to January 2012). In
21 these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo
22 (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988).
23 These abstracts were identified by combining terms indicative of psychological
24 treatment and depression (both MeSH terms and text words). We also checked the
25 references from 42 meta-analyses of psychological treatment for depression to ensure
26 that no published studies were missed. From the 13,407 abstracts (9,860 after removal
27 of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.
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30 We included (a) randomized trials (b) in which the effects of cognitive behaviour
31 therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the
32 effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive
33 disorder, (f) across a follow-up period of 6-18 months. We focused on studies that
34 compared acute CBT (without subsequent continuation) versus pharmacotherapy that
35 was either continued or withdrawn, and conducted separate comparisons on each.
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38 Studies in which CBT was continued during follow-up were excluded (although we
39 allowed a maximum of 5 booster sessions during follow-up, as long as these were not
40 regularly planned). We also excluded studies in which depression was not diagnosed
41 with a standardized diagnostic interview (such as the CIDI, SCID or MINI), as well as
42 studies in inpatients and adolescents. No language restrictions were applied.
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46 47 48 Quality assessment and data extraction

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4 The validity of included studies was assessed on four criteria of the ‘Risk of bias’
5 assessment tool developed by the Cochrane Collaboration to assess possible sources of
6 bias in randomized trials: (a) adequate generation of allocation sequence; (b)
7 concealment of allocation to conditions; (c) prevention of knowledge of the allocated
8 intervention (blinding); and (d) dealing with incomplete outcome data [11].
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12 We collected characteristics of the target population (method of recruitment,
13 definition of depression, HAM-D score at the start of the treatment to assess the severity
14 of depression, whether all randomized patients were examined at follow-up or only the
15 responders to acute phase treatment, number of treatment sessions, type of drug,
16 whether pharmacotherapy was continued across the full follow-up or only for part of
17 that period, and the country where the study was conducted. If not all information was
18 reported in the paper, we contacted the authors of the papers to request the additional
19 information (all six of whom responded).
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27 Meta-analyses

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29 For each study we used the number of patients who responded to treatment and
30 remained well as outcome measure. We calculated the odds ratio (OR) of a positive
31 outcome in CBT compared with pharmacotherapy. We calculated these ORs at the end
32 of the acute treatment (response or remission) and across the subsequent follow-up
33 (freedom from relapse or recurrence). Although at least some of the follow-ups were
34 long enough for patients free from relapse to have met criteria for recovery (and
35 subsequent episodes to be recurrences) we will use the term relapse to refer to all
36 instances of symptom return.
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42 To calculate pooled ORs, we used the computer program Comprehensive Meta-
43 Analysis (version 2.2.021). As we expected considerable heterogeneity among the
44 studies, we used a random effects model to pool the ORs. Random effects models
45 assume that the included studies are drawn from ‘populations’ of studies that differ from
46 each other systematically (heterogeneity). In this model, the effect sizes resulting from
47 included studies not only differ because of the random error within studies (as in the
48 fixed effects model), but also because of true variation in effect size from one study to
49 the next.
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4 The numbers-needed-to-be-treated (NNT) is intuitively easier to understand than the
5 OR. The NNT indicates the number of patients that would have to be treated in order to
6 generate one additional positive outcome [12]. Therefore we also calculated the NNTs
7 for all comparisons. We calculated the risk differences (RDs) for each study, pooled
8 these for all studies, and then calculated the NNT as 1/RD for the pooled studies.
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12 As a test of homogeneity of effect sizes, we calculated the I^2 -statistic which is an
13 indicator of heterogeneity in percentages. A value of 0% indicates no observed
14 heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50%
15 as moderate, and 75% as high heterogeneity [13]. We also calculated the Q-statistic, but
16 only report whether it was significant or not. We calculated 95% confidence intervals
17 around I^2 [14], using the non-central chi-squared-based approach within the heterogi
18 module for Stata [15].
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22 Subgroup analyses between different subsamples of studies were conducted
23 according to the mixed effect model. In this model, studies within subgroups are pooled
24 with the random effects model, while tests for significant differences between
25 subgroups are conducted with the fixed effects model.
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29 Publication bias was tested by inspecting funnel plots on the primary outcome
30 measures and by Duval and Tweedie's trim and fill procedure [16], which yields an
31 estimate of the effect size after adjusting for publication bias (as implemented in
32 Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the
33 intercept to quantify the bias captured by the funnel plot and test whether it was
34 significant. We also calculated Orwin's Fail safe N, which indicates the number of
35 missing studies needed to make the effect size insignificant [17].
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46 Results

47 Selection and inclusion of studies

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50 After examining a total of 13,407 abstracts (9,860 after removal of duplicates), we
51 retrieved 1,344 full-text papers for further consideration. We excluded 1,335 of the
52 retrieved papers. The flowchart describing the inclusion process, including the reasons
53 for exclusion, is presented in Figure 1. Nine of the 1,344 retrieved full-text papers
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4 reported long-term outcomes of prior CBT and were included in this meta-analysis [18-
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8 9 Characteristics of included studies

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11 In the 9 included studies, a total of 506 patients participated, 271 in CBT and 235 in
12 the ADM. Selected characteristics of the included studies are presented in Table 1.
13 Four studies recruited patients only from clinical samples, while the other five also
14 recruited patients from the community. Six studies included only patients who
15 responded to acute phase treatment in the analyses of the subsequent follow-ups, while
16 the other three included all patients randomized to acute phase treatment. The number
17 of CBT treatment sessions ranged from 18 to 24. During the follow-up phase (after
18 acute treatment had ended) three studies offered up to four CBT booster sessions, while
19 the other six did not offer any additional treatment.
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23 In five earlier studies a Tricyclic antidepressant (TCA) was used in the
24 pharmacotherapy condition, while the three more recent studies all used a Selective
25 serotonin reuptake inhibitor (SSRI); in one study phenelzine (a MAOI) was used. In
26 four studies, patients who responded to pharmacotherapy were randomized to either
27 continuation medication (for the first year of the two-year follow-up) or medication
28 withdrawal with each reported separately. In three other trials all patients were
29 withdrawn from medications, although the length of the taper differed across the trials.
30 One other trial continued medication for the first six months of the follow-up before
31 subsequent withdrawal, and in the remaining trial medication treatment was continued
32 throughout the follow-up. In most instances patients withdrawn from treatment were
33 followed naturalistically although in several studies they were encouraged not to seek
34 additional treatment until a relapse or recurrence was documented. Seven studies were
35 conducted in the United States, two in Europe (one in the UK, one in Romania).
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38 39 Quality of included studies

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41 Eight of the nine studies used an adequate sequence generation strategy and had an
42 independent party conceal allocations to conditions. Six studies reported keeping the
43 assessors blind to treatment condition and seven studies conducted intent-to-treat
44 analyses. The six studies published in the last two decades met all four quality criteria;
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4 among the three earlier studies, one study met three, another met two, and the final one
5 met none of the criteria (Table 1). The overall quality of the studies was relatively high.
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8 9 Long-term outcomes: Prior CBT versus continuation medication

10 Five studies compared the one-year outcomes of prior CBT (with nothing more than
11 occasional booster sessions) versus continuation pharmacotherapy [19-23]. There was a
12 trend ($p < 0.1$) indicating that prior CBT outperformed continuation pharmacotherapy
13 (OR=1.62; 95% CI: 0.97~2.72). Heterogeneity was zero, but the 95% confidence
14 interval was broad (0 to 79%), so this finding should be interpreted with caution. The
15 NNT was 10. The ORs and 95% confidence intervals are presented graphically in
16 Figure 2.
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22 We found no indication of publication bias (not surprising given how few studies).
23 Using Duval and Tweedie's trim and fill procedure to adjust for publication bias did not
24 change the OR (number of trimmed studies was zero) and Egger's test also was not
25 significant ($p > 0.1$). We also calculated Orwin's Fail Safe N and found that 23 studies
26 with an OR of 0.9 or eleven studies with an OR of 0.8 (in favour of pharmacotherapy)
27 or 7 studies with an OR of 0.7 would be needed to produce a pooled OR of 1.00. No
28 additional subgroup analyses were conducted because of the small number of studies.
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36 Long-term outcomes: Prior CBT versus medication discontinuation

37 Eight studies compared the one-year outcomes of prior CBT (with nothing more than
38 occasional booster sessions) versus medication discontinuation or a naturalistic design.
39 Prior CBT significantly outperformed the medication discontinuation condition to an
40 even greater extent than it had continuation medication (OR=2.61; 95% CI: 1.58~4.31;
41 $p < 0.001$). Heterogeneity was zero, but again the 95% CI was broad (0~68%). The
42 corresponding NNT was 5 (95% CI: 4~11) and the ORs and 95% CI for each study are
43 presented graphically in Figure 3.
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49 Because two studies had a very high OR [18,21] and one a very low OR [23], we
50 conducted an additional sensitivity analysis with these studies removed. The resulting
51 OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly significant
52 ($p < 0.001$) and the corresponding NNT was 6 (95% CI: 4~15).
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4 Although the number of studies was small, we did conduct some subgroup analyses.
5 We did not find any significant differences between subgroups, including medication
6 type (SSRI versus TCA), whether all randomized patients were included versus
7 inclusion of responders to the acute phase only, and the studies with the highest quality
8 (meeting all 4 criteria) versus those with lower quality (≤ 3 criteria). These outcomes
9 should be interpreted with caution, however, because of the small sample sizes in the
10 subgroups.
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16 Short-term outcomes

17 We also examined the comparative effects of CBT versus pharmacotherapy at the
18 short term (end of acute treatment), but found no significant difference (OR=1.15, n.s.;
19 Table 2). Excluding one potential outlier [24] did not affect this finding.
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24 We also examined whether we could confirm that drop-out from the intervention was
25 significantly higher in pharmacotherapy than in CBT, as has been established in earlier
26 meta-analyses [3]. Eight of the nine studies reported sufficient data on drop-out to be
27 included in the analyses. We found that the odds of dropping out in the acute phase
28 were significantly lower in CBT than in pharmacotherapy (OR=0.59; 95% CI:
29 0.34~0.99). Inspection of the funnel plot indicated that several studies could have been
30 outliers. Because of the small number of studies, however, we did not conduct any
31 additional sensitivity analyses.
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39 Discussion

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42 Not only were patients treated acutely with CBT less likely to relapse following
43 treatment termination than patients treated acutely with medication, we also found a
44 nonsignificant trend indicating that they also were less likely to relapse than patients
45 continued on medication. The first finding did not come as a surprise, since virtually all
46 of the individual studies that have compared prior CBT to prior ADM have found
47 significant differences favouring the psychosocial intervention following treatment
48 termination and this is basis for the claim that CBT has an enduring effect [4].
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54 What was surprising was the nonsignificant trend indicating that prior CBT also may
55 be superior to continuation ADM since none of the differences observed in the
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4 individual studies rose to the level of statistical significance. What makes this finding
5 even more surprising is that keeping recently remitted patients on continuation
6 medications is the recommended course of treatment and the best that modern
7 pharmacotherapy can do [6]. So few studies were involved in generating this finding, it
8 will have to be confirmed in subsequent research before it can be allowed to influence
9 clinical practice, but if it does replicate it would suggest that a relatively brief course of
10 CBT might not only be a viable alternative to medication treatment (with continuation)
11 but quite possibly superior to it. Patients are as likely to respond to CBT as to ADM and
12 less likely to drop out of treatment [3]. Moreover, there are indications that the majority
13 of patients who respond to ADM do so for nonspecific reasons; that is, they are showing
14 a placebo response and not a “true” drug effect. The same appears to be true for the
15 psychosocial treatments including CBT [27]. However, if patients as likely to respond
16 treatment (for whatever reason) that they are more likely to complete and if those same
17 patients are less likely to relapse following treatment termination than if they are kept
18 on continuation medication then a case can be made that CBT should be the treatment
19 of choice over ADM for most depressed patients [28].

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31 These results should be interpreted with caution because of the limitations of this
32 study. As noted above, the most important limitation was that the small number of
33 studies comparing CBT with continued pharmacotherapy. In such a situation, only a
34 few studies with different outcomes can turn these results from a trend to non-
35 significance. Another possible limitation is that there was considerable variation in the
36 methods used between the studies in terms of medications, measures, and other
37 characteristics. At the same time, consistency in findings in the face of variability in the
38 methods might contribute to our confidence that what we have is a robust effect that
39 will survive replication. Another possible limitation is that the follow-up of the CBT
40 conditions in most of the studies was naturalistic although most asked patients not to
41 pursue outside treatment in the absence of a documented relapse and censored those
42 events the few times that they did occur. There also was considerable variability in
43 when ADM was discontinued across the studies although that should only have led us to
44 underestimate the “true” magnitude of the advantage for prior CBT in that comparison.
45 Moreover, the quality of the studies included in this meta-analysis was high and even if
46 the next ten studies all produced an advantage for ongoing pharmacotherapy, prior CBT
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4 would still be as efficacious as continuation medication. Subsequent replication is
5 needed before the possible superiority of prior CBT over continuation medication can
6 be taken seriously, but the possibility is of sufficient importance that such efforts clearly
7 demand to be made.
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11 Finally, although CBT may like ADM work largely through nonspecific mechanisms
12 with respect to acute response [29], there are clear indications that cognitive and
13 behavioral mechanisms underlie its enduring effects [30]. Patients who show sudden
14 gains in cognitive therapy (defined as rapid drops in symptoms from one session to the
15 next) are less likely to relapse than patients who show a more stable pattern of response
16 and those instances of sudden gains typically are preceded by the recognition that it is
17 not just what happens to you but how you interpret those events that determine
18 subsequent affect and behavior [31]. Moreover, patients who best learn the cognitive
19 and behavioral skills taught in CBT are least likely to relapse following treatment
20 termination [32]. Whereas acute response to treatment is somewhat promiscuous, the
21 relatively unique enduring effect of CBT appears to be driven by the acquisition of
22 cognitive and behavioral skills as specified by theory.
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4 Contributors.

5 PC and SDH had the idea for this study. PC drafted the initial manuscript, prepared and
6 cleaned the data, and conducted the data analysis. SDH, AVS, CB, MB and GA read all
7 version of the manuscript critically and contributed to the final paper.
8

9
10 Funding.

11 This research received no specific funding.
12

13 Ethics approval.

14 No ethics approval was needed for this study.
15

16 Data sharing statement.

17 No primary data are used in this paper
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21 Competing Interests

22 None
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Table 1. Selected characteristics of studies comparing the long-term effects of cognitive behavior therapy for adult depression with those of pharmacotherapy

	Recr	Depressive disorder	Pre HAM D	Included ^{a)}	Psychotherapy				Pharmacotherapy			FU	Outcome	C	Quality			
					Acute phase	N _{sess}	Contin. Phase	N	Acute phase	Continuation phase	N				S	A	B	C
Blackburn, 1986	Clin	MDD (PSE / RDC)	NR	Resp	CBT	23	4 boosters (in first 6 months)	13	Drug of choice	Continuation of 6 months, remaining period naturalistic	9	24	Depressive symptoms needing further treatment	UK	-	-	-	-
David, 2008	Com + clin	MDD (DSM-IV) + BDI ≥ 20 + HAM-17 ≥ 14	22.1	All	CBT	20	Max 3 boosters sessions	56	Fluoxetine	Continued pharmacotherapy	57	6	No current MDD + HAMD ≤ 7	RO	+	+	+	+
Dobson, 2008	Com + clin	MDD (DSM-IV) + BDI-II ≥ 20 + HAM-D 17 ≥ 14	20.7	Resp	CBT	24	No treatment offered during follow-up	30	Paroxetine	Continued pharmacotherapy	28	12	Sustained response (no 2 wks HAMD ≥ 14)	US	+	+	+	+
Evans, 1992	Clin	MDD (RDC)	26.9	Resp	CBT	20	No continued treatment	10	Imipramine	Continued pharmacotherapy during year 1, then tapered	11	24	No relapse (BDI ≥ 16 during at least 2 weeks) + no treatment	US	+	+	+	+
Hollon, 2005	Com / clin	MDD (DSM-IV)	23.4	Resp	CBT	20	Up to 3 booster sessions	60	Paroxetine	Continued pharmacotherapy	34	12	No relapse (no HAMD ≥ 14 for two consecutive weeks)	US	+	+	+	+
Jarret, 2000	Com / clin	Atypical MDD (DSM-IV; SCID)	18.4	Resp	CBT	20	No continued treatment	6	Phenelzine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feighner) + HAM-D-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Naturalistic	18	Imipramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAMD ≥ 14	19.6	All	CBT	18	Naturalistic	59	Imipramine	Medication was gradually reduced	57	18	Recovered (LIFE-II) and no relapse (MDD / RDC)	US	+	+	+	+
Simons, 1986	Clin	DD (DIS) + HAMD ≥ 14 or BDI ≥ 20	19.9	Resp	CBT	20	No additional treatment	19	Nortriptyline	Pharmacotherapy was gradually tapered	16	12	Did not re-enter treatment + no BDI ≥ 16 at follow-up	US	+	+	-	+

Abbreviations: AC: allocation concealment; All: all randomized patients; BA: blind assessment; BDI: Beck Depression Inventory; C: country; CBT: cognitive behaviour therapy; CF: completeness of follow-up data; Clin: clinical recruitment; Com: community recruitment; DD: depressive disorder; DIS: diagnostic interview schedule; FU: follow-up; HAM-D: Hamilton

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4 depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depressive disorder; N_{sess} : number of sessions; PSE: present state examination; RDC: research
5 diagnostic criteria; Recr: recruitment; Resp: only responders to the acute phase; RO: Romania; SG: sequence generation; UK: United Kingdom; US: United States.

6 ^{a)} Only responders to the acute phase treatments or the ones who completed the acute phase treatment were included in the follow-up analyses.
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Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response ^{a)}

	<i>N</i>	<i>OR</i>	<i>95% CI</i>	<i>I</i> ²	<i>95% CI</i>	<i>NNT</i>	<i>95% CI</i>	<i>p</i> ^{c)}
<u>CBT vs continued pharmacotherapy</u>								
All studies	5	1.62	0.97~2.72 o	0	0~79	10	d)	
<u>CBT vs discontinued pharmacotherapy</u>								
All studies	8	2.61	1.58~4.31 ***	0	0~68	5	4~11	
Three possible outliers excluded ^{e)}	5	2.47	1.45~4.22 ***	0	0~79	6	4~15	
<u>Subgroups (long-term effects)</u>								
Pharmacotherapy ^{f)}								
- SSRI	2	3.02	1.29~7.04 *	0	g)	5	3~16	0.82
- TCA	5	2.66	1.40~5.04 **	0	0~79	6	4~15	
Included sample								
- All	2	1.97	0.91~4.27 o	0	g)	9	d)	0.14
- Responders	6	3.20	1.65~6.19 **	0	0~75	4	3~8	
Quality								
- All 4 criteria	5	2.31	1.28~4.16 **	0	0~79	6	2~11	0.25
- ≤ 3 criteria	3	3.58	1.39~9.22 **	0	0~90	4	2~10	
<u>Short term effects</u>								
All studies	9	1.15	0.74~1.79	53 *	0~78	20	d)	
One possible outlier excluded ^{h)}	8	0.96	0.72~1.30	0	0~68		d)	
Drop-out from intervention ⁱ⁾	8	0.59	0.34~0.99 *	48 o	0~77	9	5~143	

o: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

^{a)} according to the random effects model;

^{b)} in this column, the I^2 is reported; we also tested whether the Q-value was significant. This was the case in two comparisons (indicated with an asterisk *).

^{c)} the p-value indicates whether the subgroups differ from each other;

^{d)} the 95% confidence interval included zero; because this would result in a negative NNT we do not report this here.

^{e)} Blackburn et al., 1981; Jarrett, 2000; Kovacs et al., 1981.

^{f)} one study examined phenelzine (Jarrett, 2000); this was not included in the analyses.

^{g)} 95% CI cannot be calculated when df is lower than 2.

^{h)} Kovacs et al., 1981

ⁱ⁾ One study did not report data on drop-out (Blackburn et al., 1981)

Figure 1. Flowchart of inclusion of studies

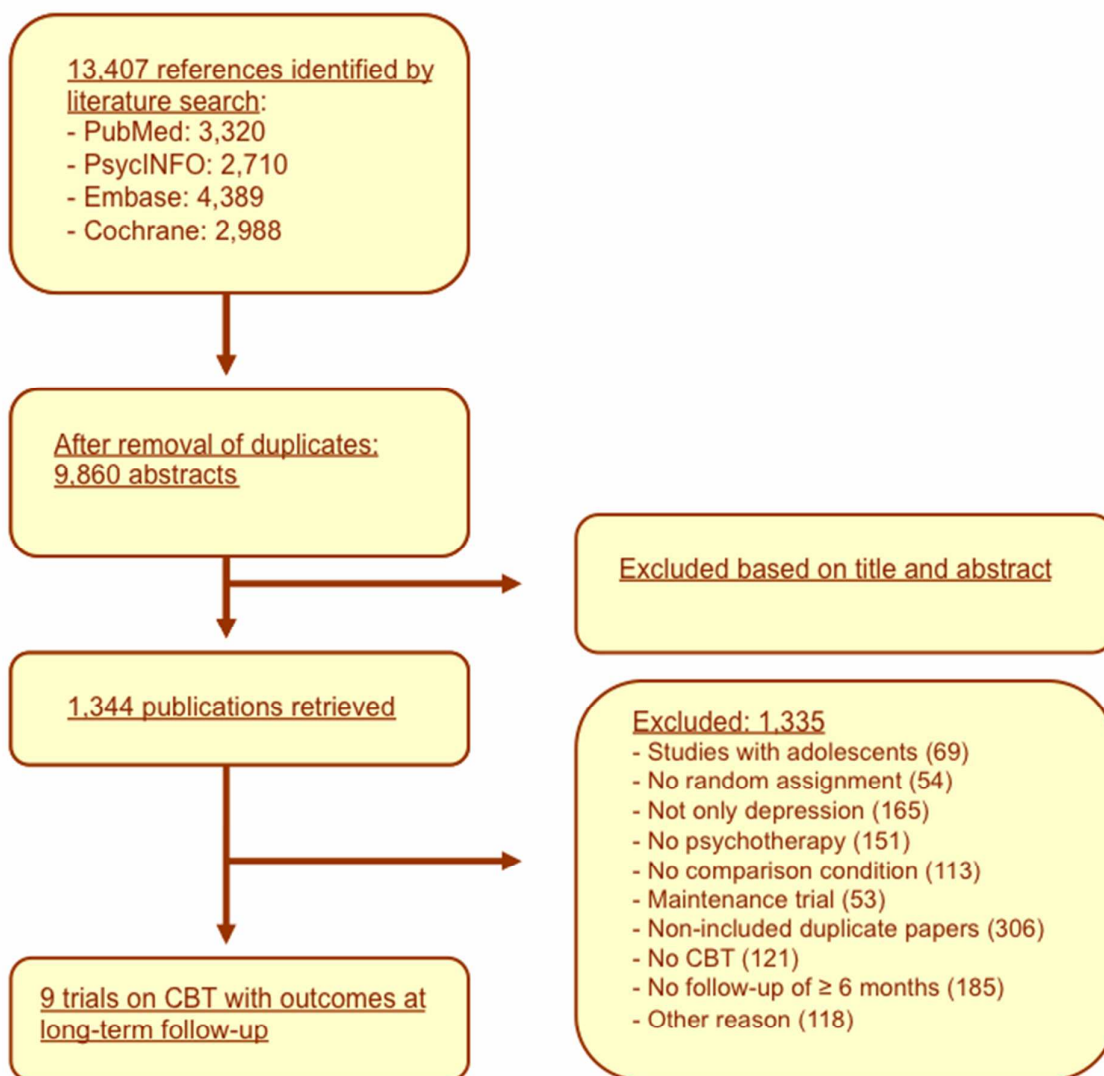
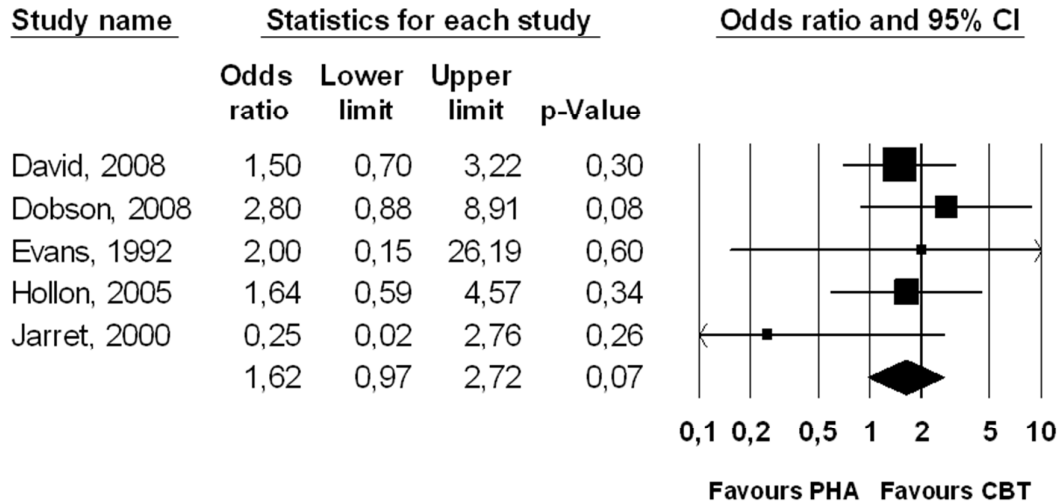
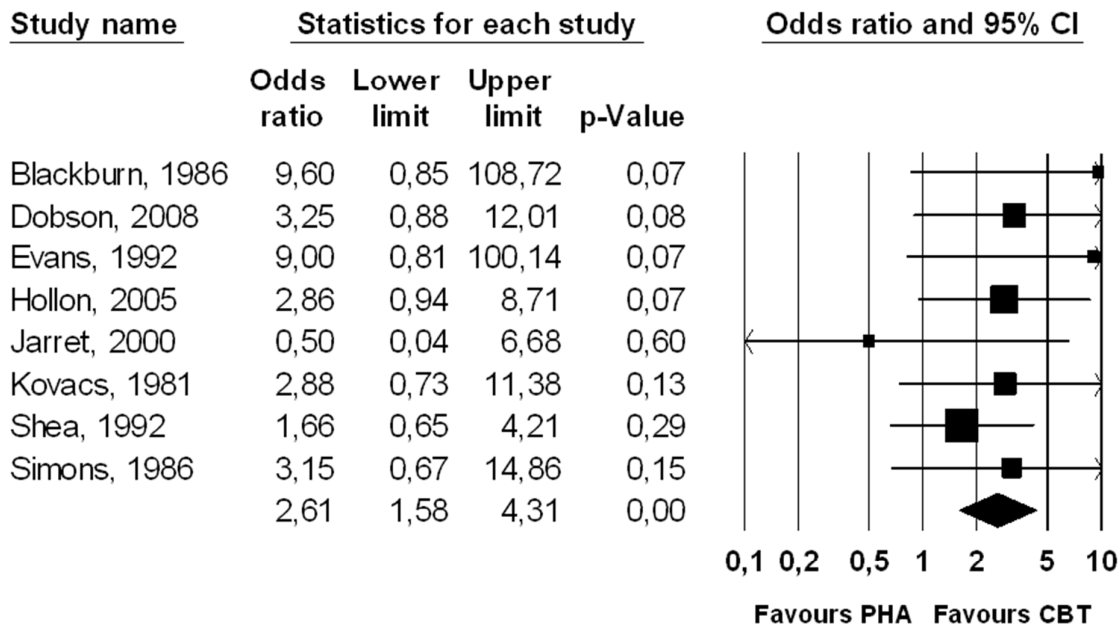


Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response



review only

Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*discontinued* during follow-up): Forest plot of Odds ratio of response



Review only

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not included
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6, 7



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8, 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, 8, 20
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, 9, 17, 18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, 17, 18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 21, 22
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10, 11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11, 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002542.R1
Article Type:	Research
Date Submitted by the Author:	06-Mar-2013
Complete List of Authors:	Cuijpers, Pim; VU University Amsterdam, Department of Clinical Psychology Hollon, Steven van Straten, Annemieke Bockting, Claudi Berking, Matthias Andersson, Gerhard
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	MENTAL HEALTH, Adult psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY

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Manuscripts

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6 Does cognitive behaviour therapy have an enduring effect that is superior to keeping
7 patients on continuation pharmacotherapy?

8 A meta-analysis

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15 Annemieke van Straten,^{1,2} Claudi Bockting,⁴ Matthias Berking,⁵ Gerhard Andersson^{6,7}

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Abstract

Objectives: Although cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of adult depression, it is not known how they compare across the longer term. In this meta-analysis we compared the effects of acute phase CBT without any subsequent treatment with the effects of pharmacotherapy that either was continued or discontinued across 6 to 18 months follow-up.

Design: We conducted systematic searches in bibliographical databases to identify relevant studies, and conducted a meta-analysis of studies meeting inclusion criteria.

Setting: mental health care

Participants: patients with depressive disorders.

Interventions: CBT and pharmacotherapy for depression.

Outcomes measures: Relapse rates at longer-term follow-up.

Results: Nine studies with 506 patients were included. The quality was relatively high. Short-term outcomes of CBT and pharmacotherapy were comparable, although dropout from treatment was significantly lower in CBT. Acute phase CBT was compared with pharmacotherapy discontinuation during follow-up in eight studies. Patients who received acute phase CBT were significantly less likely to relapse than patients who were withdrawn from pharmacotherapy (OR=2.61; 95% CI: 1.58~4.31; $p<0.001$; NNT = 5). Acute phase CBT was compared with continued pharmacotherapy at follow-up in five studies. There was no significant difference between acute phase CBT and continued pharmacotherapy, although there was a trend ($p<0.1$) indicating that patients who received acute phase CBT may be less likely to relapse following acute treatment termination than patients who were continued on pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72; NNT = 10).

Conclusions: We found that CBT has an enduring effect following termination of the acute treatment. We found no significant difference in relapse after acute phase CBT versus continuation of pharmacotherapy after remission. Given the small number of studies this finding should be interpreted with caution pending replication.

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4 Article summary
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7 Article focus
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- 9 • Cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective
10 in the acute treatment of depression
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- 12 • Longer term differential effects are not well-known
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16 Key messages
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- 18 • When acute phase CBT (without continuation treatment) was compared with
19 acute phase pharmacotherapy that was discontinued during 6 to 18 months
20 follow-up, we found that acute phase CBT was clearly more effective.
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- 22 • We found no significant difference between acute phase CBT (without
23 continuation treatment) and acute phase pharmacotherapy with continued
24 pharmacotherapy during follow-up, although there was a trend indicating that
25 there may be such a difference favouring acute phase CBT.
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31 Strengths and limitations of this study
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- 33 • Too few studies have examined the long-term effects of treatments for
34 depressive disorders
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Introduction

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It is well established that cognitive behaviour therapy (CBT) is efficacious in the treatment of adult depression. Dozens of randomized trials have shown that CBT is superior to no treatment, nonspecific controls or care-as-usual in the acute treatment of adult depression [1,2], and that the effects of CBT are comparable to those of antidepressant pharmacotherapy, albeit with lower rates of attrition for CBT [3].

What is not clear, however, is how acute CBT compares to pharmacotherapy over the longer term. It has long been claimed that psychotherapy leads to lasting change because patients learn skills that can be implemented after the treatment has ended and because they are instructed on specific techniques on how to handle relapse. CBT has been found to have an enduring effect that lasts beyond the end of treatment [4]. No such claim has ever been made for pharmacotherapy [5]. Nonetheless, it is well established that keeping patients on pharmacotherapy even after they are better can reduce the risk of subsequent symptom return and it is standard practice to keep patients with chronic or recurrent depressions on pharmacotherapy indefinitely [6].

If CBT has an enduring effect that extends beyond the end of treatment it is important to know how that compares to simply keeping patients on pharmacotherapy. This is important from a clinical point of view, since clinicians and patients have to decide which modality to choose at the outset of treatment and will want to consider information about the relative long-term effects of each in their initial decision.

Improvement during acute treatment is called *response* and the full normalization of symptoms is called *remission* [7]. Recently remitted patients typically are kept on *continuation pharmacotherapy* for another six to twelve months in order to reduce the risk of *relapse*, the return of symptoms associated with the treated episode, and patients who have gone that long without relapse are said to be *recovered*, with the presumption that the underlying episode has run its course. Keeping recovered patients on *maintenance pharmacotherapy* beyond that point is intended to reduce risk for *recurrence*, the onset of a wholly new episode, and is standard for chronic or recurrent patients [7].

Although several studies have compared the long-term effects of acute CBT with those of continuation pharmacotherapy, no meta-analysis of these studies has been

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4 conducted. One earlier review examined whether acute phase CBT had an enduring
5 effect relative to medication withdrawal, but no direct comparison was made against
6 continuation pharmacotherapy [8]. Since continued prescription of pharmacotherapy is
7 now the current standard of treatment and the key decision that clinicians need to make,
8 we decided to conduct such a meta-analysis.
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12 In this meta-analysis we focus on two research questions. The first question is
13 whether acute phase CBT without continuation treatment is as effective as acute phase
14 pharmacotherapy treatment with continuation treatment. The second question is whether
15 acute phase CBT without continuation treatment is as effective as acute phase
16 pharmacotherapy treatment without continuation treatment.
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24 Methods

25 Identification and selection of studies

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27 We used a database of 1,344 papers on the psychological treatment of depression
28 described in detail elsewhere [9] that has been used to conduct a series of published
29 meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously
30 updated through comprehensive literature searches (from 1966 to January 2012). In
31 these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo
32 (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988).
33 These abstracts were identified by combining terms indicative of psychological
34 treatment and depression (both MeSH terms and text words). We also checked the
35 references from 42 meta-analyses of psychological treatment for depression to ensure
36 that no published studies were missed. From the 13,407 abstracts (9,860 after removal
37 of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.
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40 We included (a) randomized trials (b) in which the effects of cognitive behaviour
41 therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the
42 effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive
43 disorder, (f) across a follow-up period of 6-18 months. We focused on studies that
44 compared acute CBT (without subsequent continuation) versus pharmacotherapy that
45 was either continued or withdrawn, and conducted separate comparisons on each.
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4 Studies in which CBT was continued during follow-up were excluded, although we
5 allowed a maximum of 5 booster sessions during follow-up, as long as these were not
6 regularly planned. We set the limit at 5 booster session because most psychological
7 treatments have 6 or more treatment sessions [11]. We also excluded studies in which
8 depression was not diagnosed with a standardized diagnostic interview (such as the
9 CIDI, SCID or MINI), as well as studies in inpatients and adolescents. No language
10 restrictions were applied.
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16 17 Quality assessment and data extraction

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19 The validity of included studies was assessed on four criteria of the ‘Risk of bias’
20 assessment tool developed by the Cochrane Collaboration to assess possible sources of
21 bias in randomized trials: (a) adequate generation of allocation sequence; (b)
22 concealment of allocation to conditions; (c) prevention of knowledge of the allocated
23 intervention (blinding); and (d) dealing with incomplete outcome data [12]. The two
24 other criteria of the ‘Risk of bias’ assessment tool were not used in this study, because
25 we found no clear indication in any of the studies that these had influenced the validity
26 of the study (suggestions of selective outcome reporting; and other problems that could
27 put it at a high risk of bias).
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34 We collected characteristics of the target population (method of recruitment,
35 definition of depression, HAM-D score at the start of the treatment to assess the severity
36 of depression, whether all randomized patients were examined at follow-up or only the
37 responders to acute phase treatment, number of treatment sessions, type of drug,
38 whether pharmacotherapy was continued across the full follow-up or only for part of
39 that period, and the country where the study was conducted. If not all information was
40 reported in the paper, we contacted the authors of the papers to request the additional
41 information (all six of whom responded).
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48 49 Meta-analyses

50 For each study we used the number of patients who responded to treatment and
51 remained well as outcome measure (the exact definition of the outcome in each study is
52 reported in Table 1, column “Outcome”). We calculated the odds ratio (OR) of a
53 positive outcome in CBT compared with pharmacotherapy. We calculated these ORs at
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4 the end of the acute treatment (response or remission) and across the subsequent follow-
5 up (freedom from relapse or recurrence). Although at least some of the follow-ups were
6 long enough for patients free from relapse to have met criteria for recovery (and
7 subsequent episodes to be recurrences) we will use the term relapse to refer to all
8 instances of symptom return.
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12 To calculate pooled ORs, we used the computer program Comprehensive Meta-
13 Analysis (version 2.2.021). We calculated the pooled ORs with the fixed effects model
14 as well as with the random effects model. The calculations were conducted according to
15 the procedures given by Borenstein and colleagues [13]. Because the results of these
16 analyses were almost identical, we only report the results of the random effects model.
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20 The numbers-needed-to-be-treated (NNT) is intuitively easier to understand than the
21 OR. The NNT indicates the number of patients that would have to be treated in order to
22 generate one additional positive outcome [14]. Therefore we also calculated the NNTs
23 for all comparisons. We calculated the risk differences (RDs) for each study, pooled
24 these for all studies, and then calculated the NNT as 1/RD for the pooled studies.
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28 As a test of homogeneity of effect sizes, we calculated the I^2 -statistic, an indicator of
29 heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and
30 larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and
31 75% as high heterogeneity [15]. We calculated 95% confidence intervals around I^2 [16],
32 using the non-central chi-squared-based approach within the heterogi module for Stata
33 [17].
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37 Subgroup analyses between different subsamples of studies were conducted
38 according to the mixed effect model. In this model, studies within subgroups are pooled
39 with the random effects model, while tests for significant differences between
40 subgroups are conducted with the fixed effects model.
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44 Publication bias was tested by inspecting funnel plots on the primary outcome
45 measures and by Duval and Tweedie's trim and fill procedure [18], which yields an
46 estimate of the effect size after adjusting for publication bias (as implemented in
47 Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the
48 intercept as well as Begg and Mazumbar's test to quantify the bias captured by the
49 funnel plot and test whether it was significant [19]. We also calculated Orwin's Fail safe
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4 N, which indicates the number of missing studies needed to make the effect size
5 insignificant [20].
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10 Results

11 Selection and inclusion of studies

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14 After examining a total of 13,407 abstracts (9,860 after removal of duplicates), we
15 retrieved 1,344 full-text papers for further consideration. We excluded 1,335 of the
16 retrieved papers. The flowchart describing the inclusion process, including the reasons
17 for exclusion, is presented in Figure 1. Nine of the 1,344 retrieved full-text papers
18 reported long-term outcomes of acute phase CBT and were included in this meta-
19 analysis [21-28].
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27 Characteristics of included studies

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29 In the 9 included studies, a total of 506 patients participated, 271 in CBT and 235 in
30 pharmacotherapy. Selected characteristics of the included studies are presented in Table
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34 Four studies recruited patients only from clinical samples, while the other five also
35 recruited patients from the community. Six studies included only patients who
36 responded to acute phase treatment in the analyses of the subsequent follow-ups, while
37 the other three included all patients randomized to acute phase treatment. The number
38 of CBT treatment sessions ranged from 18 to 24. During the follow-up phase (after
39 acute treatment had ended) three studies offered up to four CBT booster sessions, while
40 the other six did not offer any additional treatment.
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46 In five earlier studies a tricyclic antidepressant (TCA) was used in the
47 pharmacotherapy condition, while the three more recent studies all used a selective
48 serotonin reuptake inhibitor (SSRI); in one study phenelzine (a MAOI) was used. In
49 four studies, patients who responded to pharmacotherapy were randomized to either
50 continuation pharmacotherapy (for the first year of the two-year follow-up) or
51 pharmacotherapy withdrawal with each reported separately. In three other trials all
52 patients were withdrawn from pharmacotherapy, although the length of the taper
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4 differed across the trials. One other trial continued pharmacotherapy for the first six
5 months of the follow-up before subsequent withdrawal, and in the remaining trial
6 pharmacotherapy was continued throughout the follow-up. In most instances patients
7 withdrawn from treatment were followed naturalistically although in several studies
8 they were encouraged not to seek additional treatment until a relapse or recurrence was
9 documented. Seven studies were conducted in the United States, two in Europe (one in
10 the UK, one in Romania).

17 Quality of included studies

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19 Eight of the nine studies used an adequate sequence generation strategy and had an
20 independent party conceal allocations to conditions. Six studies reported keeping the
21 assessors blind to treatment condition and seven studies conducted intent-to-treat
22 analyses. The six studies published in the last two decades met all four of the quality
23 criteria; among the three earlier studies, one study met three, another met two, and yet
24 another met none of the criteria (Table 1). The overall quality of the studies was
25 relatively high, compared with studies on psychotherapy for adult depression in general
26 [30].
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34 Long-term outcomes: Acute phase CBT versus continuation pharmacotherapy

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36 Five studies compared the one-year outcomes of acute phase CBT (with nothing
37 more than occasional booster sessions) versus continuation pharmacotherapy [22-26].
38 There was a trend ($p < 0.1$) indicating that acute phase CBT outperformed continuation
39 pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72). Heterogeneity was zero, but the 95%
40 confidence interval was broad (0 to 79%), so this finding should be interpreted with
41 caution. The NNT was 10. The ORs and 95% confidence intervals are presented
42 graphically in Figure 2. After exclusion of a possible outlier, the OR was significant
43 (OR=1.77; 95% CI: 1.04~3.01; NNT=8). As can be seen, however, the pooled odds
44 ratios are heavily reliant on just two studies, although most of the studies pointed in the
45 same direction. The results should, therefore, be considered with caution.
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52 We found no indication of publication bias (not surprising given how few studies).
53 Using Duval and Tweedie's trim and fill procedure to adjust for publication bias did not
54 change the OR (number of trimmed studies was zero). Egger's test and Begg and
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4 Mazumbar's test were not significant ($p>0.1$). We also calculated Orwin's Fail Safe N
5 and found that 23 studies with an OR of 0.9 or eleven studies with an OR of 0.8 (in
6 favour of pharmacotherapy) or 7 studies with an OR of 0.7 would be needed to produce
7 a pooled OR of 1.00. No additional subgroup analyses were conducted because of the
8 small number of studies.
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12 13 14 Long-term outcomes: Acute phase CBT versus pharmacotherapy discontinuation

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16 Eight studies compared the one-year outcomes of acute phase CBT (with nothing
17 more than occasional booster sessions) versus pharmacotherapy discontinuation or a
18 naturalistic design. Acute phase CBT significantly outperformed the pharmacotherapy
19 discontinuation condition to an even greater extent than it had continuation
20 pharmacotherapy (OR=2.61; 95% CI: 1.58~4.31; $p<0.001$). Heterogeneity was zero, but
21 again the 95% CI was broad (0~68%). The corresponding NNT was 5 (95% CI: 4~11).
22 The ORs and 95% CI for each study are presented graphically in Figure 3.
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27 Because two studies had a very high OR [21,24] and one a very low OR [26], we
28 conducted an additional sensitivity analysis with these studies removed. The resulting
29 OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly significant
30 ($p<0.001$) and the corresponding NNT was 6 (95% CI: 4~15). Again, these results were
31 heavily reliant on just two studies, and the results should be considered with caution.
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36 Although the number of studies was small, we did conduct some subgroup analyses.
37 We did not find any significant differences between subgroups, including medication
38 type (SSRI versus TCA), whether all randomized patients were included versus
39 inclusion of responders to the acute phase only, and the studies with the highest quality
40 (meeting all 4 criteria) versus those with lower quality (≤ 3 criteria). These outcomes
41 should be interpreted with caution, however, because of the small sample sizes in the
42 subgroups.
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49 Short-term outcomes

50 We also examined the comparative effects of CBT versus pharmacotherapy at the
51 short term (end of acute treatment), but found no significant difference (OR=1.15, n.s.;
52 Table 2). Excluding one potential outlier [27] did not affect this finding.
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4 We also examined whether we could confirm that dropout from the intervention was
5 significantly higher in pharmacotherapy than in CBT, as has been established in earlier
6 meta-analyses [3]. Eight of the nine studies reported sufficient data on dropout to be
7 included in the analyses. We found that the odds of dropping out in the acute phase
8 were significantly lower in CBT than in pharmacotherapy (OR=0.59; 95% CI:
9 0.34~0.99). Inspection of the funnel plot indicated that several studies could have been
10 outliers. Because of the small number of studies, however, we did not conduct any
11 additional sensitivity analyses.
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19 Discussion

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22 We found that patients treated acutely with CBT were less likely to relapse following
23 acute treatment termination than patients treated acutely with pharmacotherapy. We did
24 not find that patients treated with acute phase CBT had a significantly lower risk of
25 relapse than patients on pharmacotherapy. There was a non-significant trend ($p<0.1$)
26 suggesting that relapse rates may be lower after acute phase CBT, but there were too
27 few studies on the long-term effects of CBT and continuation pharmacotherapy to draw
28 definite conclusions. More research is needed before this question can be resolved.
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34 It has been found in earlier research that patients are as likely to respond to CBT as
35 to pharmacotherapy and are less likely to drop out of treatment [3]. Moreover, there are
36 indications that the majority of patients who respond to pharmacotherapy do so for
37 nonspecific reasons; that is, they are showing a placebo response and not a “true” drug
38 effect. The same appears to be true for the psychosocial treatments including CBT [31].
39 The fact that CBT results in lower relapse rates than discontinued pharmacotherapy not
40 only suggests that CBT has a specific enduring effect that may operate through
41 somewhat different mechanisms than its acute effects, but also confirms its strong
42 position as a first-line treatment of acute depressive disorders.
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49 The results of this meta-analysis should be interpreted with caution because of a
50 number of limitations. The most important limitation was that the small number of
51 studies comparing CBT with continued pharmacotherapy. Also the number of patients
52 in these studies was relatively small, and the results of the main analyses relied heavily
53 on just a few studies. In such a situation, only a few additional studies with different
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4 outcomes can turn these results from a trend to non-significance. Another possible
5 limitation is that there was considerable variation in the methods used between the
6 studies in terms of pharmacotherapy, measures, and other characteristics. Some studies
7 also only included responders to the acute phase in the follow-up analyses, which may
8 have led to bias in the overall results. If high risk patients were more likely to respond
9 to pharmacotherapy than to CBT then acute treatment could have acted as a “differential
10 sieve” that systematically unbalanced the groups and led to the differential retention of
11 patients differing in *a priori* risk being misinterpreted as an enduring effect. Another
12 possible limitation is that the follow-up of the CBT conditions in most of the studies
13 was naturalistic although some asked patients not to pursue outside treatment in the
14 absence of a documented relapse and censored those events the few times that they did
15 occur. However, there were important differences between the studies in terms of the
16 treatment received during the follow-up phase. There also was considerable variability
17 in when pharmacotherapy was discontinued across the studies although that should only
18 have led us to underestimate the “true” magnitude of the advantage for acute phase CBT
19 in that comparison. Moreover, the quality of the studies included in this meta-analysis
20 was high and even if the next ten studies all produced an advantage for ongoing
21 continued pharmacotherapy, acute phase CBT would still be as efficacious as
22 continuation pharmacotherapy. Subsequent replication is needed before a possible
23 superiority of acute phase CBT over continuation pharmacotherapy can be taken
24 seriously, but the possibility is of sufficient importance that such efforts clearly should
25 be made.
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40 Studies on the long-term effects of treatments of depression are complicated, because
41 subsequent treatment is difficult to control (but not impossible to influence). Another
42 complication is that patients both need to complete and respond to acute treatment in
43 order to be at risk for subsequent relapse or recurrence; large numbers of patients need
44 to be randomized initially to differential treatment in order to have enough patients
45 remit to detect anything but the largest subsequent differences during follow-up.
46 Furthermore, acute and continuation/maintenance treatments can be offered in several
47 varieties and the latter can be changed during the course of the follow-up. The number
48 of possible comparisons is therefore large, but all are needed to give an adequate answer
49 to the question which treatment is the best for the longer-term. The most important
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4 design for a future study, however, would be a sufficiently powered trial comparing
5 acute phase CBT without subsequent continuation versus acute phase pharmacotherapy
6 with subsequent continuation (the current standard of treatment). Although some studies
7 have used this design, none had sufficient power to find significant differences of the
8 magnitude (modest but clinically relevant) between the two suggested by this meta-
9 analysis. It seems highly relevant to conduct such a trial.
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4 Contributors.

5 PC and SDH had the idea for this study. PC drafted the initial manuscript, prepared and
6 cleaned the data, and conducted the data analysis. SDH, AVS, CB, MB and GA read all
7 version of the manuscript critically and contributed to the final paper.
8

9
10 Funding.

11 This research received no specific funding.
12

13 Ethics approval.

14 No ethics approval was needed for this study.
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16 Data sharing statement.

17 No primary data are used in this paper
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Table 1. Selected characteristics of studies comparing the long-term effects of cognitive behavior therapy for adult depression with those of pharmacotherapy

	Recr	Depressive disorder	Pre HAM-D	Included ^{a)}	Psychotherapy				Pharmacotherapy			FU	Outcome	C	Quality			
					Acute phase	N _{sess}	Contin. Phase	N	Acute phase	Continuation phase	N				S	A	B	C
Blackburn, 1986	Clin	MDD (PSE / RDC)	NR	Resp	CBT	23	4 boosters (in first 6 months)	13	Drug of choice	Continuation of 6 months, remaining period naturalistic	9	24	Depressive symptoms needing further treatment	UK	-	-	-	-
David, 2008	Com + clin	MDD (DSM-IV) + BDI ≥ 20 + HAM-17 ≥ 14	22.1	All	CBT	20	Max 3 boosters sessions	56	Fluoxetine	Continued pharmacotherapy	57	6	No current MDD + HAMD ≤ 7	RO	+	+	+	+
Dobson, 2008	Com + clin	MDD (DSM-IV) + BDI-II ≥ 20 + HAM-D 17 ≥ 14	20.7	Resp	CBT	24	No treatment offered during follow-up	30	Paroxetine	Continued pharmacotherapy	28	12	Sustained response (no 2 wks HAMD ≥ 14)	US	+	+	+	+
Evans, 1992	Clin	MDD (RDC)	26.9	Resp	CBT	20	No continued treatment	10	Imipramine	Continued pharmacotherapy during year 1, then tapered	11	24	No relapse (BDI ≥ 16 during at least 2 weeks) + no treatment	US	+	+	+	+
Hollon, 2005	Com / clin	MDD (DSM-IV)	23.4	Resp	CBT	20	Up to 3 booster sessions	60	Paroxetine	Continued pharmacotherapy	34	12	No relapse (no HAMD ≥ 14 for two consecutive weeks)	US	+	+	+	+
Jarret, 2000	Com / clin	Atypical MDD (DSM-IV; SCID)	18.4	Resp	CBT	20	No continued treatment	6	Phenelzine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feighner) + HAM-D-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Naturalistic	18	Imipramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAMD ≥ 14	19.6	All	CBT	18	Naturalistic	59	Imipramine	Pharmacotherapy was gradually reduced	57	18	Recovered (LIFE-II) and no relapse (MDD / RDC)	US	+	+	+	+
Simons, 1986	Clin	DD (DIS) + HAMD ≥ 14 or BDI ≥ 20	19.9	Resp	CBT	20	No additional treatment	19	Nortriptyline	Pharmacotherapy was gradually tapered	16	12	Did not re-enter treatment + no BDI ≥ 16 at follow-up	US	+	+	-	+

Abbreviations: AC: allocation concealment; All: all randomized patients; BA: blind assessment; BDI: Beck Depression Inventory; C: country; CBT: cognitive behaviour therapy; CF: completeness of follow-up data; Clin: clinical recruitment; Com: community recruitment; DD: depressive disorder; DIS: diagnostic interview schedule; FU: follow-up; HAM-D: Hamilton

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depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depressive disorder; N_{sess}: number of sessions; PSE: present state examination; RDC: research diagnostic criteria; Recr: recruitment; Resp: only responders to the acute phase; RO: Romania; SG: sequence generation; UK: United Kingdom; US: United States.
a) Only responders to the acute phase treatments or the ones who completed the acute phase treatment were included in the follow-up analyses.

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Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response ^{a)}

	<i>N</i>	<i>OR</i>	<i>95% CI</i>	<i>I</i> ²	<i>95% CI</i>	<i>NNT</i>	<i>95% CI</i>	<i>p</i> ^{c)}
<u>CBT vs continued pharmacotherapy</u>								
All studies	5	1.62	0.97~2.72 o	0	0~79	10		e)
One possible outlier excluded ^{d)}	4	1.77	1.04~3.01	0	0~85	8	4~71	
<u>CBT vs discontinued pharmacotherapy</u>								
All studies	8	2.61	1.58~4.31 ***	0	0~68	5	4~11	
Three possible outliers excluded ^{f)}	5	2.47	1.45~4.22 ***	0	0~79	6	4~15	
<u>Subgroups (long-term effects)</u>								
Pharmacotherapy ^{g)}								
- SSRI	2	3.02	1.29~7.04 *	0	h)	5		0.82
- TCA	5	2.66	1.40~5.04 **	0	0~79	6	4~15	
Included sample								
- All	2	1.97	0.91~4.27 o	0	h)	9		0.14
- Responders	6	3.20	1.65~6.19 **	0	0~75	4	3~8	
Quality								
- All 4 criteria	5	2.31	1.28~4.16 **	0	0~79	6	2~11	0.25
- ≤ 3 criteria	3	3.58	1.39~9.22 **	0	0~90	4	2~10	
<u>Short term effects</u>								
All studies	9	1.15	0.74~1.79	53	0~78	20		e)
One possible outlier excluded ⁱ⁾	8	0.96	0.72~1.30	0	0~68			e)
Drop-out from intervention ^{j)}	8	0.59	0.34~0.99 *	48	0~77	9	5~143	

o: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

^{a)} according to the random effects model;

^{b)} in this column, the I^2 is reported; we also tested whether the Q-value was significant. This was the case in two comparisons (indicated with an asterisk *).

^{c)} the p-value indicates whether the subgroups differ from each other;

^{d)} Jarrett et al., 2000

^{e)} the 95% CI includes zero and would result in a negative NNT; therefore, we do not report the 95% of the NNT here the 95% confidence interval included zero; because this would result in a negative NNT we do not report this here.

^{f)} Blackburn et al., 1981; Jarrett, 2000; Evans et al., 1992.

^{g)} one study examined phenelzine (Jarrett, 2000); this was not included in the analyses.

^{h)} 95% CI cannot be calculated when df is lower than 2.

ⁱ⁾ Kovacs et al., 1981

^{j)} One study did not report data on drop-out (Blackburn et al., 1981)

Figure 1. Flowchart of inclusion of studies

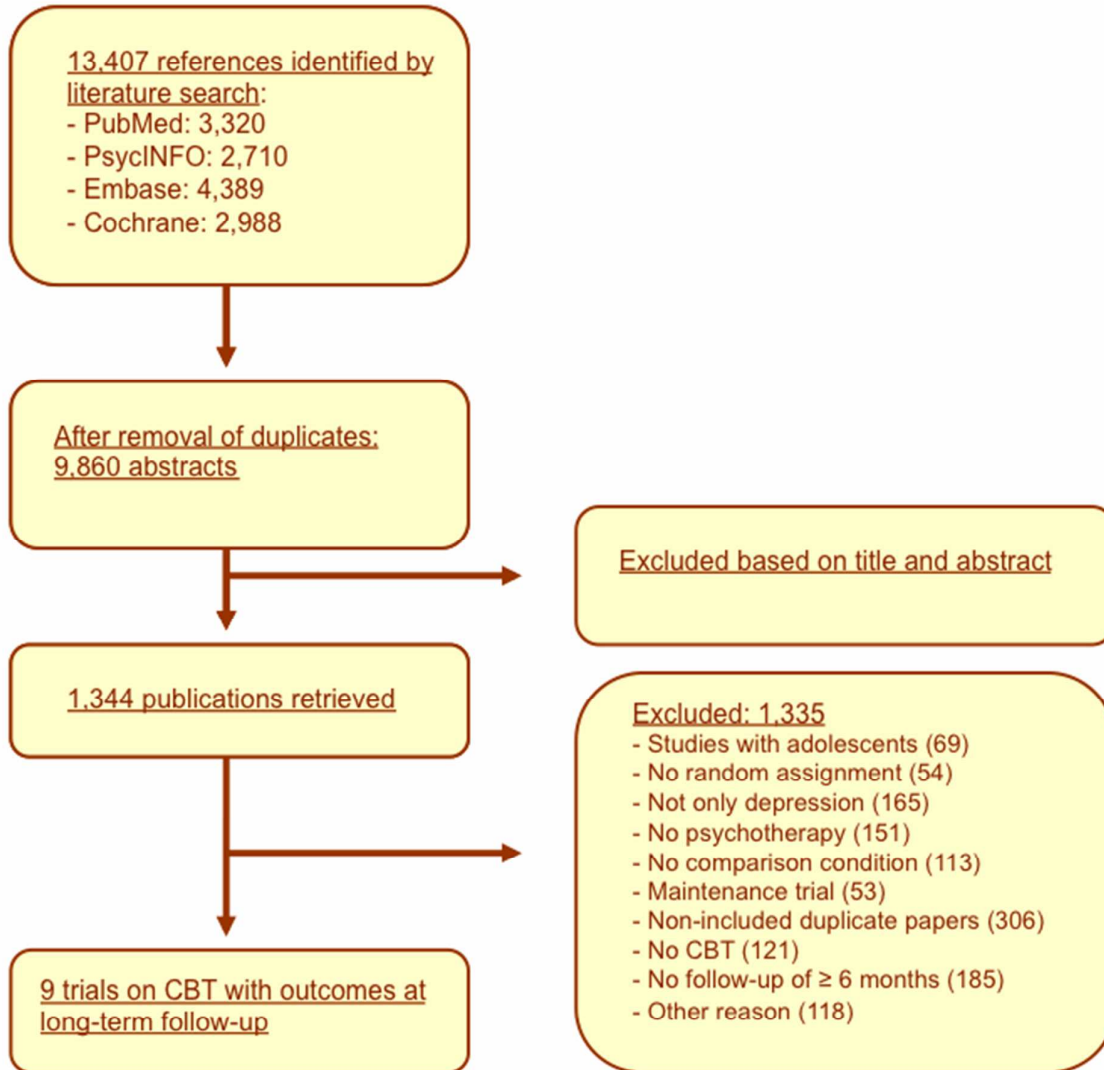
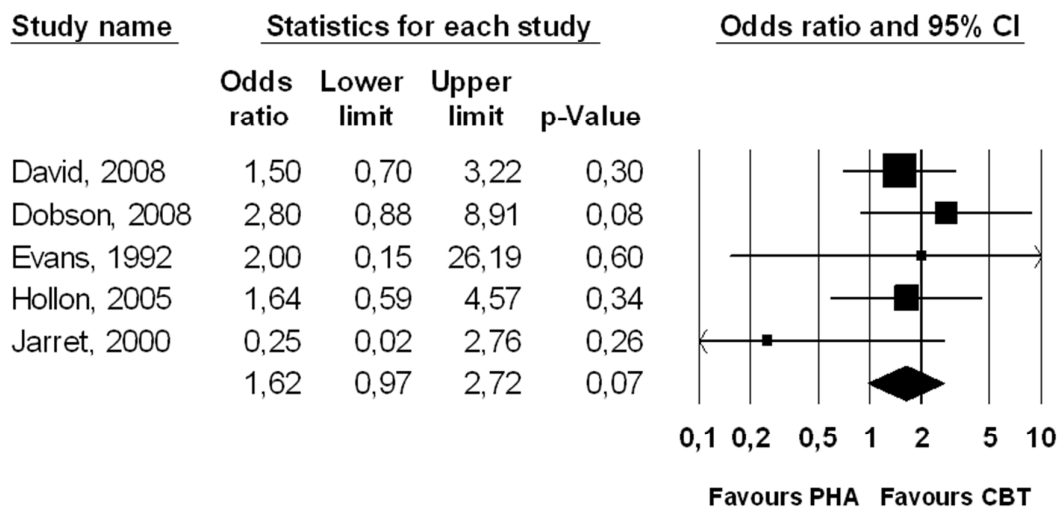


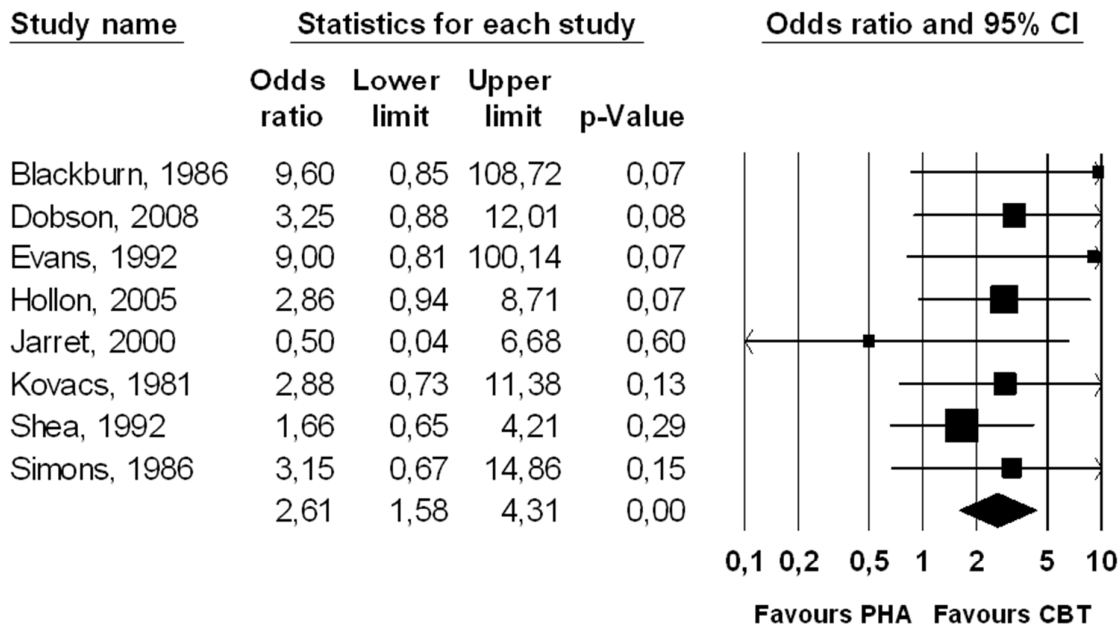
Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response



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Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*discontinued* during follow-up): Forest plot of Odds ratio of response



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Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation medication/pharmacotherapy?

A meta-analysis

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Abstract

Objectives: Although cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of adult depression, it is not known how they compare across the longer term. In this meta-analysis we compared the effects of acute phase CBT without any ~~additional-subsequent~~ treatment with the effects of pharmacotherapy that either was continued or discontinued across ~~a subsequent one-year~~ 6 to 18 month follow-up.

Design: We conducted systematic searches in bibliographical databases to identify relevant studies, and conducted a meta-analysis of studies meeting inclusion criteria.

Setting: mental health care

Participants: patients with depressive disorders.

Interventions: CBT and pharmacotherapy for depression.

Outcomes measures: Relapse rates at longer-term follow-up.

Results: Nine studies with 506 patients were included. The quality was relatively high.

Short-term outcomes of CBT and pharmacotherapy were comparable, although drop-out from treatment was significantly lower in CBT.

Acute phase CBT was compared with pharmacotherapy discontinuation during follow-up in eight studies. Patients who received acute phase CBT were significantly less likely to relapse than patients who were withdrawn from pharmacotherapy (OR=2.61; 95% CI: 1.58-4.31; p<0.001; NNT = 5). ~~Prior~~ Acute phase CBT was compared with continued pharmacotherapy during at follow-up in five studies. There was a no significant difference between acute phase CBT and continued pharmacotherapy, although there was a trend (p<0.1) indicating that patients who received prior-CBT acute phase CBT were may be less likely to relapse following acute treatment termination than patients who were continued on medication pharmacotherapy (OR=1.62; 95% CI: 0.97-2.72; NNT = 10).

~~Prior CBT was compared with medication discontinuation during follow up in eight studies. Patients who received prior CBT were significantly less likely to relapse than patients who were withdrawn from medication treatment (OR=2.61; 95% CI: 1.58-4.31; p<0.001; NNT = 5). Short term outcomes of CBT and pharmacotherapy were comparable, although drop out from treatment was significantly lower in CBT.~~

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7 Conclusions: We found a trend that prior exposure to CBT was more effective than
8 pharmacotherapy at preventing relapse across a one year follow up whether medication
9 treatment was continued or withdrawn. We found that CBT not only seems to have
10 has
11 an enduring effect following treatment termination of the acute treatment. We found no
12 significant difference in relapse after acute phase CBT versus continuation of
13 pharmacotherapy after remission. but the magnitude of this effect may even be
14 somewhat greater than keeping patients on continuation medication. Given the small
15 number of studies this finding should be interpreted with caution pending replication.
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Article summary

Article focus

- Cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of depression
- Longer term differential effects are not well-known

Key messages

- When acute phase CBT (without continuation treatment) was compared with acute phase pharmacotherapy that was discontinued during 6 to 18 months follow-up, we found that acute phase CBT was clearly more effective.
- We found no significant difference between acute phase CBT (without continuation treatment) and acute phase pharmacotherapy with continued pharmacotherapy during follow-up, although there was a trend indicating that there may be such a difference favouring acute phase CBT.
- ~~When pharmacotherapy was discontinued during follow up, relapse rates in CBT without continuation therapy were significantly lower than in pharmacotherapy~~
- ~~There were indications that patients who received CBT without continuation therapy may be less likely to relapse during follow up than patients who were continued on medication~~
- ~~When pharmacotherapy was discontinued during follow up, relapse rates in CBT without continuation therapy were significantly lower than in pharmacotherapy~~

Strengths and limitations of this study

- Too few studies have examined the long-term effects of treatments for depressive disorders

Introduction

It is well-established that cognitive behaviour therapy (CBT) is efficacious in the treatment of adult depression. Dozens of randomized trials have shown that CBT is superior to no treatment, nonspecific controls ~~and-or~~ care-as-usual in the acute treatment of adult depression [1,2], and that the effects of CBT are comparable to those of antidepressant ~~medication~~pharmacotherapy, albeit (ADM) with lower rates of attrition ~~for CBT~~ [3].

What is not clear, however, is how acute CBT compares to pharmacotherapy over the longer term. It has long been claimed that psychotherapy leads to lasting change because patients learn skills that can be implemented after the treatment has ended and because they are instructed on specific techniques on how to handle relapse. CBT has been found to have an enduring effect that lasts beyond the end of treatment [4]. No such claim has ever been made for ~~medication~~pharmacotherapy ~~treatment~~ [5]. Nonetheless, it is well established that keeping patients on ~~medication~~pharmacotherapys even after they are better can reduce the risk of subsequent symptom return and it is standard practice to keep patients with chronic or recurrent depressions on ~~medication~~pharmacotherapys indefinitely [6].

If CBT has an enduring effect that extends beyond the end of treatment it is important to know how that compares to simply keeping patients on ~~medication~~pharmacotherapy. This is important from a clinical point of view, since clinicians and patients have to decide which modality to choose at the outset of treatment and will want to consider information about the relative long-term effects of each in their initial decision.

Improvement during acute treatment is called *response* and the full normalization of symptoms is called *remission* [7]. Recently remitted patients typically are kept on *continuation* ~~medication~~pharmacotherapy for another six to twelve months in order to reduce the risk of *relapse*, the return of symptoms associated with the treated episode, and patients who have gone that long without relapse are said to be *recovered*, with the presumption that the underlying episode has run its course. Keeping recovered patients on *maintenance* ~~medication~~pharmacotherapy beyond that point is intended to reduce

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7 risk for *recurrence*, the onset of a wholly new episode, and is standard for chronic or
8 recurrent patients [7].
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10 Although several studies have compared the long-term effects of acute CBT with
11 those of continuation ~~medication~~pharmacotherapy, no meta-analysis of these studies has
12 been conducted. One earlier review examined whether ~~prior CBT~~acute phase CBT had
13 an enduring effect relative to medication withdrawal, but no direct comparison was
14 made ~~to against~~ continuation ~~medication~~pharmacotherapy [8]. Since continued
15 prescription of pharmacotherapy ~~that~~ is now the current standard of treatment and the
16 key decision that clinicians need to make, we decided to conduct such a meta-analysis.
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20 In this meta-analysis we focus on two research questions. The first question is
21 whether acute phase CBT without continuation treatment is as effective as acute phase
22 pharmacotherapy treatment with continuation treatment. The second question is whether
23 acute phase CBT without continuation treatment is as effective as acute phase
24 pharmacotherapy treatment without continuation treatment.
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32 Methods

33 Identification and selection of studies

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35 We used a database of 1,344 papers on the psychological treatment of depression
36 described in detail elsewhere [9] that has been used to conduct a series of published
37 meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously
38 updated through comprehensive literature searches (from 1966 to January 2012). In
39 these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo
40 (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988).
41 These abstracts were identified by combining terms indicative of psychological
42 treatment and depression (both MeSH terms and text words). We also checked the
43 references from 42 meta-analyses of psychological treatment for depression to ensure
44 that no published studies were missed. From the 13,407 abstracts (9,860 after removal
45 of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.
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7 We included (a) randomized trials (b) in which the effects of cognitive behaviour
8 therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the
9 effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive
10 disorder, (f) across a follow-up period of 6-18 months. We focused on studies that
11 compared acute CBT (without subsequent continuation) versus pharmacotherapy that
12 was either continued or withdrawn, and conducted separate comparisons on each.
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16 Studies in which CBT was continued during follow-up were excluded, (although we
17 allowed a maximum of 5 booster sessions during follow-up, as long as these were not
18 regularly planned). We set the limit at 5 booster session because most psychological
19 treatments have 6 or more treatment sessions [11]. We also excluded studies in which
20 depression was not diagnosed with a standardized diagnostic interview (such as the
21 CIDI, SCID or MINI), as well as studies in inpatients and adolescents. No language
22 restrictions were applied.
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27 Quality assessment and data extraction

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29 The validity of included studies was assessed on four criteria of the ‘Risk of bias’
30 assessment tool developed by the Cochrane Collaboration to assess possible sources of
31 bias in randomized trials: (a) adequate generation of allocation sequence; (b)
32 concealment of allocation to conditions; (c) prevention of knowledge of the allocated
33 intervention (blinding); and (d) dealing with incomplete outcome data [124]. The two
34 other criteria of the ‘Risk of bias’ assessment tool were not used in this study, because
35 we found no clear indication in any of the studies that these had influenced the validity
36 of the study (suggestions of selective outcome reporting; and other problems that could
37 put it at a high risk of bias).
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42 We collected characteristics of the target population (method of recruitment,
43 definition of depression, HAM-D score at the start of the treatment to assess the severity
44 of depression, whether all randomized patients were examined at follow-up or only the
45 responders to acute phase treatment, number of treatment sessions, type of drug,
46 whether pharmacotherapy was continued across the full follow-up or only for part of
47 that period, and the country where the study was conducted. If not all information was
48 reported in the paper, we contacted the authors of the papers to request the additional
49 information (all six of whom responded).
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Meta-analyses

For each study we used the number of patients who responded to treatment and remained well as outcome measure (the exact definition of the outcome in each study is reported in Table 1, column “Outcome”). We calculated the odds ratio (OR) of a positive outcome in CBT compared with pharmacotherapy. We calculated these ORs at the end of the acute treatment (response or remission) and across the subsequent follow-up (freedom from relapse or recurrence). Although at least some of the follow-ups were long enough for patients free from relapse to have met criteria for recovery (and subsequent episodes to be recurrences) we will use the term relapse to refer to all instances of symptom return.

To calculate pooled ORs, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). We calculated the pooled ORs with the fixed effects model as well as As we expected considerable heterogeneity among the studies, we used a with the random effects model to pool the ORs. The calculations were conducted according to the procedures given by Borenstein and colleagues [13]. Because the results of these analyses were almost identical, we only report the results of the random effects model. Random effects models assume that the included studies are drawn from ‘populations’ of studies that differ from each other systematically (heterogeneity). In this model, the effect sizes resulting from included studies not only differ because of the random error within studies (as in the fixed effects model), but also because of true variation in effect size from one study to the next.

The numbers-needed-to-be-treated (NNT) is intuitively easier to understand than the OR. The NNT indicates the number of patients that would have to be treated in order to generate one additional positive outcome [142]. Therefore we also calculated the NNTs for all comparisons. We calculated the risk differences (RDs) for each study, pooled these for all studies, and then calculated the NNT as 1/RD for the pooled studies.

As a test of homogeneity of effect sizes, we calculated the I^2 -statistic, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity [153]. We also calculated the Q-statistic, but only report whether it was significant or not. We calculated 95% confidence

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7 intervals around I^2 [164], using the non-central chi-squared-based approach within the
8 heterogi module for Stata [175].
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10 Subgroup analyses between different subsamples of studies were conducted
11 according to the mixed effect model. In this model, studies within subgroups are pooled
12 with the random effects model, while tests for significant differences between
13 subgroups are conducted with the fixed effects model.
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16 Publication bias was tested by inspecting funnel plots on the primary outcome
17 measures and by Duval and Tweedie's trim and fill procedure [186], which yields an
18 estimate of the effect size after adjusting for publication bias (as implemented in
19 Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the
20 intercept as well as Begg and Mazumbar's test to quantify the bias captured by the
21 funnel plot and test whether it was significant [19].- We also calculated Orwin's Fail
22 safe N, which indicates the number of missing studies needed to make the effect size
23 insignificant [2047].
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31 Results

32 Selection and inclusion of studies

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34 After examining a total of 13,407 abstracts (9,860 after removal of duplicates), we
35 retrieved 1,344 full-text papers for further consideration. We excluded 1,335 of the
36 retrieved papers. The flowchart describing the inclusion process, including the reasons
37 for exclusion, is presented in Figure 1. Nine of the 1,344 retrieved full-text papers
38 reported long-term outcomes of prior CBT acute phase CBT and were included in this
39 meta-analysis [2148-286].
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45 Characteristics of included studies

46 In the 9 included studies, a total of 506 patients participated, 271 in CBT and 235 in
47 the ADM pharmacotherapy. Selected characteristics of the included studies are
48 presented in Table 1.
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50 Four studies recruited patients only from clinical samples, while the other five also
51 recruited patients from the community. Six studies included only patients who
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7 responded to acute phase treatment in the analyses of the subsequent follow-ups, while
8 the other three included all patients randomized to acute phase treatment. The number
9 of CBT treatment sessions ranged from 18 to 24. During the follow-up phase (after
10 acute treatment had ended) three studies offered up to four CBT booster sessions, while
11 the other six did not offer any additional treatment.

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14 In five earlier studies a ~~t~~tricyclic antidepressant (TCA) was used in the
15 pharmacotherapy condition, while the three more recent studies all used a ~~s~~selective
16 serotonin reuptake inhibitor (SSRI); in one study phenelzine (a MAOI) was used. In
17 four studies, patients who responded to pharmacotherapy were randomized to either
18 continuation ~~medicationpharmacotherapy~~ (for the first year of the two-year follow-up)
19 or ~~medicationpharmacotherapy~~ withdrawal with each reported separately. In three other
20 trials all patients were withdrawn from ~~medicationpharmacotherapys~~, although the
21 length of the taper differed across the trials. One other trial continued
22 ~~medicationpharmacotherapy~~ for the first six months of the follow-up before subsequent
23 withdrawal, and in the remaining trial ~~medicationpharmacotherapy treatment~~ was
24 continued throughout the follow-up. In most instances patients withdrawn from
25 treatment were followed naturalistically although in several studies they were
26 encouraged not to seek additional treatment until a relapse or recurrence was
27 documented. Seven studies were conducted in the United States, two in Europe (one in
28 the UK, one in Romania).

37 38 Quality of included studies

39 Eight of the nine studies used an adequate sequence generation strategy and had an
40 independent party conceal allocations to conditions. Six studies reported keeping the
41 assessors blind to treatment condition and seven studies conducted intent-to-treat
42 analyses. The six studies published in the last two decades met all four ~~of the~~ quality
43 criteria; among the three earlier studies, ~~one~~ study met three, another met two, and ~~the~~
44 ~~yet final another one~~ met none of the criteria (Table 1). The overall quality of the
45 studies was relatively high, ~~compared with studies on psychotherapy for adult~~
46 ~~depression in general~~ [30].
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7 Long-term outcomes: ~~Prior CBT~~Acute phase CBT versus continuation
8 medication pharmacotherapy

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10 Five studies compared the one-year outcomes of ~~prior CBT~~acute phase CBT (with
11 nothing more than occasional booster sessions) versus continuation pharmacotherapy
12 [[2219-263](#)]. There was a trend ($p < 0.1$) indicating that ~~prior CBT~~acute phase CBT
13 outperformed continuation pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72).

14 Heterogeneity was zero, but the 95% confidence interval was broad (0 to 79%), so this
15 finding should be interpreted with caution. The NNT was 10. The ORs and 95%
16 confidence intervals are presented graphically in Figure 2. After exclusion of a possible
17 outlier, the OR was significant (OR=1.77; 95% CI: 1.04~3.01; NNT=8). As can be
18 seen, however, the pooled odds ratios are heavily reliant on just two studies, although
19 most of the studies pointed in the same direction. The results should, therefore, be
20 considered with caution.

21 We found no indication of publication bias (not surprising given how few studies).
22 Using Duval and Tweedie's trim and fill procedure to adjust for publication bias did not
23 change the OR (number of trimmed studies was zero), ~~and~~ Egger's test and Begg and
24 Mazumbar's test were also was not significant ($p > 0.1$). We also calculated Orwin's Fail
25 Safe N and found that 23 studies with an OR of 0.9 or eleven studies with an OR of 0.8
26 (in favour of pharmacotherapy) or 7 studies with an OR of 0.7 would be needed to
27 produce a pooled OR of 1.00. No additional subgroup analyses were conducted because
28 of the small number of studies.

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39 Long-term outcomes: ~~Prior CBT~~Acute phase CBT versus ~~medication pharmacotherapy~~
40 discontinuation

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42 Eight studies compared the one-year outcomes of ~~prior CBT~~acute phase CBT (with
43 nothing more than occasional booster sessions) versus ~~medication pharmacotherapy~~
44 discontinuation or a naturalistic design. ~~Prior CBT~~Acute phase CBT significantly
45 outperformed the ~~medication pharmacotherapy~~ discontinuation condition to an even
46 greater extent than it had continuation ~~medication pharmacotherapy~~ (OR=2.61; 95% CI:
47 1.58~4.31; $p < 0.001$). Heterogeneity was zero, but again the 95% CI was broad
48 (0~68%). The corresponding NNT was 5 (95% CI: 4~11). ~~and~~ †The ORs and 95% CI
49 for each study are presented graphically in Figure 3.
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7 Because two studies had a very high OR [21+8,24+] and one a very low OR [263],
8 we conducted an additional sensitivity analysis with these studies removed. The
9 resulting OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly
10 significant (p<0.001) and the corresponding NNT was 6 (95% CI: 4~15). Again, these
11 results were heavily reliant on just two studies, and the results should be considered
12 with caution.

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16 Although the number of studies was small, we did conduct some subgroup analyses.
17 We did not find any significant differences between subgroups, including medication
18 type (SSRI versus TCA), whether all randomized patients were included versus
19 inclusion of responders to the acute phase only, and the studies with the highest quality
20 (meeting all 4 criteria) versus those with lower quality (≤ 3 criteria). These outcomes
21 should be interpreted with caution, however, because of the small sample sizes in the
22 subgroups.
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27 Short-term outcomes

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29 We also examined the comparative effects of CBT versus pharmacotherapy at the
30 short term (end of acute treatment), but found no significant difference (OR=1.15, n.s.;
31 Table 2). Excluding one potential outlier [274] did not affect this finding.

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33 We also examined whether we could confirm that drop-out from the intervention was
34 significantly higher in pharmacotherapy than in CBT, as has been established in earlier
35 meta-analyses [3]. Eight of the nine studies reported sufficient data on drop-out to be
36 included in the analyses. We found that the odds of dropping out in the acute phase
37 were significantly lower in CBT than in pharmacotherapy (OR=0.59; 95% CI:
38 0.34~0.99). Inspection of the funnel plot indicated that several studies could have been
39 outliers. Because of the small number of studies, however, we did not conduct any
40 additional sensitivity analyses.
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46 Discussion

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49 Not only wereWe found that patients treated acutely with CBT were less likely to
50 relapse following acute treatment termination than patients treated acutely with
51 medicationpharmacotherapy. we also found a nonsignificant trend indicating that they
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7 also were less likely to relapse than patients continued on medication. The first finding
8 did not come as a surprise, since virtually all of the individual studies that have
9 compared prior CBT to prior ADM have found significant differences favouring the
10 psychosocial intervention following treatment termination and this is basis for the claim
11 that CBT has an enduring effect [4]. We did not find that patients treated with acute
12 phase CBT had a significantly lower risk of relapse than patients on pharmacotherapy.
13 There was a non-significant trend ($p < 0.1$) suggesting that relapse rates may be lower
14 after acute phase CBT, but there were

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WHAT WAS SURPRISING WAS THE NONSIGNIFICANT TREND INDICATING THAT PRIOR cbt ALSO MAY BE SUPERIOR TO CONTINUATION adm SINCE NONE OF THE DIFFERENCES OBSERVED IN THE INDIVIDUAL STUDIES ROSE TO THE LEVEL OF STATISTICAL SIGNIFICANCE. WHAT MAKES THIS FINDING EVEN MORE SURPRISING IS THAT KEEPING RECENTLY REMITTED PATIENTS ON CONTINUATION MEDICATIONS IS THE RECOMMENDED COURSE OF TREATMENT AND THE BEST THAT MODERN PHARMACOTHERAPY CAN DO [6]. SO TOO FEW STUDIES ON THE LONG-TERM EFFECTS OF CBT AND CONTINUATION PHARMACOTHERAPY TO DRAW DEFINITE CONCLUSIONS. MORE RESEARCH IS NEEDED BEFORE THIS QUESTION CAN BE RESOLVED.

It has been found in earlier research that were involved in generating this finding, it will have to be confirmed in subsequent research before it can be allowed to influence clinical practice, but if it does replicate it would suggest that a relatively brief course of CBT might not only be a viable alternative to medication treatment (with continuation) but quite possibly superior to it. Patients are as likely to respond to CBT as to ADM pharmacotherapy and are less likely to drop out of treatment [3]. Moreover, there are indications that the majority of patients who respond to ADM pharmacotherapy do so for nonspecific reasons; that is, they are showing a placebo response and not a "true" drug effect. The same appears to be true for the psychosocial treatments including CBT [31,27]. The fact that CBT results in lower relapse rates than discontinued pharmacotherapy not only suggests that CBT has a specific enduring effect that may operate through somewhat different mechanisms than its acute effects, but also confirms its strong position as a first-line treatment of acute depressive disorders.

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7 However, if patients are likely to respond to treatment (for whatever reason) that they
8 are more likely to complete and if those same patients are less likely to relapse
9 following treatment termination than if they are kept on continuation medication then a
10 case can be made that CBT should be the treatment of choice over ADM for most
11 depressed patients [28].

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14 These results of this meta-analysis should be interpreted with caution because of the
15 a number of limitations of this study. As noted above, the most important limitation
16 was that the small number of studies comparing CBT with continued pharmacotherapy.
17 Also the number of patients in these studies was relatively small, and the results of the
18 main analyses relied heavily on just a few studies. In such a situation, only a few
19 additional studies with different outcomes can turn these results from a trend to non-
20 significance. Another possible limitation is that there was considerable variation in the
21 methods used between the studies in terms of medication pharmacotherapies, measures,
22 and other characteristics. Some studies also only included responders to the acute phase
23 in the follow-up analyses, which may have led to bias in the overall results. If high risk
24 patients were more likely to respond to pharmacotherapy than to CBT then acute
25 treatment could have acted as a “differential sieve” that systematically unbalanced the
26 groups and led to the differential retention of patients differing in a priori risk being
27 misinterpreted as an enduring effect. At the same time, consistency in findings in the
28 face of variability in the methods might contribute to our confidence that what we have
29 is a robust effect that will survive replication. Another possible limitation is that the
30 follow-up of the CBT conditions in most of the studies was naturalistic although most
31 some asked patients not to pursue outside treatment in the absence of a documented
32 relapse and censored those events the few times that they did occur. However, there
33 were important differences between the studies in terms of the treatment received
34 during the follow-up phase. There also was considerable variability in when ADM
35 pharmacotherapy was discontinued across the studies although that should only have led
36 us to underestimate the “true” magnitude of the advantage for prior CBT acute phase
37 CBT in that comparison. Moreover, the quality of the studies included in this meta-
38 analysis was high and even if the next ten studies all produced an advantage for ongoing
39 continued pharmacotherapy, prior CBT acute phase CBT would still be as efficacious as
40 continuation medication pharmacotherapy. Subsequent replication is needed before the a
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possible superiority of ~~prior CBT~~ acute phase CBT over continuation ~~medication~~ pharmacotherapy can be taken seriously, but the possibility is of sufficient importance that such efforts clearly ~~demand~~ should ~~to~~ be made.

Studies on the long-term effects of treatments of depression are complicated, because subsequent treatment is difficult to control (but not impossible to influence). Another complication is that patients both need to complete and respond to acute treatment in order to be at risk for subsequent relapse or recurrence; large numbers of patients need to be randomized initially to differential treatment in order to have enough patients remit to detect anything but the largest subsequent differences during follow-up. Furthermore, acute and continuation/maintenance treatments can be offered in several varieties and the latter can be changed during the course of the follow-up. The number of possible comparisons is therefore large, but all are needed to give an adequate answer to the question which treatment is the best for the longer-term. The most important design for a future study, however, would be a sufficiently powered trial comparing acute phase CBT without subsequent continuation versus acute phase pharmacotherapy with subsequent continuation (the current standard of treatment). Although some studies have used this design, none had sufficient power to find significant differences of the magnitude (modest but clinically relevant) between the two suggested by this meta-analysis. It seems highly relevant to conduct such a trial.

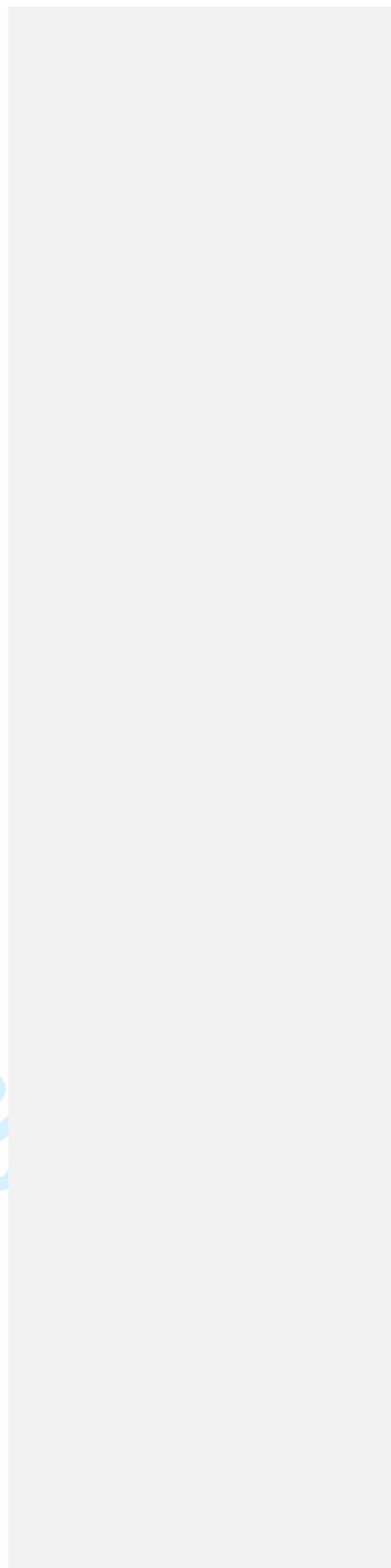
Finally, although CBT may like ADM work largely through nonspecific mechanisms with respect to acute response [29], there are clear indications that cognitive and behavioral mechanisms underlie its enduring effects [30]. Patients who show sudden gains in cognitive therapy (defined as rapid drops in symptoms from one session to the next) are less likely to relapse than patients who show a more stable pattern of response and those instances of sudden gains typically are preceded by the recognition that it is not just what happens to you but how you interpret those events that determine subsequent affect and behavior [31]. Moreover, patients who best learn the cognitive and behavioral skills taught in CBT are least likely to relapse following treatment termination [32]. Whereas acute response to treatment is somewhat promiscuous, the relatively unique enduring effect of CBT appears to be driven by the acquisition of cognitive and behavioral skills as specified by theory.

Comment [SH1]: I am not sure that I would consider the difference between acute phase CBT and acute phase pharmacotherapy small when both are subsequently discontinued (the OR was well in excess of 2). I think the larger problem is that patients both need to complete and respond to acute treatment in order to be at risk for relapse or recurrence and that you have to start with larger samples in order to get enough patients to remit in order to get a large enough sample in order to test your hypothesis.

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7 Contributors.

8 PC and SDH had the idea for this study. PC drafted the initial manuscript, prepared and
9 cleaned the data, and conducted the data analysis. SDH, AVS, CB, MB and GA read all
10 version of the manuscript critically and contributed to the final paper.
11

12 Funding.

13 This research received no specific funding.
14

15 Ethics approval.

16 No ethics approval was needed for this study.
17

18 Data sharing statement.

19 No primary data are used in this paper
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Table 1. Selected characteristics of studies comparing the long-term effects of cognitive behavior therapy for adult depression with those of pharmacotherapy

Recr	Depressive disorder	Pre HAM D	Included ^{a)}	Psychotherapy				Pharmacotherapy			FU	Outcome	C	Quality				
				Acute phase	N _{sess}	Contin. Phase	N	Acute phase	Continuation phase	N				S	A	B	C	
Blackburn, 1986	Clin	MDD (PSE / RDC)	NR	Resp	CBT	23	4 boosters (in first 6 months)	13	Drug of choice	Continuation of 6 months, remaining period naturalistic	9	24	Depressive symptoms needing further treatment	UK	-	-	-	-
David, 2008	Com + clin	MDD (DSM-IV) + BDI ≥ 20 + HAM-17 ≥ 14	22.1	All	CBT	20	Max 3 boosters sessions	56	Fluoxetine	Continued pharmacotherapy	57	6	No current MDD + HAM-D ≤ 7	RO	+	+	+	+
Dobson, 2008	Com + clin	MDD (DSM-IV) + BDI-II ≥ 20 + HAM-D 17 ≥ 14	20.7	Resp	CBT	24	No treatment offered during follow-up	30	Paroxetine	Continued pharmacotherapy	28	12	Sustained response (no 2 wks HAM-D ≥ 14)	US	+	+	+	+
Evans, 1992	Clin	MDD (RDC)	26.9	Resp	CBT	20	No continued treatment	10	Imipramine	Continued pharmacotherapy during year 1, then tapered	11	24	No relapse (BDI ≥ 16 during at least 2 weeks) + no treatment	US	+	+	+	+
Hollon, 2005	Com / clin	MDD (DSM-IV)	23.4	Resp	CBT	20	Up to 3 booster sessions	60	Paroxetine	Continued pharmacotherapy	34	12	No relapse (no HAM-D ≥ 14 for two consecutive weeks)	US	+	+	+	+
Jarret, 2000	Com / clin	Atypical MDD (DSM-IV; SCID)	18.4	Resp	CBT	20	No continued treatment	6	Phenelzine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feighner) + HAM-D-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Naturalistic	18	Imipramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAM-D ≥ 14	19.6	All	CBT	18	Naturalistic	59	Imipramine	MedicationPharmacotherapy was gradually reduced	57	18	Recovered (LIFE-II) and no relapse (MDD / RDC)	US	+	+	+	+
Simons, 1986	Clin	DD (DIS) + HAM-D ≥ 14 or BDI ≥ 20	19.9	Resp	CBT	20	No additional treatment	19	Nortriptyline	Pharmacotherapy was gradually tapered	16	12	Did not re-enter treatment + no BDI ≥ 16 at follow-up	US	+	+	-	+

Abbreviations: AC: allocation concealment; All: all randomized patients; BA: blind assessment; BDI: Beck Depression Inventory; C: country; CBT: cognitive behaviour therapy; CF: completeness of follow-up data; Clin: clinical recruitment; Com: community recruitment; DD: depressive disorder; DIS: diagnostic interview schedule; FU: follow-up; HAM-D: Hamilton

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8 depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depressive disorder; N_{sess}: number of sessions; PSE: present state examination; RDC: research
9 diagnostic criteria; Recr: recruitment; Resp: only responders to the acute phase; RO: Romania; SG: sequence generation; UK: United Kingdom; US: United States.

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a) Only responders to the acute phase treatments or the ones who completed the acute phase treatment were included in the follow-up analyses.

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Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response ^{a)}

	<i>N</i>	<i>OR</i>	<i>95% CI</i>	<i>I</i> ²	<i>95% CI</i>	<i>NNT</i>	<i>95% CI</i>	<i>p</i> ^{e)}
CBT vs continued pharmacotherapy								
All studies	5	1.62	0.97~2.72 o	0	0~79	10	4~71	^{e)}
One possible outlier excluded ^{d)}	4	1.77	1.04~3.01 o	0	0~85	8	4~71	
CBT vs discontinued pharmacotherapy								
All studies	8	2.61	1.58~4.31 ***	0	0~68	5	4~11	
Three possible outliers excluded ^{f)}	5	2.47	1.45~4.22 ***	0	0~79	6	4~15	
Subgroups (long-term effects)								
Pharmacotherapy ^{g)}								
- SSRI	2	3.02	1.29~7.04 *	0	^{h)}	5		0.82
- TCA	5	2.66	1.40~5.04 **	0	0~79	6	4~15	
- All	2	1.97	0.91~4.27 o	0	^{h)}	9	^{e)}	0.14
Included sample								
- Responders	6	3.20	1.65~6.19 **	0	0~75	4	3~8	
Quality								
- All 4 criteria	5	2.31	1.28~4.16 **	0	0~79	6	2~11	0.25
- ≤ 3 criteria	3	3.58	1.39~9.22 **	0	0~90	4	2~10	
Short term effects								
All studies	9	1.15	0.74~1.79	53 [±]	0~78	20	^{e)}	
One possible outlier excluded ^{h)}	8	0.96	0.72~1.30	0	0~68		^{e)}	
Drop-out from intervention ⁱ⁾	8	0.59	0.34~0.99 *	48 [±]	0~77	9	5~143	

o: p<0.1; *: p<0.05; **: p<0.01; ***: p<0.001.

^{a)} according to the random effects model;
^{b)} in this column, the *I*² is reported; we also tested whether the Q-value was significant. This was the case in two comparisons (indicated with an asterisk *).
^{c)} the p-value indicates whether the subgroups differ from each other;
^{d)} Jarrett et al., 2000
^{e)} the 95% CI includes zero and would result in a negative NNT; therefore, we do not report the 95% of the NNT here
the 95% confidence interval included zero; because this would result in a negative NNT we do not report this here.
^{f)} Blackburn et al., 1981; Jarrett, 2000; Evans et al., 1992.
^{g)} one study examined phenelzine (Jarrett, 2000); this was not included in the analyses.
^{h)} 95% CI cannot be calculated when df is lower than 2.
ⁱ⁾ Kovacs et al., 1981
^{j)} One study did not report data on drop-out (Blackburn et al., 1981)

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Figure 1. Flowchart of inclusion of studies

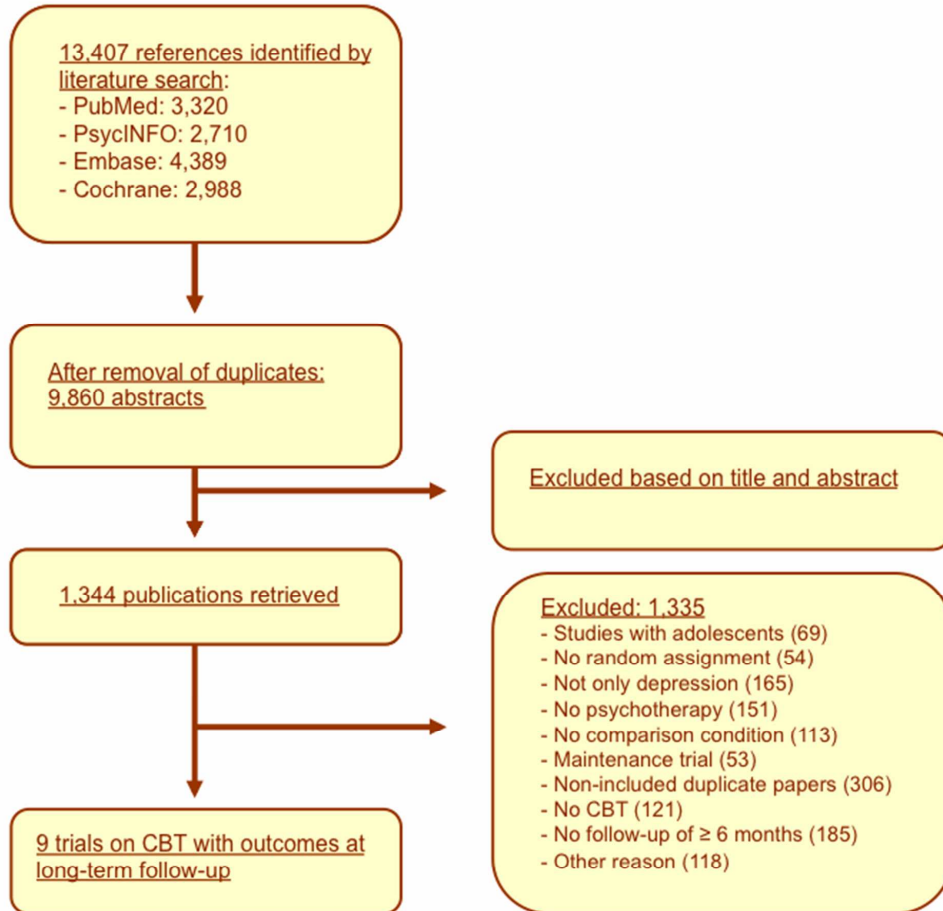
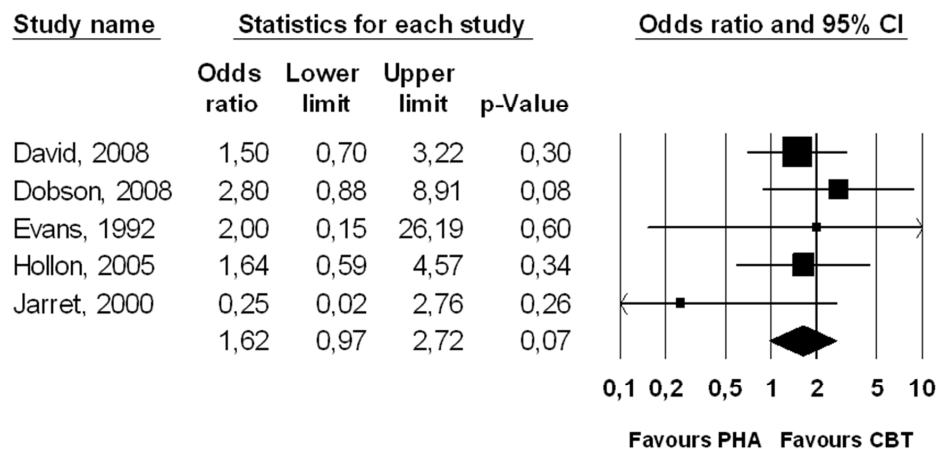
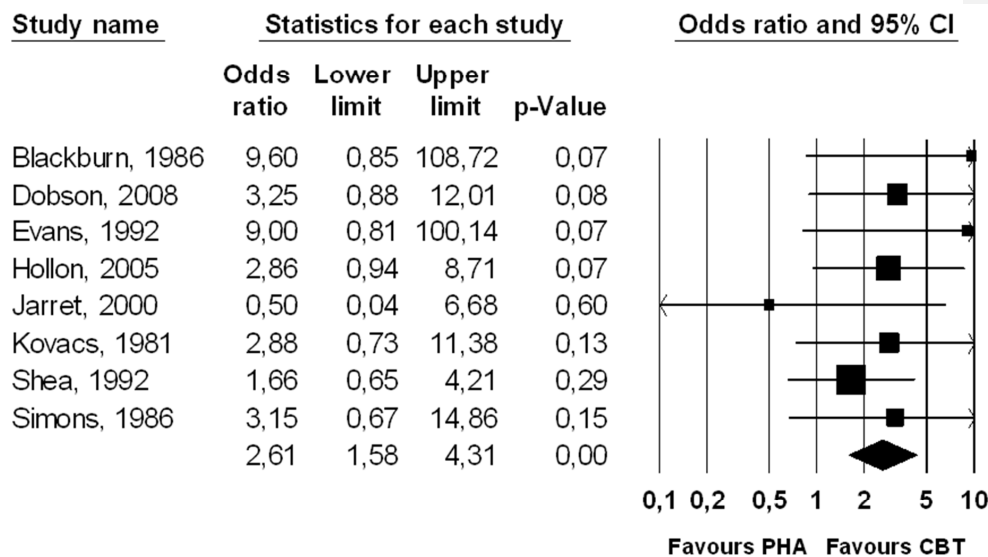


Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response



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Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (discontinued during follow-up): Forest plot of Odds ratio of response



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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not included
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6, 7



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8, 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, 8, 20
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, 9, 17, 18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, 17, 18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 21, 22
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10, 11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11, 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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