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Review

Effectiveness of psychological interventions in preventing recurrence of depressive disorder: Meta-analysis and meta-regression

Karolien E.M. Biesheuvel-Leliefeld [a,*], Gemma D. Kok [b], Claudi L.H. Bockting [c], Pim Cuijpers [c,d], Steven D. Hollon [e], Harm W.J. van Marwijk [a], Filip Smit [c,f,g]

[a] Department of General Practice and Elderly Care Medicine, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands
[b] Department of Clinical and Experimental Psychology, Groningen University, Groningen, The Netherlands
[c] Department of Clinical Psychology, EMGO Institute for Health and Care Research, VU University and VU University Medical Centre, Amsterdam, The Netherlands
[d] Leuphana University, Lüneburg, Germany
[e] Department of Psychology, Vanderbilt University, Nashville, TN, USA
[f] Department of Public Mental Health, Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands
[g] Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands

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ABSTRACT

Background: Major depression is probably best seen as a chronically recurrent disorder, with patients experiencing another depressive episode after remission. Therefore, attention to reduce the risk of relapse or recurrence after remission is warranted. The aim of this review is to meta-analytically examine the effectiveness of psychological interventions to reduce relapse or recurrence rates of depressive disorder.

Methods: We systematically reviewed the pertinent trial literature until May 2014. The random-effects model was used to compute the pooled relative risk of relapse or recurrence (RR). A distinction was made between two comparator conditions: (1) treatment-as-usual and (2) the use of antidepressants. Other sources of heterogeneity in the data were explored using meta-regression.

Results: Twenty-five randomised trials met inclusion criteria. Preventive psychological interventions were significantly better than treatment-as-usual in reducing the risk of relapse or recurrence (RR=0.64, 95% CI=0.53–0.76, $z=4.89$, $p<0.001$, NNT=5) and also more successful than antidepressants (RR=0.83, 95% CI=0.70–0.97, $z=2.40$, $p=0.017$, NNT=13). Meta-regression showed homogeneity in effect size across a range of study, population and intervention characteristics, but the preventive effect of psychological intervention was usually better when the prevention was preceded by treatment in the acute phase ($b=-1.94$, SEb=0.68, $z=-2.84$, $p=0.005$).

Limitations: Differences between the primary studies in methodological design, composition of the patient groups and type of intervention may have caused heterogeneity in the data, but could not be evaluated in a meta-regression owing to poor reporting.

Conclusions: We conclude that there is supporting evidence that preventive psychological interventions reduce the risk of relapse or recurrence in major depression.

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* Corresponding author.
Tel.: +31 204448395, 31 624762533; fax: +31 204448361.
E-mail address: k.leliefeld@vumc.nl (K.E.M. Biesheuvel-Leliefeld).

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1. Introduction

Major depressive disorder (MDD) affects 16% of the population on a lifetime basis (Kessler et al., 2005). Of all people with MDD, at least 45% experience recurrences, typically with seven to eight depressive episodes over the course of their life (Kruijshaar et al., 2005) and spending as much as 21% of their lifetime in a depressed condition (Vos et al., 2004). MDD is therefore perhaps best seen as a largely chronically recurrent disorder with much of its disease burden stemming from its recurrent nature (Judd, 1997).

Treatments for depression are often delivered in an episodic fashion during the acute disease stage. As a result, the burden of depression is only partly alleviated. Therefore, longer-term strategies to reduce the risk of relapse or recurrence are needed. The National Institute for Health and Clinical Excellence (NICE Clinical Guidelines, 2009) recommends to continue antidepressant medication (ADM) in medication-responders for at least 6 months after remission or even to continue for at least 2 years if there is a significant risk of relapse. The strength of these recommendations is under debate as the optimal duration of the continuation- or maintenance phase has not been studied well enough (Geddes et al., 2003; Kaymaz et al., 2008), there is divergent information about discontinuation of continuation- or maintenance ADM and the relation to relapse or recurrence (Bockting et al., 2008) and reported levels of non-adherence have been consistently high. Continuation of ADM may therefore not be the most optimal strategy from a clinical and a public health perspective.

Fortunately, increasing attention is being paid to preventive psychological interventions after remission. NICE recommends providing individual cognitive behavioural therapy (CBT) for people who have relapsed despite antidepressants and for people with a significant history of depression and residual symptoms despite treatment. For people who are currently well but have had 3 or more episodes of depression, NICE recommends to provide mindfulness-based cognitive therapy (MCT). These recommendations are based on data from controlled studies on the efficacy of psychological interventions after remission from a depressive episode. In 2007, a meta-analysis on cognitive (behavioural) interventions versus non-active (assessment only) and active controls (ADM and treatment-as-usual (TAU)) in recurrent depression was conducted by Vittengl et al. Their conclusion was that among acute-phase responders, cognitive therapy (CT) reduced relapse–recurrence significantly compared with non-active controls (assessment only) at the end of continuation treatment (21% reduction) and at follow-up (29% reduction). CT also reduced relapse–recurrence compared with active controls at the end of continuation treatment (non-significant reduction, 12%) and at follow-up (significant reduction, 14%). A meta-analysis by Guidi et al. (2011) showed that the sequential administration of psychotherapy (alone or in combination with antidepressant medication) may have a protective effect against relapse or recurrence in MDD versus active control (ADM and TAU). A meta-analysis by Piet and Hougaard (2011) indicates that mindfulness-based cognitive therapy after remission is an effective intervention for the prevention of relapse when compared to TAU and placebo.

These meta-analyses show that several psychological interventions reduce the risk on relapse or recurrence. However, there are four important drawbacks: 1) Previous meta-analyses do not include all types of psychological interventions. Vittengl et al. (2007) merely included CBT, Piet and Hougaard (2011) merely included MCT and Guidi et al (2011) included CBT and MCT. In our meta-analysis we expand on these meta-analyses by including more types of psychological interventions (e.g. problem-solving therapy and psychodynamic/psychoanalytic therapy), and also by including various modes of delivery (e.g. booster sessions and therapy over the Internet). 2) Results of previous meta-analyses are difficult to interpret as their active controls-group is defined rather broadly. Vittengl et al. (2007) defined active control as 'ADM or another active therapy (e.g. MCT)', Guidi et al. (2011) defined active control as 'ADM or TAU' and Piet and Hougaard (2011) did not include ADM as comparator at all. However, according to NICE guidelines, continuation of ADM is the first step in the treatment of recurrent depression. In order to draw conclusions on the use of ADM versus a preventive psychological intervention in remitted patients, our argument for the present meta-analysis is to more clearly define active control as 'ADM (possibly plus TAU)' and

non-active controls 'TAU only'. 3) Two meta-analyses, Vittengl et al. (2007) and Guidi et al. (2011), report on the effect of psychological interventions on 'acute-phase responders'. In our meta-analyses we include patients 'who are in remission'. These patients may have had a directly preceding acute-phase intervention but this is not necessary. This corresponds best with real life practice where patients recover, stay depression-free for a while—with or without continuation or maintenance treatment—and then relapse or recur. 4) Previous meta-analyses are not up-to-date (2007 and 2011) and need an update including new and current trials in this dynamic field.

In our meta-analysis we summarize the current randomised trial literature of psychological interventions for the prevention of relapse or recurrence following (partial) remission of depressive disorder, and evaluate to what extent these interventions are effective compared to TAU and ADM. Our hypotheses are as follows: (H1) Psychological interventions are superior to TAU; (H2) Psychological interventions are not inferior to ADM; and (H3) The different types of psychological interventions are equally effective. We also assess the effect of several moderators (mean age, number of previous episodes, percentage females, previous acute-phase treatment (if any), duration of preventive intervention, length of follow-up and setting (community, primary care, secondary care)).

This meta-analysis assesses the effects of preventive psychological interventions, ADM and TAU on reducing the risk of relapse of recurrence. Assessing which intervention works best for remitted patients who are at risk for relapse or recurrence may be an important step in improving existing guidelines and ultimately the outcomes of treatment.

2. Methods

2.1. Primary studies

We included studies in the meta-analysis when the following inclusion criteria were met: a) a randomised controlled trial, b) examining adult patients in the age bracket of 18–64 years, c) with recurrent MDD, d) who were in remission (according to their own definition in the individual trial-paper) at randomisation, e) receiving a preventive psychological intervention, f) with the aim of reducing the risk of relapse or recurrence and g) with a comparison to a control condition. Control conditions could be classed as TAU (routine clinical management, assessments only, no treatment and waiting-list control with unrestricted access to TAU) or ADM. Each study had to report relapse or recurrence rates using established screeners with a predefined cut-off point for MDD, such as the Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1960) and Beck Depression Inventory (BDI) (Beck et al., 1961), or a diagnostic interview such as the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-1) (First et al., 1996).

Psychological interventions could be classed as 'cognitive (behavioural) therapy' (CT), 'mindfulness-based cognitive therapy' (MCT), 'interpersonal therapy' (IPT), problem-solving therapy (PST) and psychodynamic-(psychoanalytic) therapy (PDT). Besides the more usual mode of delivery of interventions (e.g. group- or face-to-face interventions) we included all modes of delivery like booster-sessions during follow-up and therapy over the Internet. Table 1 summarises these interventions including a brief overview.

2.2. Central clinical end-term

The central clinical outcome was the relapse or recurrence rate of MDD as defined by study investigators (i.e. crossing the cut-off on a depression rating scale or a change in diagnostic depression status based on clinical assessment). Outcomes were evaluated at the longest available follow-up.

2.3. Search methods for identification of studies

A literature search was conducted in May 2014. Free text and MeSH terms were used for searches in Medline, PsycInfo, CINAHL, Embase and the Cochrane database. The studies had to be published in English. Keyword searches were conducted by combining the following main terms: cognitive, cognitive behaviour therapy, mindfulness, mindfulness-based cognitive therapy, interpersonal therapy, problem-solving, problem-solving therapy, psychodynamic, psychodynamic therapy, psychoanalytic, psychoanalytic therapy, continuation, maintenance, relapse, recurrence, prevention, therapy, treatment, recurrent, recurrence, depressive disorder and depression. Additional delimiters were adults and randomised controlled trials (Appendix S1). To supplement the searches of published research, the Internet was also utilised to find additional studies.

2.4. Data collection and analysis

2.4.1. Selection of trials

Studies were searched, selected and reviewed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA (Moher et al., 2010) (Appendix S2). The first selection was the responsibility of the first author (KBL) and was made using the title, abstract and keywords whereby the full-text article was retrieved when in doubt. All authors of significant papers in the research field were contacted and asked to complete the list of selected publications. Two independent researchers (KBL and GK) carried out the final selection. Any disagreement was resolved by consensus.

2.4.2. Assessment of risk of bias in included studies

Flaws in the design, conduct, analysis, and reporting of randomised trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane risk-of-bias method (Higgins and Green, 2008) was applied for assessing risk of bias to make the process

Table 1
Psychological interventions included in the meta-analysis.

Name therapy	Approach
Cognitive (behavioural) therapy (CT)	Negative automatic thoughts, maladaptive information processing, and avoidance behaviour play a key role in the development and recurrence of depression (Beck et al., 1979).
Mindfulness based cognitive therapy (MCT)	Protocol-led, group-based skills training program designed to teach recovered depressed patients how to disengage from automatic, cognitive processing patterns linked to relapse (Segal et al., 2002).
Interpersonal therapy (IPT)	Originates from interpersonal theory by Klerman et al. (1987). It links stressful life events and insufficient social support to the development and recurrence of depressive symptoms (Weissman et al., 2007).
Problem solving therapy (PST)	Brief treatment focused on strengthening practical problem-solving skills. The goal is to stimulate an active attitude towards everyday problems and, hereby, to achieve a reduction in mental health problems (Hawton and Kirk, 1989).
Psychodynamic therapy (PDT)	Focuses on the affective, behavioural and cognitive aspects of relationships from a psychodynamic point of view (De Jonghe et al., 1994; De Jonghe, 2013). It comprises intervention methods such as clarification, interpretation and confrontation each addressing intra-psychic conflict and resistance (Watzke et al., 2008).

clearer and more accurate (Appendix S3). This Cochrane list consists of six items. Two items assess the strength of the randomisation process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (masking) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raises the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. This item requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances such as sponsorship bias.

2.4.3. Data extraction

We collated an evidence table in which extracted data of each study was recorded. Two reviewers (KBL and GK) extracted the data independently. The initial inter-rater agreement reached in extracting data ranged from 85% to 100%. All disagreements were discussed between the two reviewers and consensus was obtained between these two raters.

Extracted data included mean age, number of previous episodes, percentage females, type of previous intervention and comparator (if any), type of current intervention and comparator, type and duration of current intervention, length of follow-up, setting (community, primary care, secondary care), number of patients per study-arm, definition of relapse or recurrence and relapse or recurrence rates.

2.4.4. Data analysis

The primary outcome in this meta-analysis was the reduction in the relapse or recurrence rate in the intervention group as compared with the comparator condition. This gave rise to an effect size called relative risk (RR). A RR below 1 indicates that the intervention is more effective than the comparator condition, because fewer relapses or recurrences occur.

The meta-analysis was based on DerSimonian and Laird's random-effects model (DerSimonian and Laird, 1986), because heterogeneity was likely to be substantial in the context of various intervention types and comparator conditions, while follow-up measurements ranged from 17 to 332 weeks. An α-level of 0.05 (2-tailed) was used for hypothesis testing. In addition to the RR, the risk-difference (RD) was calculated and transformed by inversion into the number-needed-to-treat (NNT).

Heterogeneity was evaluated using the I^2 statistic (Higgins and Thompson, 2002) and can be interpreted as the percentage of between-study variance that cannot be explained by random sample error of the primary studies alone. As a rule, heterogeneity is deemed low, moderate or high when I^2 is 25%, 50% or 75%, respectively. The 95% confidence-interval of I^2 was estimated using STATA's downloadable 'heterogi'-procedure.

The presence of publication bias was evaluated using Duval and Tweedie's Trim and fill procedure (Duval and Tweedie, 2000). Essentially, this procedure re-estimates the meta-analytically pooled effect size after considering publication bias by imputing missing studies. The bias can then be observed as the difference between the unadjusted pooled effect size and the adjusted one. We also computed the fail-safe *N* for the pooled RR as another way to gauge the robustness of the pooled RR in the possible presence of publication bias.

The correlation between the effect size of the interventions and the characteristics of the primary studies was explored using meta-regression. In meta-regression, the effect size (RR) of each the primary studies is regressed on the characteristics of the studies, the study population and the intervention. The meta-analytic regression model contained seven predictor variables: mean age, number of previous episodes, percentage females, type of previous treatment (if any), duration of preventive intervention, length of follow-up and setting (community, primary care, secondary care).

Subgroup analyses were performed to study the results on long effectiveness of psychological interventions (one year or more, two years or more) and on the use of diagnostic interviews at follow up.

The meta-analytic dataset was analysed with help of Comprehensive Meta-Analysis (CMA, Version 2.2.057, 2010) (2012, http://www.meta-analysis.com). Stata (StataCorp, Version 8.2, 2009) was used for carrying out the multivariate meta-regression and calculating the 95% confidence intervals of the I^2-statistic.

All findings were summarised in a table according to the methodology described by the GRADE working group (Guyatt et al., 2008) (Appendix S4).

3. Results

3.1. Description of included studies

Having examined a total of 3537 abstracts, we retrieved 69 full text papers. Of these, 44 studies were excluded because they did not meet the inclusion criteria (Appendix S5). The remaining 25 studies met all inclusion criteria. Five trials compared 3 conditions, thus testing multiple contrasts. As a result, this meta-analysis was based on 25 studies and 30 contrasts. In case of multiple contrasts, data on variables (sample size of control, mean age, etc.) were adjusted accordingly per arm. Fig. 1 depicts the flow chart of the selection process.

No trials evaluating PST or PDT met the inclusion criteria. Sixteen trials (17 contrasts) evaluated preventive CT, 3 trials (6 contrasts) evaluated IPT, and 6 trials (7 contrasts) evaluated MCT. Thirteen contrasts compared a psychological intervention with ADM and 17 contrasts compared a psychological intervention with TAU. Fourteen studies were conducted in Europe, 10 in the United States and 1 in Australia. Duration of follow-up ranged between 17 weeks and 332 weeks (mean follow-up 115 weeks).

CT after remission was delivered through various modes; weekly group sessions, individual sessions, over the Internet and as booster sessions (various number of sessions during various duration of periods with a minimum of 3 sessions). All trials evaluating MCT consisted of 2 h weekly sessions over 8 consecutive weeks, eventually followed by a few booster sessions. IPT was delivered in individual sessions (varying from monthly maintenance sessions over 8 months to weekly maintenance sessions over 4 months).

The 25 primary studies encompassed 2055 patients in total. In 21 contrasts the patients had been recipients of a preceding acute-phase therapy during the same trial, which was either medication or cognitive therapy or a combination of both. At randomisation, all patients were depression free (with or without residual symptoms) and therefore 'at risk' of a relapse or recurrence into yet another episode of MDD. A total of 932 patients were randomised to an intervention condition: 529 received preventive CT, 142 IPT and 261 MCT. The remaining 1123 patients were randomised to comparator conditions: 670 receiving TAU and 453 receiving ADM.

Mean age was 43.3 years (95% CI, 43.11–43.39), 70.4% of the participants was female (95% CI, 69.9–70.91) and the mean number of previous episodes was 3.8 (95% CI, 3.77–3.92). Selected characteristics are presented in Table 2.

3.2. Psychological interventions versus treatment-as-usual

3.2.1. Pooled RR

We obtained 17 randomised trials that compared a psychological intervention with TAU (routine clinical management, assessments only, no treatment, waiting-list control with unrestricted access to TAU). The pooled relative risk was 0.64 (95% CI 0.53–0.76) and was statistically significant ($z=4.89$, $p<0.001$), indicating that

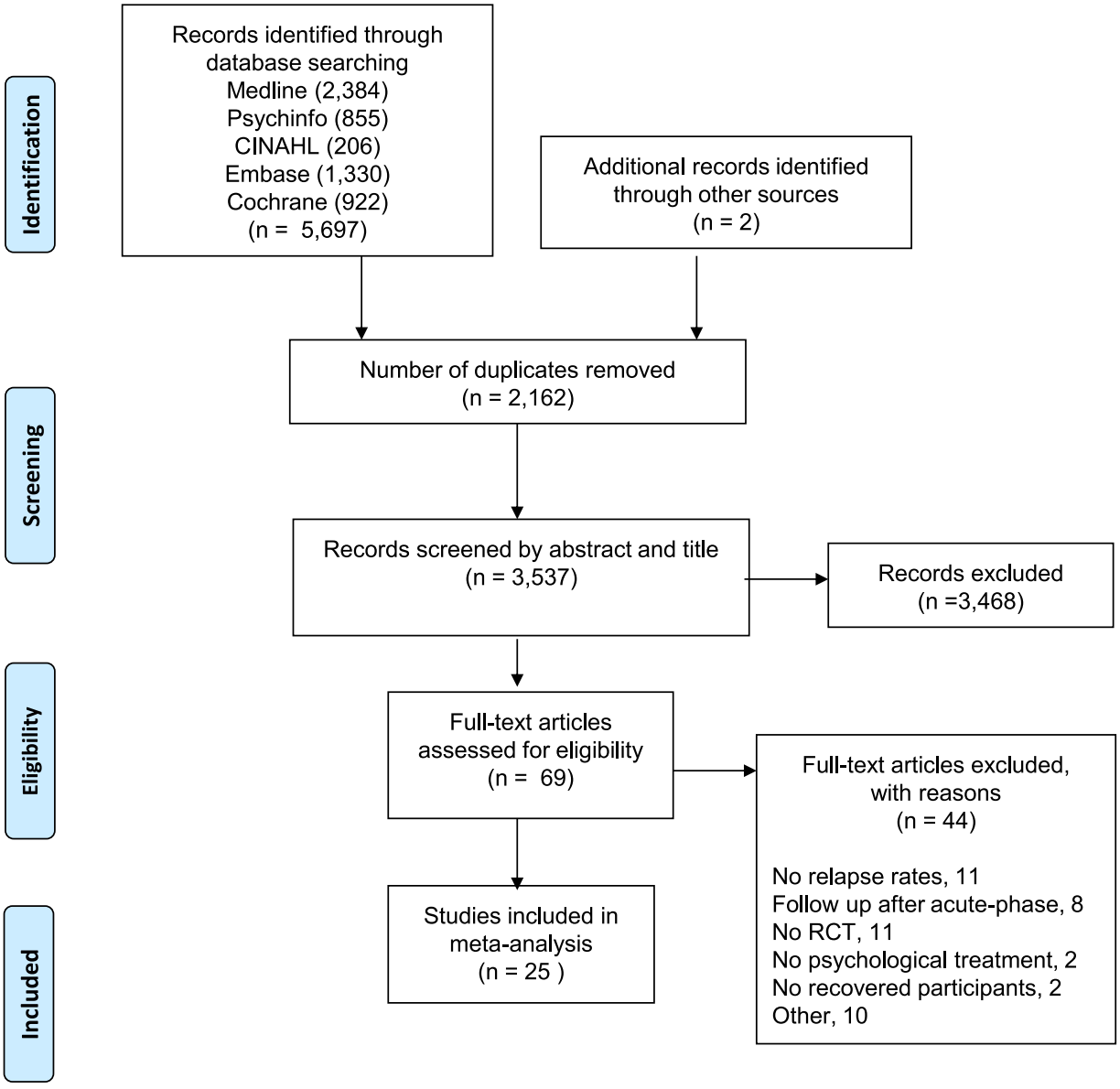

Fig. 1. PRISMA flow chart of the literature search.

psychological interventions were more successful in decreasing the risk of relapse or recurrence than TAU over a mean follow-up time of two-year (115 weeks) (Fig. 2).

3.2.2. Pooled RD and NNT

The risk-difference was 0.19 (95% CI 0.13–0.26), corresponding to a number-needed-to-treat (NNT) of 5.3. In other words, it takes 5 patients to be treated with a psychological intervention (CT, MCT or IPT) rather than TAU to prevent one relapse or recurrence.

3.2.3. Heterogeneity

The test of heterogeneity indicated that the observed variability in effect sizes across the studies was greater than that expected by chance alone ($\chi^2=32.41$, df$=16$, $p=0.009$). The corresponding I^2 was 51% (95% CI 14–72%) corresponding with moderate heterogeneity (Higgins et al., 2003).

3.2.4. Meta-regression

A meta-regression analysis was used to identify sources of heterogeneity in the effects across the studies in terms of sample characteristics (mean age, gender, number of previous depressive episodes) and the study's methodological characteristics (previous intervention in the acute phase (if any), mean treatment duration, mean follow-up duration and setting). Whether or not there was any intervention in the acute phase (CT, MCT, IPT, ADM or combination) helped partially explain heterogeneity across outcomes: the preventive effect of psychological intervention was usually better when the prevention was preceded by treatment in the acute phase ($b=-1.94$, SEb$=0.68$, $z=-2.84$, $p=0.005$). The other investigated variables in the meta-regression were not associated with the effect size. Other sources of heterogeneity (e.g. variability in delivery mode of intervention and comorbidity) may also have contributed to the heterogeneity, but were insufficiently reported to be included in the meta-regression.

3.2.5. Publication bias

The Egger test showed that publication bias was likely in this meta-analysis of psychological interventions versus TAU (intercept$=-1.65$, SE$=0.41$, $p<0.001$). This was confirmed by Duvall and Tweedie's adjusted estimate of RR$=0.82$ (95% CI 0.68–0.99),

Table 2
Selected characteristics of 25 included studies [a].

Author	Year	Mean age	% Female	No. of previous episodes	Previous intervention[b]	Previous comparator[b]	Current intervention	Current comparator	Follow-up (wks)	Definition recurrence	Setting	Length of intervention (wks)	Risk rate intervention	Risk rate comparator
Baker and Wilson (1985)	1985	40	74	n/a	Group CBT	Group CBT	CBT	TAU	22	BDI ≥ 17	Community	12	6/10	7/9
Blackburn et al. (1986)	1986	4	84	2	CT	ADM	CT	ADM	104	HRSD ≥ 8 and BDI ≥ 9 or retreatment	Primary and secondary care	26	3/13	7/9
Blackburn and Moore (1997)	1997	40	59	3	CT	ADM	CT	ADM	52	HRSD ≥ 14	Secondary care	104	4/17	4/13
Bockting et al. (2009)	2009	45	73	4	n/a	n/a	CT+TAU	TAU	286	MDE according to SCID	Community, primary and secondary care	8	69/88	73/84
Bondolfi et al. (2010)	2010	48	72	4	n/a	n/a	MCT+TAU	TAU	60	MDE according to SCID	Community, primary and secondary care	8	9/27	10/28
Conradi et al. (2007)	2007	44	61	Not clear	n/a	n/a	CBT	TAU	156	MDE (CIDI)	Primary care	156	21/38	39/62
Fava et al. (1998)	1998	46	68	Not clear	ADM	ADM	CT	TAU	332	MDE (RDC defined)	Secondary care	20	10/20	15/20
Fava et al. (2002)	2002	44	60	4	ADM	ADM	CT+ADM	ADM	60	MDE (RDC defined)	Secondary care	6	1/4	4/4
Fava et al. (2004)	2004	47	60	4	ADM	ADM	CT	TAU	332	MDE (RDC defined)	Secondary care	20	8/20	18/20
Frank et al. (1990)	1990	40	77	7	ADM+IPT	ADM+IPT	IPT	TAU	156	MDE (RDC defined)+ HSRD ≥ 15+Raskin ≥ 7	Unknown	156	1/26	1/23
Frank et al. (1990)	1990	40	77	7	ADM+IPT	ADM+IPT	IPT	ADM	156	MDE (RDC defined)+ HSRD ≥ 15+Raskin ≥ 7	Unknown	156	1/26	0/28
Godfrin and van Heeringen (2010)	2010	46	81	Not clear	n/a	n/a	MCT+TAU	TAU	56	MDE according to DSM-IV	Secondary care	8	12/40	32/47
Hollandare et al. (2011)	2011	45	85	6	n/a	n/a	CBT (internet)	TAU	26	MDD according to SCID	Community	10	4/38	14/37
Hollon et al. (2005)	2005	40	59	2	CT	ADM	CT	ADM	104	MDE or HRSD ≥ 14, at least 2 weeks	Secondary care	52	5/20	7/14
Jarrett et al. (2000)	2000	41	84	2	CT	TAU	CT	TAU	104	MDE (RDC defined) or retreatment	Secondary care	10	3/7	6/7
Jarrett et al. (2000)	2000	41	84	2	CT	ADM	CT	ADM	104	MDE (RDC defined) or retreatment	Secondary care	10	3/7	4/7
Jarrett et al. (2001)	2001	43	73	3	CT	CT	CT	TAU	104	MDD (DSM defined)	Community, primary and secondary care	36	15/41	22/43
Jarrett et al., (2013)	2013	43	67	4	CT	n/a	CT	ADM	140	MDD (DSM defined, LIFE	Secondary care secondary care	34	11/25	12/28
Klein et al. (2004)	2004	45	67	2	CBASP (CBT)	CBASP (CBT)	CBASP (CBT)	TAU	52	PSR=5 or 6, 2 cons weeks) MDD and HRSD ≥ 16 for ≥ 2 visits	Secondary care	52	1/42	8/40
Klerman et al. (1974)	1974	Not clear	100	Not clear	ADM	ADM	IPT	TAU	35	Not clear	Secondary care	36	4/25	9/25
Klerman et al. (1974)	1974	Not clear	100	Not clear	ADM	ADM	IPT	ADM	35	Not clear	Secondary care	36	4/25	3/25
Kuyken et al. (2008)	2008	49	77	6	n/a	n/a	MCT+TAU	ADM	65	MDE according to SCID	Primary care	52	29/61	37/62
Ma and Teasdale (2004)	2004	45	76	3	n/a	n/a	MCT+TAU	TAU	60	MDE (DSM-IV defined)	Primary care and community	36	14/36	23/37
Paykel et al. (2005)	2005	4	49	2	n/a	n/a	CBT+ADM	ADM	275	MDD > 4 weeks or HAMD ≥ 13, at least 8 weeks	Secondary care	32	48/80	51/78
	2002	40	55	5	ADM	ADM	CT+ADM	ADM	28		Secondary care	26	4/66	5/66

Table 2 (*continued*)

Author	Year	Mean age	% Female	No. of previous episodes	Previous intervention[b]	Previous comparator[b]	Current intervention	Current comparator	Follow-up (wks)	Definition recurrence	Setting	Length of intervention (wks)	Risk rate intervention	Risk rate comparator
Perlis et al. (2002)										MDE at any visit, HRSD ≥ 15 at two consecutive visits				
Schulberg et al. (1996)	1996	38	83	Not clear	IPT	TAU	IPT	TAU	17	Symptomatic (HRSD ≥ 13)	Primary care	18	17/91	44/92
Schulberg et al. (1996)	1996	38	83	Not clear	IPT	ADM	IPT	ADM	17	Symptomatic (HRSD ≥ 13)	Primary care	18	17/91	23/91
Segal et al. (2010)	2010	43	59	5	ADM	ADM	MCT	TAU	78	HRSD ≥ 16 2 consecutive weeks + MDE on SCID	Community, primary and secondary care	8	10/26	18/30
Segal et al. (2010)	2010	45	61	5	ADM	ADM	MCT	ADM	78	HRSD ≥ 16 2 consecutive weeks + MDE on SCID	Community, primary and secondary care	8	10/26	13/28
Teasdale et al. (2000)	2000	41	71	5	n/a	n/a	MCT+TAU	TAU	60	Recovery or remission, HRSD-17 < 10	Community, primary and secondary care	26	31/71	38/66

[a] Abbreviations: ADM, anti-depressant medication; BDI, Beck Depression Inventory (Beck et al., 1961); CBASP; 'Cognitive Behavioural Analysis System of Psychotherapy'; C(B)T, Cognitive (Behaviour) Therapy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; HRSD, Hamilton Rating Scale for Depression (Hamilton, 1960); IPT, interpersonal therapy; MCT, mindfulness based cognitive therapy; MDD, major depressive disorder; MDE, Major Depressive Episode; Raskin, Raskin Depression Rating Scale (Raskin et al., 1969); RCT, randomised controlled trial; RDC, Research Diagnostic Criteria; SCID, Structured Clinical Interview for Depression (First et al., 1996); TAU, treatment-as-usual; wks, weeks.

[b] An intervention in the acute phase as part of this specific RCT.

based on eight additionally imputed studies. The adjusted estimate differed somewhat from the original (unadjusted) estimate of RR = 0.64 (95% CI 0.53–0.76): the 95% confidence intervals have a considerable overlap, but the point estimates of RR fall outside the alternative intervals. That said, the conclusion that psychological interventions are statistically superior to TAU remained unaffected (Egger et al., 1997; Rothstein et al., 2005). The robustness of the findings was further supported by a fail-safe *N* of 197, meaning that 197 undetected studies with no effect (RR = 1) need to be included in the meta-analysis before the pooled effect would cease to be statistically significant at $p < 0.05$ (2-tailed).

3.3. Psychological interventions versus antidepressant medication

Thirteen studies compared psychological interventions with ADM (Fig. 3). The pooled effect size was RR = 0.83 (95% CI 0.70–0.97), which was statistically significant ($z = 2.39$, $p = 0.017$). No evidence was obtained for heterogeneity ($\chi^2 = 9.09$, df = 12, $p = 0.695$, $I^2 = 0\%$, 95% CI 0–57), although the wide 95% CI of the I^2 leaves room for other interpretations. The mean follow-up period was somewhat less than two years (90 weeks). The risk-difference was 0.075 (95% CI 0.001–0.149) and the corresponding NNT was 13.3, demonstrating that 13 patients would need to be treated with a preventive psychological intervention rather than ADM to prevent one relapse or recurrence.

The Egger test and Duvall and Tweedie's Trim and fill did not suggest the presence of a significant publication bias (Egger test intercept = −0.47, SE = 0.41, $p = 0.27$, Duvall and Tweedie's adjusted RR = 0.86, 95% CI 0.73–1.00, based on two imputed studies).

Three trials comparing preventive psychological interventions with ADM (Paykel et al. (2005), Perlis et al. (2002) and Fava et al. (2002)) allowed ADM intake in the intervention group. In a subgroup analysis of preventive psychological interventions versus ADM without these three trials the pooled effect size was RR = 0.78 (95% CI = 0.625–0.961) and did not change results.

3.4. The effectiveness of different types of psychological interventions

Sixteen trials (17 contrasts) included CT, 3 trials included IPT (6 contrasts) and 6 trials (7 contrasts) included MCT (Table 3). The effect sizes of the different psychological interventions were roughly similar.

3.5. Subgroup analyses

Subgroup analyses of psychological interventions versus TAU and ADM on results on long effectiveness (follow-up more than one year and more than two years) and on the use of diagnostic interviews at follow-up showed no remarkable differences.

3.6. Quality of included studies

We created GRADE profiles and classified the overall quality of evidence (high, moderate, low) based on the GRADE system using 6 criteria (Guyatt et al., 2008); study design (all RCT's), study limitations, inconsistency, indirectness, imprecision and other bias (e.g. publication bias). Overall, the quality of the studies was low (Appendix S4). We conducted a meta-regression to analyse whether the size of the effects (RR) systematically co-varied with study quality. This was not the case ($b = 0.242$, SEb = 0.945, $z = 0.26$, $p = 0.798$).

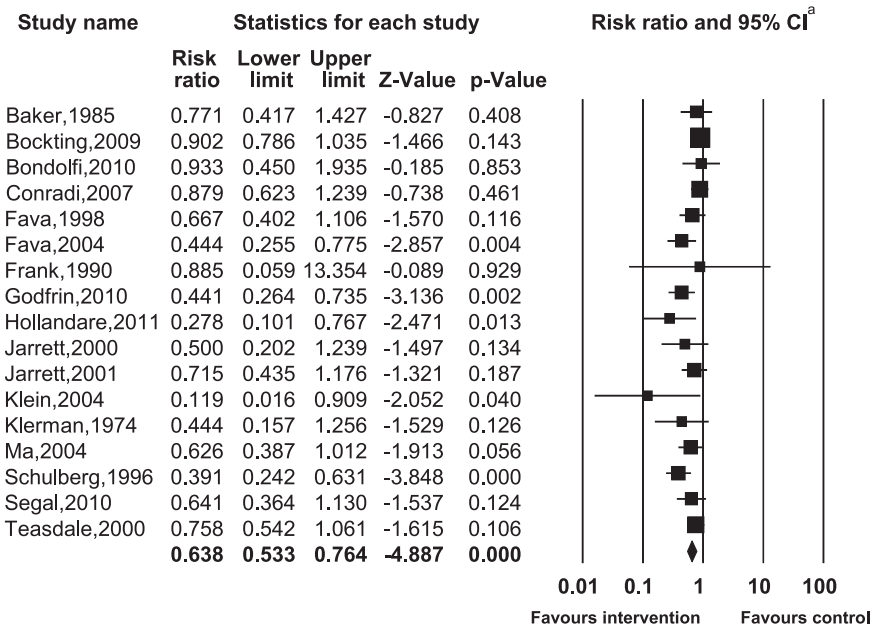

Fig. 2. Forest plot of risk ratios and 95% confidence-intervals for psychological interventions versus treatment-as-usual. Abbreviations: CI, confidence interval.

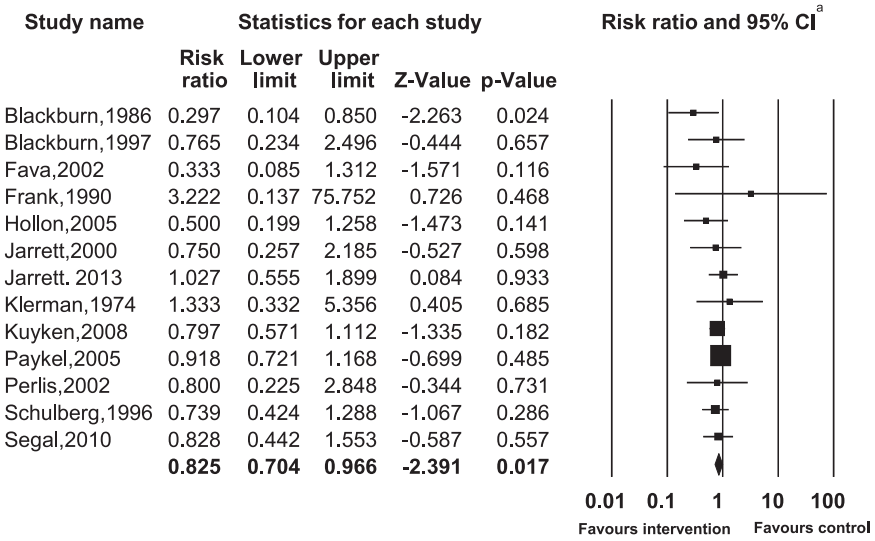

Fig. 3. Forest plot of risk ratios and 95% confidence-intervals for psychological interventions versus antidepressant medication. Abbreviations: CI, confidence interval.

Table 3
Risk ratios of different types of psychological interventions versus treatment-as-usual (TAU) and antidepressant medication (ADM) according to the random-effects model (DerSimonian and Laird)[a].

	Intervention	*K*	RR D–L (95% CI)	Test	RD (95% CI)	NNT	I^2 (%)
Versus TAU	**All**	17	0.64 (0.53; 0.76)	$z=-4.89$ $p=0.000$	−0.190 (−0.255; −0.125)	5	51
	CT	9	0.68 (0.54; 0.87)	$z=-3.12$ $p=0.002$	−0.196 (−0.28; −0.11)	5	52
	MCT	5	0.66 (0.53; 0.82)	$z=-3.81$ $p=0.000$	−0.205 (−0.32; −0.09)	4	0
	IPT	3	0.41 (0.27; 0.63)	$z=-4.10$ $p=0.000$	−0.160 (−0.37; −0.04)	6	0
Versus ADM	**All**	13	0.83 (0.70; 0.97)	$z=-2.39$ $p=0.017$	−0.075 (−0.149; −0.001)	13	0
	CT	8	0.79 (0.61; 1.02)	$z=-1.80$ $p=0.072$	−0.16 (−0.30; −0.016)	6	9
	MCT	2	0.80 (0.60; 1.08)	$z=-1.46$ $p=0.146$	−0.11 (−0.25; −0.04)	9	0
	IPT	3	0.83 (0.50; 1.38)	$z=-0.71$ $p=0.477$	−0.002 (−0.068; −0.073)	n/a	0

[a] Abbreviations: ADM, anti-depressant medication; CT, Cognitive (Behaviour) Therapy; CI, confidence interval; I^2, heterogeneity; IPT, Interpersonal Therapy; *K*, number of contrasts; MCT, mindfulness-based cognitive therapy; NNT, number-needed-to-treat; RD, risk difference; RR D–L, random-effects according to DerSimonian and Laird; TAU, treatment-as-usual.

4. Discussion

4.1. Main findings

We obtained 25 randomised controlled trials with a total of 2055 patients examining the effect of psychological interventions to prevent the occurrence of yet another depressive episode. The psychological interventions were based on cognitive (behavioural) therapy, mindfulness-based cognitive therapy and interpersonal therapy. We found no prevention trials based on problem-solving therapy or psychodynamic therapy that met inclusion criteria. We hypothesised (H1) that psychological interventions were superior to TAU. Meta-analysis of the available studies indeed demonstrated that psychological interventions were considerably more effective than TAU in preventing relapse or recurrences over two years (RR=0.64, $p<0.001$; NNT=5). After correcting for publication bias, the adjusted estimate—based on eight additionally imputed studies—appeared less effective (adjusted RR=0.82, 95% CI 0.68–0.99). The heterogeneity in this meta-analysis was moderate. Second meta-analysis, we hypothesised (H2) that psychological interventions were not inferior to ADM. Indeed, we found that psychological interventions were more effective in reducing the risk of a relapse or recurrence compared to ADM (RR=0.83, $p=0.017$; NNT=13). After correcting for publication bias, the adjusted estimate—based on two additionally imputed studies—appeared slightly less effective (adjusted RR=0.86, 95% CI 0.73–1.00). In this meta-analysis, we found no evidence of heterogeneity between studies. The effect sizes of the different psychological interventions were roughly similar, as stated in our third hypothesis (H3). An unanticipated finding was that the effectiveness of preventive interventions was enhanced when the patient had received an intervention (psychological intervention, antidepressant medication or both) during the acute phase of the depression in the same trial.

4.2. Strengths and limitations

This is the first systematic review and meta-regression investigating the effect of all types of preventive psychological interventions on relapse or recurrence after remission. Moreover, this meta-analysis includes ADM and TAU as *separate* control groups which is new and very much awaited in the field, as ADM is a separate guideline-based treatment choice. A large number of studies (25) are included in this review and current state-of-the-art meta-analytic techniques are used.

We also recognise a number of limitations. First, there were many differences in methodological design of the included trials such as definition of remission, recovery, relapse and recurrence, type or duration of interventions and whether or not there was a preceding acute intervention in the same trial. For example, treatment-as-usual was often described inadequately and information on the exact method of determining recurrence (interview versus questionnaire) was sometimes not provided. These differences are likely to have caused some heterogeneity in the data, but owing to e.g. poor reporting could not be evaluated in a meta-regression.

A second limitation, which is a limitation of the included studies, is the low overall quality of the studies according to the GRADE evidence profile. This lack of quality limits our confidence in the overall effect size estimates. However, due to the nature of psychological interventions and the difficulty to compare these with 'placebo' interventions, highest quality evidence may not be possible in such studies. Factors that lower the quality of evidence, like differences in interventions (e.g. client-therapist relations) and difficulties in blinding of participants, outcome reporters and/or personnel, will probably remain in studies investigating the effect of psychological interventions.

Third, publication bias could not be ruled out in the meta-analysis of psychological interventions versus TAU and it is possible that unpublished trials showed null findings or even adverse outcomes. After correcting for publication bias, the adjusted estimate appeared less effective than the original estimate.

Fourth, it is unlikely that the exact number of previous depressive episodes has been reported reliably in the primary studies. The number of previous episodes is most likely under-reported (Andrews et al., 2005). The fact that we did not find an effect of number of previous episodes in our meta-analysis might be caused by a downward bias due to under-reporting.

Fifth, we found that the effect sizes of the different psychological interventions were roughly similar. However, this finding is not based on (scarce) head-on comparisons but on the pooled results of studies that compared the preventive psychological interventions with ADM or TAU. Results on head-on comparisons of psychological interventions (e.g. MCT versus IPT) should be analysed in order to draw definite conclusions about the effect sizes of different psychological interventions.

4.3. Implications

Treatment of acute depression is the core business of mental health care, but this approach is only partially successful in reducing the overall disease burden stemming from depression. As said, depression is characterised by a large number of patients experiencing multiple relapses and recurrences, with patients spending as much as 21% of their lifetime in a depressed condition (Vos et al., 2004). This has important implications for the longer-term management of depression.

The National Institute for Health and Clinical Excellence (NICE; NICE Clinical Guidelines, 2009) recommends to continue medication in ADM responders for at least 6 months after remission or even to continue for at least 2 years if there is a significant risk of relapse. However, not all remitted patients feel comfortable taking antidepressants for a long period, they may feel unnecessarily dependent on them, and may find it difficult to adhere over extended periods of time (ten Doesschate et al., 2009). Thus, an alternative for the longer-term use of ADM is sorely needed.

Psychological interventions in the acute phase have been studied extensively and more and more attention is being paid to the effects of psychological interventions after remission. Examples are the meta-analyses by Guidi et al. (2011), Vittengl et al. (2007) and Piet and Hougaard (2011), who conclude that (some types of) preventive psychological interventions after remission are effective in reducing relapse or recurrence. Our meta-analysis of 25 studies adds that preventive psychological interventions outperform continuation of ADM, which is now a first step intervention in remitted patients.

In clinical practice however, an important question is 'What works for whom?'. Therefore, NICE recommends specific types of psychological interventions (CT/MCT over others), optimal treatment duration (16–20 sessions over 3–4 months) and format of intervention (individual CBT/group MCT) and takes into account the number of previous episodes. In our meta-regression we found homogeneity in effect size across the different modalities and target populations so we could not make a meaningful distinction among the various psychological interventions, treatment durations, settings nor previous episodes. This seems to suggest that practically no stratification is necessary. The only unanticipated finding in our meta-analysis was that the effectiveness of preventive interventions was enhanced when the patient had received an intervention (psychological intervention, antidepressant medication or both) during the acute phase of the depression in the same trial. In other words, it might be

important to look at depression as a series of disease-stages that need to be taken care of both during the acute-phase and also directly after remission in the continuation- or maintenance phase. Treatment after remission should then be embedded in an integrated way, seamlessly following up on the acute-phase treatment.

Finally, against a background of financial constraints in many health care systems, cost of treatment is of great concern. Cost-effective solutions demand an optimal balance between accessible, acceptable, effective and economically affordable treatments for the many patients suffering from recurrent depressions. Possible ways of offering psychological interventions are over the Internet (Hollandare et al., 2011; Kelders et al., 2013), by a nurse (Bosmans et al., 2012), by self-help (Biesheuvel-Leliefeld et al., 2012) or by low intensity psychological interventions (Rodgers et al., 2012). More trials focussing on the question how to optimise the cost-effectiveness of psychological interventions after remission is worthy of further consideration and should be placed on the research agenda. Also, more attention should be directed at other psychological interventions like problem-solving therapy and psychodynamic therapy as possibly valuable alternatives in the prevention of recurrent depression. A lot of research is needed to shed light on the unresolved issues. Despite that, this meta-analysis has shown that preventive psychological interventions after remission may reduce the highly significant disease burden stemming from recurrent MDD.

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Conflict of interest

The authors have no actual or potential conflicts of interest to disclose, related to this manuscript.

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Appendix A. Supporting information

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