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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 Patients who received prior CBT were significantly less likely to relapse than patients who were withdrawn from medication treatment (OR=2.61; 95% CI: 1.58~4.31; $p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than pharmacotherapy at preventing relapse across a one-year follow-up whether medication treatment was continued or withdrawn.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.

Article summary

Article focus

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

Key messages

- There were indications that patients who received CBT without continutation 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 therapu 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 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

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

Methods

Identification and selection of studies

We used a database of 1,344 papers on the psychological treatment of depression described in detail elsewhere [9] that has been used to conduct a series of published meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously updated through comprehensive literature searches (from 1966 to January 2012). In these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). We also checked the references from 42 meta-analyses of psychological treatment for depression to ensure that no published studies were missed. From the 13,407 abstracts (9,860 after removal of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.

We included (a) randomized trials (b) in which the effects of cognitive behaviour therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive disorder, (f) across a follow-up period of 6-18 months. We focused on studies that compared acute CBT (without subsequent continuation) versus pharmacotherapy that was either continued or withdrawn, and conducted separate comparisons on each.

Studies in which CBT was continued during follow-up were excluded (although we allowed a maximum of 5 booster sessions during follow-up, as long as these were not regularly planned). We also excluded studies in which depression was not diagnosed with a standardized diagnostic interview (such as the CIDI, SCID or MINI), as well as studies in inpatients and adolescents. No language restrictions were applied.

Quality assessment and data extraction

The validity of included studies was assessed on four criteria of the 'Risk of bias' assessment tool developed by the Cochrane Collaboration to assess possible sources of bias in randomized trials: (a) adequate generation of allocation sequence; (b) concealment of allocation to conditions; (c) prevention of knowledge of the allocated intervention (blinding); and (d) dealing with incomplete outcome data [11].

We collected characteristics of the target population (method of recruitment, definition of depression, HAM-D score at the start of the treatment to assess the severity of depression, whether all randomized patients were examined at follow-up or only the responders to acute phase treatment, number of treatment sessions, type of drug, whether pharmacotherapy was continued across the full follow-up or only for part of that period, and the country where the study was conducted. If not all information was reported in the paper, we contacted the authors of the papers to request the additional information (all six of whom responded).

Meta-analyses

For each study we used the number of patients who responded to treatment and remained well as outcome measure. 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). As we expected considerable heterogeneity among the studies, we used a random effects model to pool the ORs. 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 [12]. 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 [13]. We also calculated the Q-statistic, but only report whether it was significant or not. We calculated 95% confidence intervals around I^2 [14], using the non-central chi-squared-based approach within the heterogi module for Stata [15].

Subgroup analyses between different subsamples of studies were conducted according to the mixed effect model. In this model, studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model.

Publication bias was tested by inspecting funnel plots on the primary outcome measures and by Duval and Tweedie's trim and fill procedure [16], which yields an estimate of the effect size after adjusting for publication bias (as implemented in Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant. We also calculated Orwin's Fail safe N, which indicates the number of missing studies needed to make the effect size insignificant [17].

Results

Selection and inclusion of studies

After examining a total of 13,407 abstracts (9,860 after removal of duplicates), we retrieved 1,344 full-text papers for further consideration. We excluded 1,335 of the retrieved papers. The flowchart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. Nine of the 1,344 retrieved full-text papers

reported long-term outcomes of prior CBT and were included in this meta-analysis [18-26].

Characteristics of included studies

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

In five earlier studies a Tricyclic antidepressant (TCA) was used in the pharmacotherapy condition, while the three more recent studies all used a Selective serotonin reuptake inhibitor (SSRI); in one study phenelzine (a MAOI) was used. In four studies, patients who responded to pharmacotherapy were randomized to either continuation medication (for the first year of the two-year follow-up) or medication withdrawal with each reported separately. In three other trials all patients were withdrawn from medications, although the length of the taper differed across the trials. One other trial continued medication for the first six months of the follow-up before subsequent withdrawal, and in the remaining trial medication treatment was continued throughout the follow-up. In most instances patients withdrawn from treatment were followed naturalistically although in several studies they were encouraged not to seek additional treatment until a relapse or recurrence was documented. Seven studies were conducted in the United States, two in Europe (one in the UK, one in Romania).

Quality of included studies

Eight of the nine studies used an adequate sequence generation strategy and had an independent party conceal allocations to conditions. Six studies reported keeping the assessors blind to treatment condition and seven studies conducted intent-to-treat analyses. The six studies published in the last two decades met all four quality criteria;

among the three earlier studies, one study met three, another met two, and the final one met none of the criteria (Table 1). The overall quality of the studies was relatively high.

Long-term outcomes: Prior CBT versus continuation medication

Five studies compared the one-year outcomes of prior CBT (with nothing more than occasional booster sessions) versus continuation pharmacotherapy [19-23]. There was a trend ($p<0.1$) indicating that prior CBT outperformed continuation pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72). Heterogeneity was zero, but the 95% confidence interval was broad (0 to 79%), so this finding should be interpreted with caution. The NNT was 10. The ORs and 95% confidence intervals are presented graphically in Figure 2.

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

Long-term outcomes: Prior CBT versus medication discontinuation

Eight studies compared the one-year outcomes of prior CBT (with nothing more than occasional booster sessions) versus medication discontinuation or a naturalistic design. Prior CBT significantly outperformed the medication discontinuation condition to an even greater extent than it had continuation medication (OR=2.61; 95% CI: 1.58~4.31; $p<0.001$). Heterogeneity was zero, but again the 95% CI was broad (0~68%). The corresponding NNT was 5 (95% CI: 4~11) and the ORs and 95% CI for each study are presented graphically in Figure 3.

Because two studies had a very high OR [18,21] and one a very low OR [23], we conducted an additional sensitivity analysis with these studies removed. The resulting OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly significant ($p<0.001$) and the corresponding NNT was 6 (95% CI: 4~15).

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

Short-term outcomes

We also examined the comparative effects of CBT versus pharmacotherapy at the short term (end of acute treatment), but found no significant difference (OR=1.15, n.s.; Table 2). Excluding one potential outlier [24] did not affect this finding.

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

Discussion

Not only were patients treated acutely with CBT less likely to relapse following treatment termination than patients treated acutely with medication, we also found a nonsignificant trend indicating that they also were less likely to relapse than patients continued on medication. The first finding did not come as a surprise, since virtually all of the individual studies that have compared prior CBT to prior ADM have found significant differences favouring the psychosocial intervention following treatment termination and this is basis for the claim that CBT has an enduring effect [4].

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 few studies 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 and less likely to drop out of treatment [3]. Moreover, there are indications that the majority of patients who respond to ADM 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 [27]. However, if patients as likely to respond treatment (for whatever reason) that they are more likely to complete and if those same patients are less likely to relapse following treatment termination than if they are kept on continuation medication then a case can be made that CBT should be the treatment of choice over ADM for most depressed patients [28].

These results should be interpreted with caution because of the limitations of this study. As noted above, the most important limitation was that the small number of studies comparing CBT with continued pharmacotherapy. In such a situation, only a few studies with different outcomes can turn these results from a trend to non-significance. Another possible limitation is that there was considerable variation in the methods used between the studies in terms of medications, measures, and other characteristics. At the same time, consistency in findings in the face of variability in the methods might contribute to our confidence that what we have is a robust effect that will survive replication. Another possible limitation is that the follow-up of the CBT conditions in most of the studies was naturalistic although most asked patients not to pursue outside treatment in the absence of a documented relapse and censored those events the few times that they did occur. There also was considerable variability in when ADM was discontinued across the studies although that should only have led us to underestimate the "true" magnitude of the advantage for prior CBT in that comparison. Moreover, the quality of the studies included in this meta-analysis was high and even if the next ten studies all produced an advantage for ongoing pharmacotherapy, prior CBT

would still be as efficacious as continuation medication. Subsequent replication is needed before the possible superiority of prior CBT over continuation medication can be taken seriously, but the possibility is of sufficient importance that such efforts clearly demand to be made.

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 proceeded 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.

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

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Ethics approval.
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Data sharing statement.
No primary data are used in this paper

Competing Interests
None

Table 1. Selected characteristics of studies comparing the long-term effects of cognitive behavior therapy for adult depression with those of pharmacotherapy

					Psychotherapy				Pharmacotherapy			FU		C	Quality			
	Recr	Depressive disorder	Pre HAM D	Included [a)]	Acute phase	N_{sess}	Contin. Phase	N	Acute phase	Continuation phase	N		Outcome		SG	AC	BA	CF
Black-burn, 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	Fluo-xetine	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	Paro-xetine	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	Imi-pramine	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	Paro-xetine	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	Phenel zine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feigh-ner) + HAMD-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Natural-istic	18	Imi-pramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAMD ≥ 14	19.6	All	CBT	18	Natural-istic	59	Imi-pramine	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	Nortrip-tyline	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

depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depreesive 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.

Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response [a)]

		N	*OR*	*95% CI*	I^2	*95% CI*	*NNT*	*95% CI*	*p* [c)]
CBT vs continued pharmacotherapy									
All studies		5	1.62	0.97~2.72 o	0	0~79	10	[d)]	
CBT vs discontinued pharmacotherapy									
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	
Subgroups (long-term effects)									
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	
Short term effects									
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

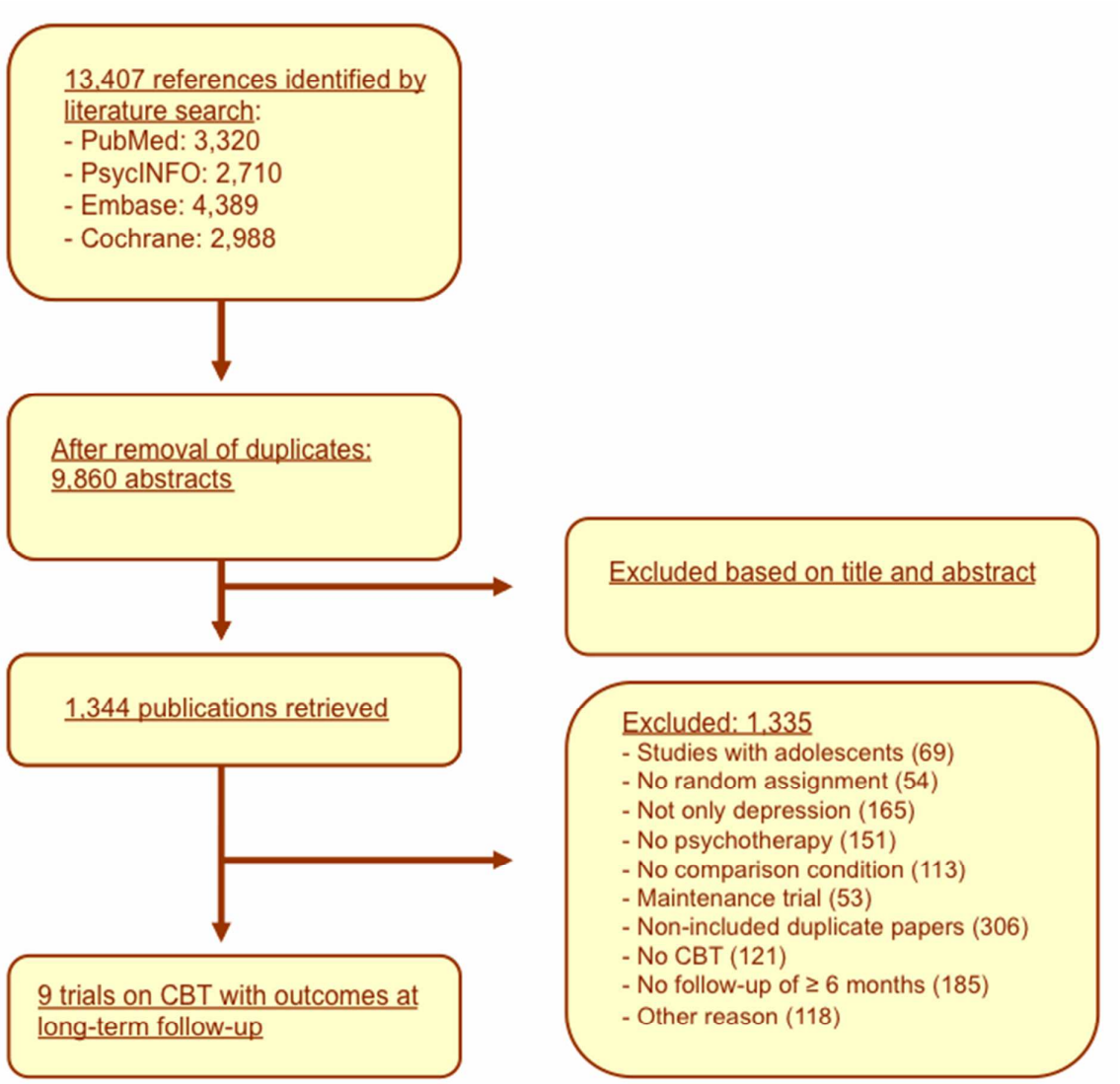


Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response

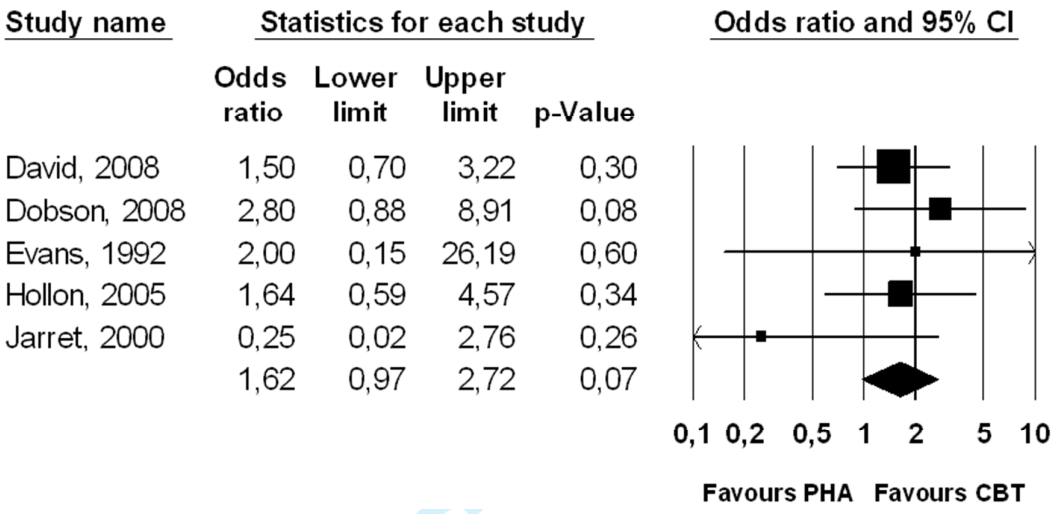
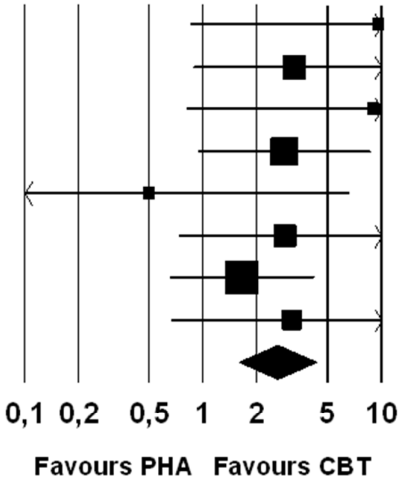


Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*discontinued* during follow-up): Forest plot of Odds ratio of response

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Blackburn, 1986	9,60	0,85	108,72	0,07
Dobson, 2008	3,25	0,88	12,01	0,08
Evans, 1992	9,00	0,81	100,14	0,07
Hollon, 2005	2,86	0,94	8,71	0,07
Jarret, 2000	0,50	0,04	6,68	0,60
Kovacs, 1981	2,88	0,73	11,38	0,13
Shea, 1992	1,66	0,65	4,21	0,29
Simons, 1986	3,15	0,67	14,86	0,15
	2,61	1,58	4,31	0,00



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

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

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Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation 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 subsequent treatment with the effects of pharmacotherapy that either was continued or discontinued across 6 to 18 montsh 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.

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.

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 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

conducted. One earlier review examined whether acute phase CBT had an enduring effect relative to medication withdrawal, but no direct comparison was made against continuation pharmacotherapy [8]. Since continued prescription of pharmacotherapy is now the current standard of treatment and the key decision that clinicians need to make, we decided to conduct such a meta-analysis.

In this meta-analysis we focus on two research questions. The first question is whether acute phase CBT without continuation treatment is as effective as acute phase pharmacotherapy treatment with continuation treatment. The second question is whether acute phase CBT without continuation treatment is as effective as acute phase pharmacotherapy treatment without continuation treatment.

Methods

Identification and selection of studies

We used a database of 1,344 papers on the psychological treatment of depression described in detail elsewhere [9] that has been used to conduct a series of published meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously updated through comprehensive literature searches (from 1966 to January 2012). In these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). We also checked the references from 42 meta-analyses of psychological treatment for depression to ensure that no published studies were missed. From the 13,407 abstracts (9,860 after removal of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.

We included (a) randomized trials (b) in which the effects of cognitive behaviour therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive disorder, (f) across a follow-up period of 6-18 months. We focused on studies that compared acute CBT (without subsequent continuation) versus pharmacotherapy that was either continued or withdrawn, and conducted separate comparisons on each.

Studies in which CBT was continued during follow-up were excluded, although we allowed a maximum of 5 booster sessions during follow-up, as long as these were not regularly planned. We set the limit at 5 booster session because most psychological treatments have 6 or more treatment sessions [11]. We also excluded studies in which depression was not diagnosed with a standardized diagnostic interview (such as the CIDI, SCID or MINI), as well as studies in inpatients and adolescents. No language restrictions were applied.

Quality assessment and data extraction

The validity of included studies was assessed on four criteria of the 'Risk of bias' assessment tool developed by the Cochrane Collaboration to assess possible sources of bias in randomized trials: (a) adequate generation of allocation sequence; (b) concealment of allocation to conditions; (c) prevention of knowledge of the allocated intervention (blinding); and (d) dealing with incomplete outcome data [12]. The two other criteria of the 'Risk of bias' assessment tool were not used in this study, because we found no clear indication in any of the studies that these had influenced the validity of the study (suggestions of selective outcome reporting; and other problems that could put it at a high risk of bias).

We collected characteristics of the target population (method of recruitment, definition of depression, HAM-D score at the start of the treatment to assess the severity of depression, whether all randomized patients were examined at follow-up or only the responders to acute phase treatment, number of treatment sessions, type of drug, whether pharmacotherapy was continued across the full follow-up or only for part of that period, and the country where the study was conducted. If not all information was reported in the paper, we contacted the authors of the papers to request the additional information (all six of whom responded).

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 with the random effects model. 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.

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 [14]. 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, 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 [15]. We calculated 95% confidence intervals around I^2 [16], using the non-central chi-squared-based approach within the heterogi module for Stata [17].

Subgroup analyses between different subsamples of studies were conducted according to the mixed effect model. In this model, studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model.

Publication bias was tested by inspecting funnel plots on the primary outcome measures and by Duval and Tweedie's trim and fill procedure [18], which yields an estimate of the effect size after adjusting for publication bias (as implemented in Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the intercept as well as Begg and Mazumbar's test to quantify the bias captured by the funnel plot and test whether it was significant [19]. We also calculated Orwin's Fail safe

N, which indicates the number of missing studies needed to make the effect size insignificant [20].

Results

Selection and inclusion of studies

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

Characteristics of included studies

In the 9 included studies, a total of 506 patients participated, 271 in CBT and 235 in pharmacotherapy. Selected characteristics of the included studies are presented in Table 1.

Four studies recruited patients only from clinical samples, while the other five also recruited patients from the community. Six studies included only patients who responded to acute phase treatment in the analyses of the subsequent follow-ups, while the other three included all patients randomized to acute phase treatment. The number of CBT treatment sessions ranged from 18 to 24. During the follow-up phase (after acute treatment had ended) three studies offered up to four CBT booster sessions, while the other six did not offer any additional treatment.

In five earlier studies a tricyclic antidepressant (TCA) was used in the pharmacotherapy condition, while the three more recent studies all used a selective serotonin reuptake inhibitor (SSRI); in one study phenelzine (a MAOI) was used. In four studies, patients who responded to pharmacotherapy were randomized to either continuation pharmacotherapy (for the first year of the two-year follow-up) or pharmacotherapy withdrawal with each reported separately. In three other trials all patients were withdrawn from pharmacotherapy, although the length of the taper

differed across the trials. One other trial continued pharmacotherapy for the first six months of the follow-up before subsequent withdrawal, and in the remaining trial pharmacotherapy was continued throughout the follow-up. In most instances patients withdrawn from treatment were followed naturalistically although in several studies they were encouraged not to seek additional treatment until a relapse or recurrence was documented. Seven studies were conducted in the United States, two in Europe (one in the UK, one in Romania).

Quality of included studies

Eight of the nine studies used an adequate sequence generation strategy and had an independent party conceal allocations to conditions. Six studies reported keeping the assessors blind to treatment condition and seven studies conducted intent-to-treat analyses. The six studies published in the last two decades met all four of the quality criteria; among the three earlier studies, one study met three, another met two, and yet another met none of the criteria (Table 1). The overall quality of the studies was relatively high, compared with studies on psychotherapy for adult depression in general [30].

Long-term outcomes: Acute phase CBT versus continuation pharmacotherapy

Five studies compared the one-year outcomes of acute phase CBT (with nothing more than occasional booster sessions) versus continuation pharmacotherapy [22-26]. There was a trend ($p<0.1$) indicating that acute phase CBT outperformed continuation pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72). Heterogeneity was zero, but the 95% confidence interval was broad (0 to 79%), so this finding should be interpreted with caution. The NNT was 10. The ORs and 95% confidence intervals are presented graphically in Figure 2. After exclusion of a possible outlier, the OR was significant (OR=1.77; 95% CI: 1.04~3.01; NNT=8). As can be seen, however, the pooled odds ratios are heavily reliant on just two studies, although most of the studies pointed in the same direction. The results should, therefore, be considered with caution.

We found no indication of publication bias (not surprising given how few studies). Using Duval and Tweedie's trim and fill procedure to adjust for publication bias did not change the OR (number of trimmed studies was zero). Egger's test and Begg and

Mazumbar's test were not significant (p>0.1). We also calculated Orwin's Fail Safe N and found that 23 studies with an OR of 0.9 or eleven studies with an OR of 0.8 (in favour of pharmacotherapy) or 7 studies with an OR of 0.7 would be needed to produce a pooled OR of 1.00. No additional subgroup analyses were conducted because of the small number of studies.

Long-term outcomes: Acute phase CBT versus pharmacotherapy discontinuation

Eight studies compared the one-year outcomes of acute phase CBT (with nothing more than occasional booster sessions) versus pharmacotherapy discontinuation or a naturalistic design. Acute phase CBT significantly outperformed the pharmacotherapy discontinuation condition to an even greater extent than it had continuation pharmacotherapy (OR=2.61; 95% CI: 1.58~4.31; p<0.001). Heterogeneity was zero, but again the 95% CI was broad (0~68%). The corresponding NNT was 5 (95% CI: 4~11). The ORs and 95% CI for each study are presented graphically in Figure 3.

Because two studies had a very high OR [21,24] and one a very low OR [26], we conducted an additional sensitivity analysis with these studies removed. The resulting OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly significant (p<0.001) and the corresponding NNT was 6 (95% CI: 4~15). Again, these results were heavily reliant on just two studies, and the results should be considered with caution.

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

Short-term outcomes

We also examined the comparative effects of CBT versus pharmacotherapy at the short term (end of acute treatment), but found no significant difference (OR=1.15, n.s.; Table 2). Excluding one potential outlier [27] did not affect this finding.

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

Discussion

We found that patients treated acutely with CBT were less likely to relapse following acute treatment termination than patients treated acutely with pharmacotherapy. We did not find that patients treated with acute phase CBT had a significantly lower risk of relapse than patients on pharmacotherapy. There was a non-significant trend ($p<0.1$) suggesting that relapse rates may be lower after acute phase CBT, but there were 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 patients are as likely to respond to CBT as to pharmacotherapy and are less likely to drop out of treatment [3]. Moreover, there are indications that the majority of patients who respond to 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]. 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.

The results of this meta-analysis should be interpreted with caution because of a number of limitations. The most important limitation was that the small number of studies comparing CBT with continued pharmacotherapy. Also the number of patients in these studies was relatively small, and the results of the main analyses relied heavily on just a few studies. In such a situation, only a few additional studies with different

outcomes can turn these results from a trend to non-significance. Another possible limitation is that there was considerable variation in the methods used between the studies in terms of pharmacotherapy, measures, and other characteristics. Some studies also only included responders to the acute phase in the follow-up analyses, which may have led to bias in the overall results. If high risk patients were more likely to respond to pharmacotherapy than to CBT then acute treatment could have acted as a "differential sieve" that systematically unbalanced the groups and led to the differential retention of patients differing in *a priori* risk being misinterpreted as an enduring effect. Another possible limitation is that the follow-up of the CBT conditions in most of the studies was naturalistic although some asked patients not to pursue outside treatment in the absence of a documented relapse and censored those events the few times that they did occur. However, there were important differences between the studies in terms of the treatment received during the follow-up phase. There also was considerable variability in when pharmacotherapy was discontinued across the studies although that should only have led us to underestimate the "true" magnitude of the advantage for acute phase CBT in that comparison. Moreover, the quality of the studies included in this meta-analysis was high and even if the next ten studies all produced an advantage for ongoing continued pharmacotherapy, acute phase CBT would still be as efficacious as continuation pharmacotherapy. Subsequent replication is needed before a possible superiority of acute phase CBT over continuation pharmacotherapy can be taken seriously, but the possibility is of sufficient importance that such efforts clearly should 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.

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

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No primary data are used in this paper

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*	*Inclu-ded* [a)]	*Psychotherapy*				*Pharmacotherapy*			*FU*	*Outcome*	*C*	*Quality*			
					Acute phase	N_{sess}	*Contin. Phase*	*N*	*Acute phase*	*Continuation phase*	*N*				*SG*	*AC*	*BA*	*CF*
Black-burn, 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	Fluo-xetine	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	Paro-xetine	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	Imi-pramine	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	Paro-xetine	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	Phenel zine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feigh-ner) + HAMD-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Natural-istic	18	Imi-pramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAMD ≥ 14	19.6	All	CBT	18	Natural-istic	59	Imi-pramine	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	Nortrip-tyline	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

depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depreesive 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.

Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response [a)]

		N	*OR*	*95% CI*	I^2	*95% CI*	*NNT*	*95% CI*	*p* [c)]
CBT vs continued pharmacotherapy									
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	
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	
Included sample	- All	2	1.97	0.91~4.27 o	0	[h)]	9	[e)]	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	
Short term effects									
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

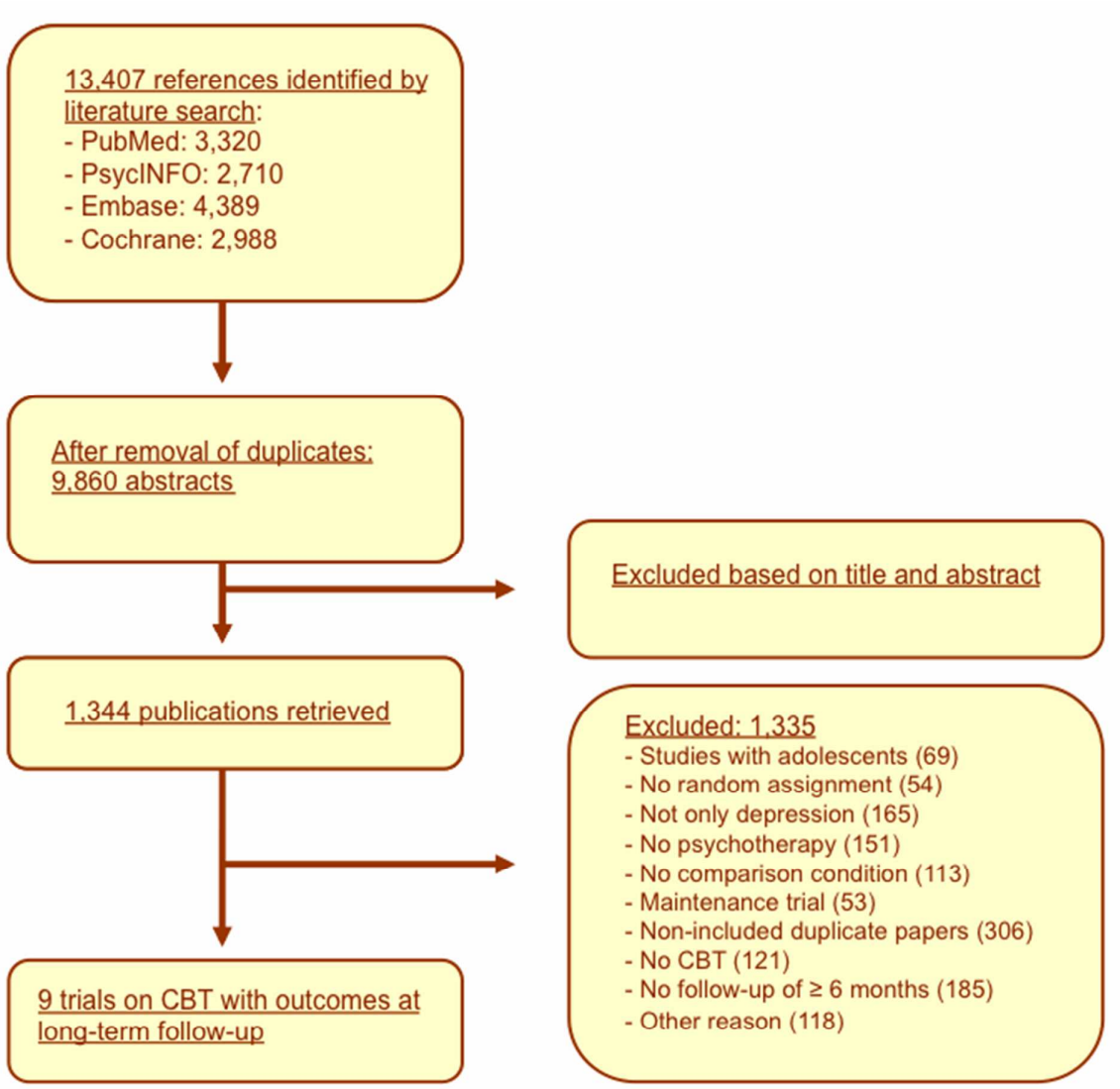


Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response

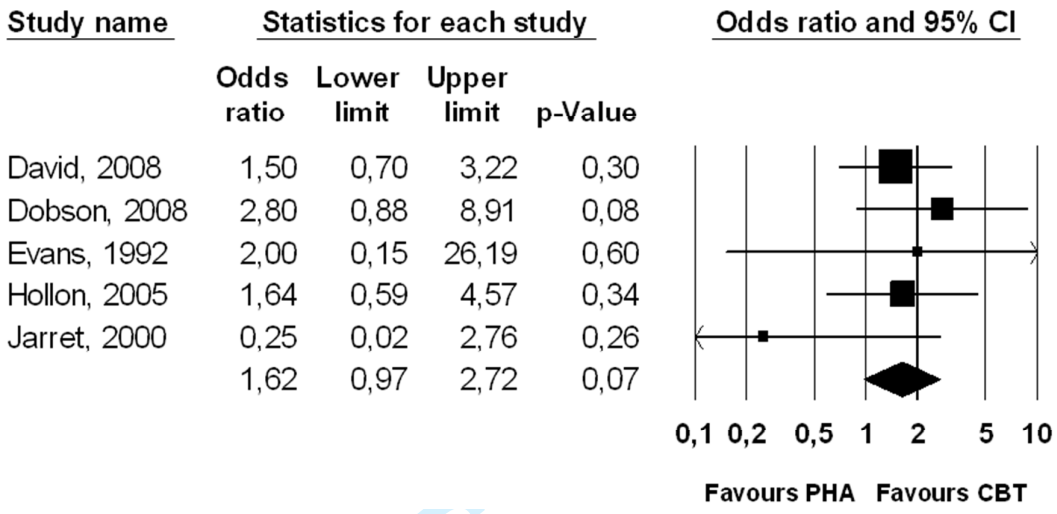
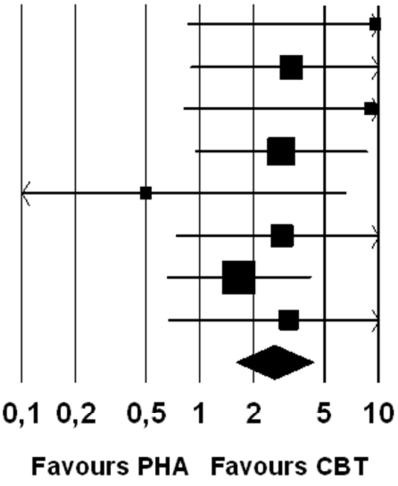


Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*discontinued* during follow-up): Forest plot of Odds ratio of response

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Blackburn, 1986	9,60	0,85	108,72	0,07
Dobson, 2008	3,25	0,88	12,01	0,08
Evans, 1992	9,00	0,81	100,14	0,07
Hollon, 2005	2,86	0,94	8,71	0,07
Jarret, 2000	0,50	0,04	6,68	0,60
Kovacs, 1981	2,88	0,73	11,38	0,13
Shea, 1992	1,66	0,65	4,21	0,29
Simons, 1986	3,15	0,67	14,86	0,15
	2,61	1,58	4,31	0,00



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 montsh 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.~~

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.~~ We found that CBT ~~not only seems to have~~ has an enduring effect following ~~treatment~~ termination of the acute treatment. We found no significant difference in relapse after acute phase CBT versus continuation of pharmacotherapy after remission. ~~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.

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 therapu were significantly lower than in pharmacotherapy~~
- ~~There were indications that patients who received CBT without continutation 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 therapu 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~~pharmacotherapy~~s~~ 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~~pharmacotherapy~~s~~ 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

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~~pharmacotherapy, no meta-analysis of these studies has been conducted. One earlier review examined whether ~~prior CBT~~acute phase CBT had an enduring effect relative to medication withdrawal, but no direct comparison was made ~~to~~ against continuation ~~medication~~pharmacotherapy [8]. Since continued prescription of pharmacotherapy ~~that~~ is now the current standard of treatment and the key decision that clinicians need to make, we decided to conduct such a meta-analysis.

In this meta-analysis we focus on two research questions. The first question is whether acute phase CBT without continuation treatment is as effective as acute phase pharmacotherapy treatment with continuation treatment. The second question is whether acute phase CBT without continuation treatment is as effective as acute phase pharmacotherapy treatment without continuation treatment.

Methods

Identification and selection of studies

We used a database of 1,344 papers on the psychological treatment of depression described in detail elsewhere [9] that has been used to conduct a series of published meta-analyses (www.evidencebasedpsychotherapies.org). This database is continuously updated through comprehensive literature searches (from 1966 to January 2012). In these searches we examined 13,407 abstracts in Pubmed (3,320 abstracts), PsycInfo (2,710), Embase (4,389) and the Cochrane Central Register of Controlled Trials (2,988). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). We also checked the references from 42 meta-analyses of psychological treatment for depression to ensure that no published studies were missed. From the 13,407 abstracts (9,860 after removal of duplicates) 1,344 full-text papers were retrieved for possible database inclusion.

We included (a) randomized trials (b) in which the effects of cognitive behaviour therapy (c) according the manual by Beck and colleagues [10] (c) were compared to the effects of pharmacological treatment (d) in adults (e) with a diagnosed depressive disorder, (f) across a follow-up period of 6-18 months. We focused on studies that compared acute CBT (without subsequent continuation) versus pharmacotherapy that was either continued or withdrawn, and conducted separate comparisons on each.

Studies in which CBT was continued during follow-up were excluded, (although we allowed a maximum of 5 booster sessions during follow-up, as long as these were not regularly planned). We set the limit at 5 booster session because most psychological treatments have 6 or more treatment sessions [11]. We also excluded studies in which depression was not diagnosed with a standardized diagnostic interview (such as the CIDI, SCID or MINI), as well as studies in inpatients and adolescents. No language restrictions were applied.

Quality assessment and data extraction

The validity of included studies was assessed on four criteria of the 'Risk of bias' assessment tool developed by the Cochrane Collaboration to assess possible sources of bias in randomized trials: (a) adequate generation of allocation sequence; (b) concealment of allocation to conditions; (c) prevention of knowledge of the allocated intervention (blinding); and (d) dealing with incomplete outcome data [12]. The two other criteria of the 'Risk of bias' assessment tool were not used in this study, because we found no clear indication in any of the studies that these had influenced the validity of the study (suggestions of selective outcome reporting; and other problems that could put it at a high risk of bias).

We collected characteristics of the target population (method of recruitment, definition of depression, HAM-D score at the start of the treatment to assess the severity of depression, whether all randomized patients were examined at follow-up or only the responders to acute phase treatment, number of treatment sessions, type of drug, whether pharmacotherapy was continued across the full follow-up or only for part of that period, and the country where the study was conducted. If not all information was reported in the paper, we contacted the authors of the papers to request the additional information (all six of whom responded).

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 [14~~2~~]. 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 [15~~3~~]. ~~We also calculated the Q-statistic, but only report whether it was significant or not.~~ We calculated 95% confidence

intervals around I^2 [164], using the non-central chi-squared-based approach within the heterogi module for Stata [175].

Subgroup analyses between different subsamples of studies were conducted according to the mixed effect model. In this model, studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model.

Publication bias was tested by inspecting funnel plots on the primary outcome measures and by Duval and Tweedie's trim and fill procedure [186], which yields an estimate of the effect size after adjusting for publication bias (as implemented in Comprehensive Meta-analysis, version 2.2.021). We conducted Egger's test of the intercept as well as Begg and Mazumbar's test to quantify the bias captured by the funnel plot and test whether it was significant [19]. We also calculated Orwin's Fail safe N, which indicates the number of missing studies needed to make the effect size insignificant [2017].

Results

Selection and inclusion of studies

After examining a total of 13,407 abstracts (9,860 after removal of duplicates), we retrieved 1,344 full-text papers for further consideration. We excluded 1,335 of the retrieved papers. The flowchart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. Nine of the 1,344 retrieved full-text papers reported long-term outcomes of prior CBTacute phase CBT and were included in this meta-analysis [2118-2886].

Characteristics of included studies

In the 9 included studies, a total of 506 patients participated, 271 in CBT and 235 in the ADMpharmacotherapy. Selected characteristics of the included studies are presented in Table 1.

Four studies recruited patients only from clinical samples, while the other five also recruited patients from the community. Six studies included only patients who

responded to acute phase treatment in the analyses of the subsequent follow-ups, while the other three included all patients randomized to acute phase treatment. The number of CBT treatment sessions ranged from 18 to 24. During the follow-up phase (after acute treatment had ended) three studies offered up to four CBT booster sessions, while the other six did not offer any additional treatment.

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

Quality of included studies

Eight of the nine studies used an adequate sequence generation strategy and had an independent party conceal allocations to conditions. Six studies reported keeping the assessors blind to treatment condition and seven studies conducted intent-to-treat analyses. The six studies published in the last two decades met all four of the quality criteria; among the three earlier studies, ~~-~~one study met three, another met two, and ~~the~~ yet ~~final~~ another ~~one~~ met none of the criteria (Table 1). The overall quality of the studies was relatively high, compared with studies on psychotherapy for adult depression in general [30].

Long-term outcomes: ~~Prior CBT~~Acute phase CBT versus continuation ~~medication~~pharmacotherapy

Five studies compared the one-year outcomes of ~~prior CBT~~acute phase CBT (with nothing more than occasional booster sessions) versus continuation pharmacotherapy [22~~19~~-26~~3~~]. There was a trend ($p<0.1$) indicating that ~~prior CBT~~acute phase CBT outperformed continuation pharmacotherapy (OR=1.62; 95% CI: 0.97~2.72). Heterogeneity was zero, but the 95% confidence interval was broad (0 to 79%), so this finding should be interpreted with caution. The NNT was 10. The ORs and 95% confidence intervals are presented graphically in Figure 2. After exclusion of a possible outlier, the OR was significant (OR=1.77; 95% CI: 1.04~3.01; NNT=8). As can be seen, however, the pooled odds ratios are heavily reliant on just two studies, although most of the studies pointed in the same direction. The results should, therefore, be considered with caution.

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

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

Eight studies compared the one-year outcomes of ~~prior CBT~~acute phase CBT (with nothing more than occasional booster sessions) versus ~~medication~~pharmacotherapy discontinuation or a naturalistic design. ~~Prior CBT~~Acute phase CBT significantly outperformed the ~~medication~~pharmacotherapy discontinuation condition to an even greater extent than it had continuation ~~medication~~pharmacotherapy (OR=2.61; 95% CI: 1.58~4.31; $p<0.001$). Heterogeneity was zero, but again the 95% CI was broad (0~68%). The corresponding NNT was 5 (95% CI: 4~11). ~~and t~~The ORs and 95% CI for each study are presented graphically in Figure 3.

Because two studies had a very high OR [21~~18~~,24~~1~~] and one a very low OR [26~~3~~], we conducted an additional sensitivity analysis with these studies removed. The resulting OR was somewhat smaller (OR=2.47; 95% CI: 1.45~4.22), but still highly significant (p<0.001) and the corresponding NNT was 6 (95% CI: 4~15). Again, these results were heavily reliant on just two studies, and the results should be considered with caution.

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

Short-term outcomes

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

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

Discussion

~~Not only were~~We found that patients treated acutely with CBT were less likely to relapse following acute treatment termination than patients treated acutely with ~~medication~~pharmacotherapy~~,~~ ~~we also found a nonsignificant trend indicating that they~~

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

~~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. P~~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.

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

The~~se~~ results of this meta-analysis should be interpreted with caution because of ~~the~~ a number of limitations ~~of this study~~. ~~As noted above, t~~The most important limitation was that the small number of studies comparing CBT with continued pharmacotherapy. Also the number of patients in these studies was relatively small, and the results of the main analyses relied heavily on just a few studies. In such a situation, only a few additional studies with different outcomes can turn these results from a trend to non-significance. Another possible limitation is that there was considerable variation in the methods used between the studies in terms of ~~medication~~pharmacotherapy~~s~~, measures, and other characteristics. Some studies also only included responders to the acute phase in the follow-up analyses, which may have led to bias in the overall results. If high risk patients were more likely to respond to pharmacotherapy than to CBT then acute treatment could have acted as a "differential sieve" that systematically unbalanced the groups and led to the differential retention of patients differing in *a priori* risk being misinterpreted as an enduring effect. ~~At the same time, consistency in findings in the face of variability in the methods might contribute to our confidence that what we have is a robust effect that will survive replication.~~ Another possible limitation is that the follow-up of the CBT conditions in most of the studies was naturalistic although ~~most~~ some asked patients not to pursue outside treatment in the absence of a documented relapse and censored those events the few times that they did occur. However, there were important differences between the studies in terms of the treatment received during the follow-up phase. There also was considerable variability in when ~~ADM~~ pharmacotherapy was discontinued across the studies although that should only have led us to underestimate the "true" magnitude of the advantage for ~~prior CBT~~acute phase CBT in that comparison. Moreover, the quality of the studies included in this meta-analysis was high and even if the next ten studies all produced an advantage for ongoing continued pharmacotherapy, ~~prior CBT~~acute phase CBT would still be as efficacious as continuation ~~medication~~pharmacotherapy. Subsequent replication is needed before ~~the~~ a

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

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Ethics approval.
No ethics approval was needed for this study.

Data sharing statement.
No primary data are used in this paper

Table 1. Selected characteristics of studies comparing the long-term effects of cognitive behavior therapy for adult depression with those of pharmacotherapy

					Psychotherapy				*Pharmacotherapy*			*FU*		*C*	*Quality*			
	Recr	*Depressive disorder*	*Pre HAM D*	*Included* [a)]	*Acute phase*	N_{sess}	*Contin. Phase*	*N*	*Acute phase*	*Continuation phase*	*N*		*Outcome*		*SG*	*AC*	*BA*	*CF*
Black-burn, 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	Fluo-xetine	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	Paro-xetine	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	Imi-pramine	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	Paro-xetine	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	Phenel zine	Continued pharmacotherapy	6	24	Relapse/recurrence according to RDC	US	+	+	+	+
Kovacs, 1981	Com / clin	DD (Feigh-ner) + HAMD-17 ≥ 14 + BDI ≥ 20	21.5	Resp	CBT	20	Natural-istic	18	Imi-pramine	Naturalistic	17	12	All monthly BDI scores during follow-up ≤ 16	US	+	+	-	-
Shea, 1992	Clin	MDD (RDC) + HAMD ≥ 14	19.6	All	CBT	18	Natural-istic	59	Imi-pramine	~~Medication~~Pharma cotherapy 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	Nortrip-tyline	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

depression rating scale; LIFE-II: Longitudinal interval follow-up evaluation; MDD: major depreesive 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.

Table 2. Long-term effects of CBT compared with pharmacotherapy: Odds ratios of response [a)]

		N	*OR*	*95% CI*	I^2	*95% CI*	*NNT*	*95% CI*	*p* [c)]
CBT vs continued pharmacotherapy									
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	
CBT vs discontinued pharmacotherapy									
All studies		8	2.61	1.58~4.31 ***	0	0~68	5	4~11	
Three possible outliers excluded [fe)]		5	2.47	1.45~4.22 ***	0	0~79	6	4~15	
Subgroups (long-term effects)									
Pharmacotherapy [gf)]	- SSRI	2	3.02	1.29~7.04 *	0	[hg)]	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	[hg)]	9	[e)]	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	
Short term effects									
All studies		9	1.15	0.74~1.79	53 *	0~78	20	[e)]	
One possible outlier excluded [ih)]		8	0.96	0.72~1.30	0	0~68		[e)]	
Drop-out from intervention [ji)]		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)] 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.
[fe)] Blackburn et al., 1981; Jarrett, 2000; Evans et al., 1992.
[gf)] one study examined phenelzine (Jarrett, 2000); this was not included in the analyses.
[hg)] 95% CI cannot be calculated when df is lower than 2.
[ih)] Kovacs et al., 1981
[ji)] One study did not report data on drop-out (Blackburn et al., 1981)

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Figure 1. Flowchart of inclusion of studies

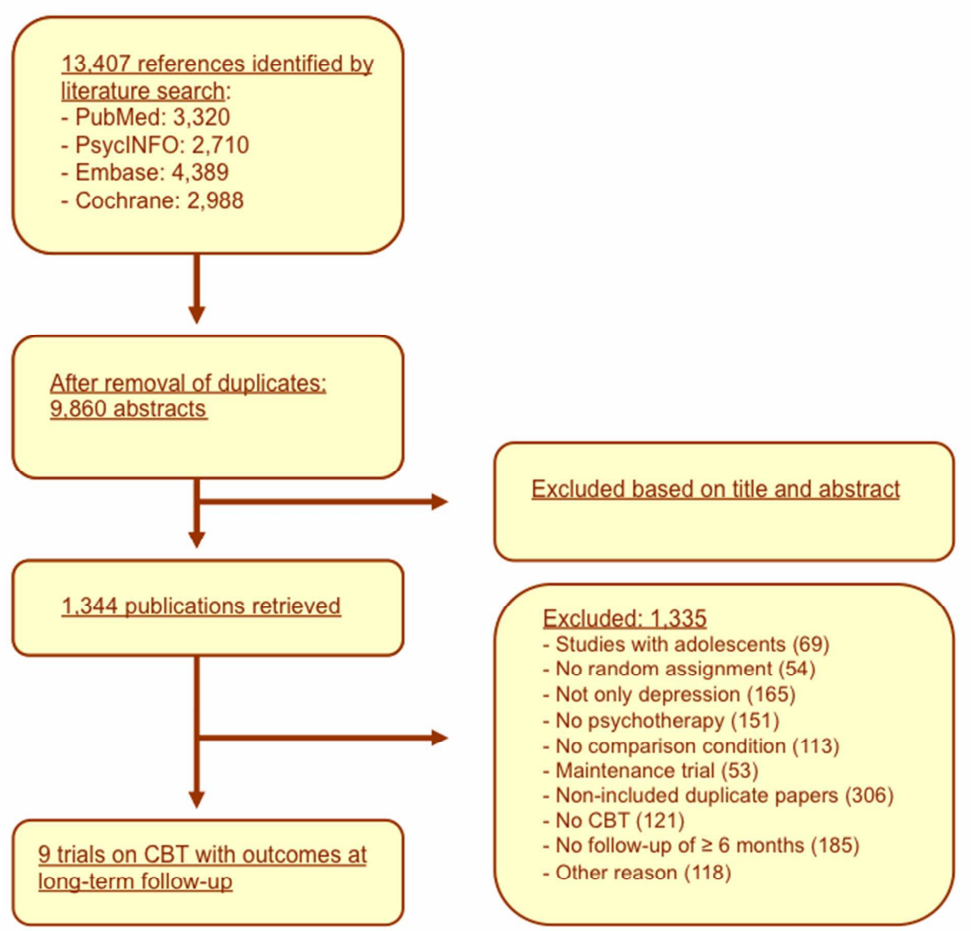


Figure 2. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*continued* during follow-up): Forest plot of Odds ratio of response

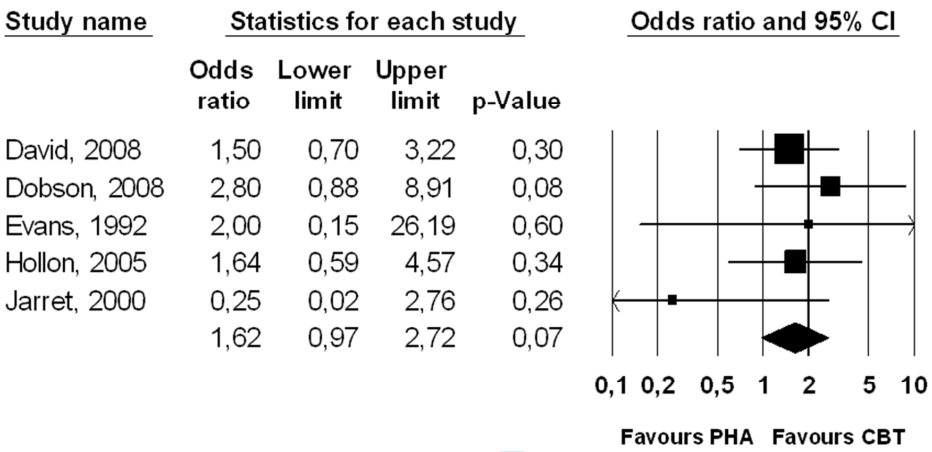
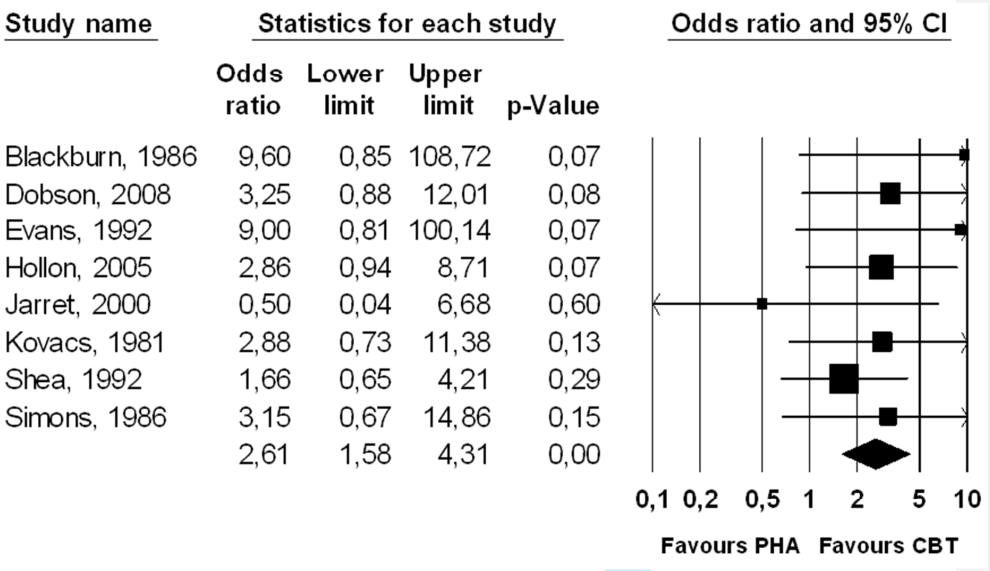


Figure 3. Long-term effects of CBT (without continuation during follow-up) compared with pharmacotherapy (*discontinued* during follow-up): Forest plot of Odds ratio of response



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

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

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