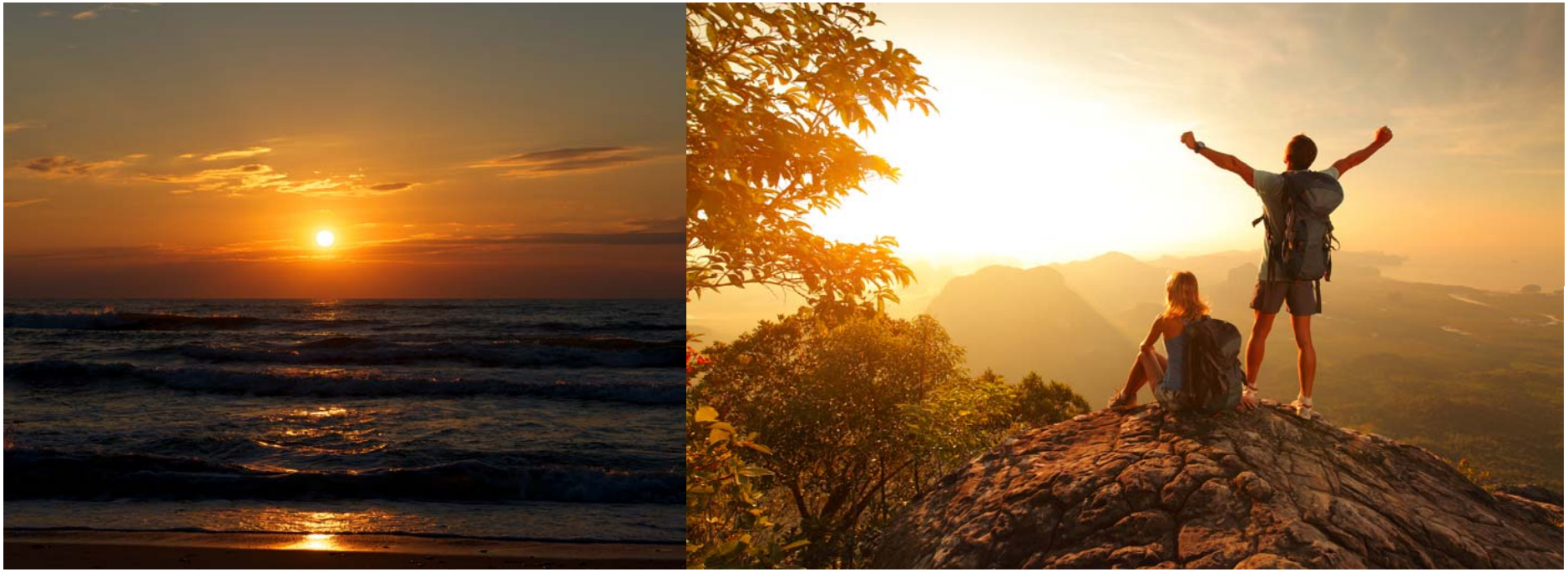
KCE REPORT 230

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

THE LONG-TERM EFFICACY OF PSYCHOTHERAPY, ALONE OR IN COMBINATION WITH ANTIDEPRESSANTS, IN THE TREATMENT OF ADULT MAJOR DEPRESSION



KCE REPORT 230
GOOD CLINICAL PRACTICE

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THE LONG-TERM EFFICACY OF PSYCHOTHERAPY, ALONE OR IN COMBINATION WITH ANTIDEPRESSANTS, IN THE TREATMENT OF ADULT MAJOR DEPRESSION

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COLOPHON

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADM	Antidepressant medication
BA	Behavioural activation
CBT	Cognitive behavioural therapy
CI	Confidence interval
CIDI	Composite Diagnostic International Interview
CPG	Clinical practice guideline
DDD	Daily defined doses
DSM	Diagnostic and Statistical Manual of Mental Disorders
FOD	Federale Overheidsdienst
GDG	Guideline development group
GP	General practitioner
ICD	International Statistical Classification of Diseases
IPT	Interpersonal psychotherapy
MOI	Monoamine oxidase inhibitor
MBCT	Mindfulness based cognitive therapy
MDD	Major depressive disorder
MINI	Mini- International Neuropsychiatric Interview
NIHDI (RIZIV-INAMI)	National Institute of Health and Disability Insurance
NNT	Number needed to treat
OR	Odds ratio
PDT	Psychodynamic therapy
PST	Problem solving therapy
RCD	Research diagnostic criteria
RCT	Randomized controlled trial
REBT	Rational emotive behaviour therapy
SCID	Structured clinical interview for DSM disorders
SD	Standard deviation
SMD	Standardized mean difference

SNRI	Serotonin–norepinephrine reuptake inhibitor
Systematic review	Systematic review
SSRI	Selective serotonin reuptake inhibitors
SST	Social skills training
TAU	Treatment as usual
TCA	Tricyclic antidepressants
UK	United Kingdom
US	United States
YCG	Yearly contact group

SCIENTIFIC REPORT

1 INTRODUCTION

Major depression is a common mental health disorder, characterized by the loss of interest or pleasure in ordinary things and experiences, low mood and a wide range of associated emotional, cognitive, physical and behavioral symptoms. The identification and diagnosis of major depression (which is also called 'clinical depression' or just 'depression') is based not only on the severity of symptoms but also on their persistence, the presence of other symptoms, and the degree of functional and social impairment.[1]

There is not a clear 'cut-off' between 'clinically significant' and 'normal' degrees of depression and it is best to consider the symptoms of depression as occurring on a continuum of severity; the greater the severity of depression, the greater the morbidity and adverse consequences.[2] When adding other aspects that need to be considered, including duration, stage of illness and treatment history, there are considerable problems in attempting to classify depression into categories.[1]

The aim of interventions for depression is to relieve symptoms, restore functions and, in long-term, prevent relapse. Treatment continues to be hampered by resistance at the individual level to seek help and the failure, especially in primary care, to correctly identify those who are truly depressed. The most common interventions (treatments) for depression, are psychological and/or pharmacological treatments.

1.1 Incidence and prevalence

Mental diseases, in particular depression, are the first cause of disability in Belgium. Results from the health interview survey from the Scientific Institute of Public Health (WIV-ISP) in 2008 indicated a self-reported prevalence of depression of 9%, with 6% of the responders stating that they suffered from major depression during the past year. Among the responders who stated they had a depression, 88% received care from a health professional, 41% followed psychotherapy and 82% used antidepressant medications.[3]

The Intego network is the first computerized network of general practitioners who voluntarily serve as a sentinel in Flanders. The network provides estimates on incidence and prevalence of all diseases registered in general practice in Flanders. The registration network includes approximately 55 practices spread across the Flanders region, representing 1.05% of all GPs working in Flanders.

Incidence rates for diseases are available on the Intego website, using International Classification of Primary Care, 2nd edition (ICPC2) codes per year and per age-group (http://www.intego.be/). For example, in 2008, there were 90 324 different patients seen in the 55 general practices. This is called the yearly contact group (YCG). Bartholomeeusen et al.[4] proposed a method to use the yearly contact group to estimate the entire practice population (estimated to be approximately twice the size of the yearly contact group). Based on this method, the average yearly incidence of depression was calculated to be 12.9 per 1000 persons per year (1.29% per year), during the time period 1994-2010.[5] This incidence, however, is based on the primary health care classification ICPC-2 code classification system (and not on the likely more stringent DSM-IV classification), and therefore may be an overestimation of the actual incidence of major depressive disorder.

Additionally, Boffin et al. [6] reported on general practice-based data collected on all patients of >18 years who were diagnosed by their GP with a new episode of depression in Belgian sentinel general practices during 2008. Data on 1739 persons were recorded by 172 sentinel general practices. Incidence rates for GP-diagnosed depression were estimated to be 719/100 000 for men and 1440/100 000 for women. Of these patients, 31% were GP-diagnosed with a mild depression, 50% with a moderate depression and 19% with a severe depression. The criteria for the depression diagnosis was left to the judgement of the individual GP. Moreover, not all patients with a depression go to a GP for their problem.

Worldwide estimates of the incidence rates and prevalence of depression varies between studies and settings. It is suggested that the best estimate of the proportion of people, who are likely to experience a major depression at some point in their life lie between 4 and 10%.[7] Prevalence rates have consistently been found to be between 1.5 and 2.5 times higher in women than men.[7] Depression can occur at any age from early childhood to old age, and across all social classes. However, in a UK survey, described in the NICE guideline on depression from 2010, people with a depression were more likely to be aged between 35 and 54, be separated or divorced and living alone or as a lone parent. Socioeconomic factors such as unemployment or belonging to lower social classes were also found to be associated with a higher prevalence rate.[1]

1.2 Diagnosis and classification of major depression.

The diagnosis and classification of depression were considered out of scope. As a basis for discussion with the guideline development group (GDG), the current two major classification systems DSM-IV_TR and ICD-10 were used. However, all studies based on previous versions of the DSM classification system or on Feighner or Research Diagnostic Criteria were considered. Please see section 3.4.3 for a detailed overview of the diagnostic classifications included.

1.3 Course of the disease

The following information is extracted from the NICE guideline on depression from 2010.[1] References to the studies mentioned below can also be found in the NICE guideline.

Depression used to be viewed as a time-limited disorder, lasting on average 4 to 6 months with complete recovery afterwards. However, it is now clear that incomplete recovery and relapse are common. A WHO study of mental disorders in 14 centres across the world found that 50% of patients still had a diagnosis of depression 1 year later and at least 10% had persistent or chronic depression. At least 50% of people, following their first episode of major depression, will go on to have at least one more episode and, after the second and third episodes, the risk of further relapse rises to 70 and 90%, respectively. People with early onset depression (at or before 20 years of age) and depression occurring in old age have a significantly increased vulnerability to relapse. Thus, while the outlook for a first episode is good, the outlook for recurrent episodes over the long-term can be poor with many patients experiencing symptoms of depression over many years.

2 OBJECTIVES AND SCOPE OF THIS GUIDELINE

2.1 Background

According to a report from the Superior Health Council (Hoge Gezondheidsraad-Conseil Supérieur de la Santé) the prescription of antidepressants in Belgium has increased from 100 million daily defined doses (DDDs) in 1997 to 250 million DDDs in 2008.[8] Based on this report, the Belgian Ministry of Health created a scientific platform for psychopharmacology drugs in 2012, designed to provide advice regarding the use of psychopharmacology drugs or alternative treatment forms. This platform submitted the topic psychotherapy in major depression to the KCE due to the lack of useful data comparing antidepressants and psychotherapy for major depression.

2.2 The need for a guideline

While the short-term efficacy of antidepressants and psychotherapy is similar, and the differences between the various antidepressants and different forms of psychotherapy are small,[9] evidence on the long-term efficacy has not been synthesized in a structured way. Further, there is a recent recognition of the profession of psychologist, see section 9.2: therefore it is important to understand the effect of psychotherapy, alone or in combination with antidepressants, and to analyze whether there is a difference in safety associated with psychotherapy and/or antidepressants in the long-term. A Belgium surveillance study[10] further argues that there is a need for policy recommendations in this domain. The authors analyzed six months follow-up data on 900 patients diagnosed with a new episode of mild depression or a first episode of moderate depression by their GP, and examined factors such as treatment continuation, remission and the match between treatments initiated and delivered. Complete treatment drop-out was found in 9% of patients and treatment discontinuation in 40%. Half a year after diagnosis, half of the patients continued to visit their GP and of these patients 60% remained depressed. Notably, the lowest match between initiated and delivered treatment was observed for non-pharmacological support by the GP with 43% (95%CI: 33-54%) receiving the support that was initiated. The highest match was found for psychopharmacological treatment with 91% (95%CI: 87-95%) having taken the prescribed psychoactive agent.

2.3 Scope

This guideline aims to provide guidance on the role of psychotherapy in the long-term treatment of confirmed adult major depression. The target population are adult outpatients and inpatients with major depressive disorder (MDD).

Individuals having dysthymic disorder or elevated depressive symptoms (subthreshold depressive symptoms) are not addressed in this guideline. The present guideline does not cover diagnostics. A distinction between the different types of psychotherapy was considered out of scope.

2.4 Remit of the guideline

2.4.1 Overall objectives

A clinical practice guideline (CPG) on major depression:

- Will assist clinicians, in collaboration with the individual patient, in making appropriate treatment choices for major depression.
- Will provide scientific background for a possible future KCE project related to antidepressants and psychotherapy.

The definitions used and selection criteria are described in the methods section below.

The objective of this guideline is to provide recommendations based on current scientific evidence for psychotherapy alone, or in combination with antidepressants in the treatment of adult major depression. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

2.4.2 Target users of the guideline

This guideline could be useful for health care professionals involved in the care of patients with major depression across the care continuum. This includes general practitioners, psychiatrists, psychiatric nurses, and psychotherapists/psychologists. Policy makers and administration can also use the recommendations to adapt reimbursement rules or other regulations. The content is based on scientific evidence and may not always be in line with the current criteria for NIHDI (RIZIV – INAMI) reimbursement of therapeutic interventions.

2.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with major depression.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

2.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

3 METHODOLOGY

3.1 Introduction

The KCE guideline is drawn up according to highly codified principles, based on scientific information regularly updated from the international literature. KCE analyses current clinical practices on the basis of existing recommendations. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline:

- The topic was suggested by the platform for psychopharmacology drugs, Federal Public Service, see 2.1;
- Clinical questions were developed by KCE researchers;
- A literature review was performed;
- Results of the literature review were used to assign levels of evidence according to the GRADE approach and to formulate recommendations.

3.2 The guideline development group

This guideline was developed by a multidisciplinary group consisting of practising clinicians and methodology experts. The composition of the GDG is documented in the Appendix. The KCE Expert team provided guideline development and literature review expertise, support, and facilitation.

The roles assigned to the GDG were:

- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

3.3 Clinical research questions

This clinical practice guideline (CPG) addresses the following clinical research questions:

1. What is the long-term efficacy of main psychotherapy interventions in the treatment of adults with major depression?
2. Is there a difference between the long-term efficacy of anti-depressive agents and psychotherapy in adults treated for major depression?
3. Is there an advantage in combining both treatments in adults with major depression in the long-term?

3.4 Selection criteria

3.4.1 Type of studies

Systematic reviews as well as randomized controlled trials were eligible. Reviews without a systematic search in at least one database, and without any form of quality assessment were excluded. If no ´formal´ quality assessment was done, but randomized controlled trials (RCTs) were checked on methodological items, this was deemed sufficient for inclusion. Studies written in Dutch, English, French or German were considered for inclusion. A search for guidelines was not performed due to the limited scope requested from the platform for psychopharmacology drugs.

3.4.2 Definitions

Symptomatic phase:

- The phase in which patients have clinically relevant symptoms of depression

Acute phase:

- The phase in which patients have clinically relevant symptoms of depression and receive their first treatment

Maintenance phase:

- The phase after the acute treatment

Literature has not adopted standard definitions on the characteristics with respect to target group and duration of the various treatment phases. For example, some studies on maintenance treatment include patients in

remission while others include patients with relapse. Additionally, the duration for the various treatment phases varies across studies.

3.4.3 Type of patients

Adult patients with MDD defined according to the DSM5, DSM-IV, DSM-III-R, DSM-III, Feighner or Research Diagnostic Criteria. More specifically, studies in patients with diagnosed depressive disorder, or for maintenance studies (see below) patients with a depressive disorder who were in remission were included. The MDD had to have been established through a diagnostic interview conducted by a third person (e.g. SCID, CIDI, MINI). The study had to state explicitly that all included patients had MDD. Studies aimed at people who scored high on a self-report measure, but who were not examined by a clinical interview, were excluded, as were studies that included both patients with a major depressive disorder and patients with e.g. dysthymia or a minor depression, if outcomes were not reported separately for patients with a major depression. Studies in outpatients as well as in inpatients were included. Co-morbid general medical conditions (e.g. diabetes, migraine, cancer) or other psychiatric disorders were not used as an exclusion criterion.

3.4.4 Types of interventions

Psychotherapy was defined as an intervention in which verbal communication between a therapist and a patient is the core element, or in which a psychological treatment is contained in book format (bibliotherapy) or electronic format (internet-based treatment) that the patient works through more or less independently, but with some kind of personal support from a therapist (guided by telephone, e-mail, or otherwise).[11] Types of psychotherapy that have been identified as main type of psychotherapy in an expert taxonomy of psychotherapy for depression were examined.[11] Here, psychotherapy was classified into seven different types: interpersonal therapy, behavioural activation, cognitive-behavioural therapy, problem solving therapy, social skills training, psychodynamic therapy, and supportive counselling. The operational definitions of each type of therapy are given in the Appendix 1 on page 63. Marital/couple therapy was excluded by the present review because it involves the partners of depressed patients in the therapeutic intervention and has the relationship of the couples as a primary focus, rather than the depression. Additionally, the supportive consultation talk that likely often take place between a GP or a psychiatrist and the patient (for example as a supplement to the prescription of antidepressants) were not considered as a type of psychotherapy intervention (out of scope).

Treatments aimed at relapse prevention (time-limited psychotherapies aimed at patients who have recovered in full or partially from depressive disorder) and maintenance treatment studies (psychotherapies in which patients receive maintenance therapy sessions at low frequency rates, for example once per month) were considered for inclusion. The selected interventions, stated per research question, were:

- Research question 1: main psychotherapy interventions without antidepressive agents; we distinguihed between studies without any maintenance; relapse prevention studies; and maintenance studies
- Research question 2: main psychotherapy interventions without antidepressive agents (we used the same distinction between studies without any maintenance; relapse prevention studies; and maintenance studies)
- Research question 3: main psychotherapy interventions combined with antidepressive agents (studies without any maintenance; relapse prevention studies; and maintenance studies)

There are more than 250 types of psychotherapy, some of which have more than one ´brand´ name. In the current project we will focus therefore on the types of psychotherapy that have been examined in randomized controlled trials. There is no generally accepted classification of psychotherapies, although most clinicians and researchers would agree on a traditional classification of cognitive-behavioral, client-centered, psychodynamic, and system-oriented approaches. For most of types of therapies there are no clear definitions either and some of the best examined therapies for depression cannot be classified in one of these categories (especially interpersonal psychotherapy). Although there are some attempts to cluster types of psychotherapy in an empirical way (for example in the Common for Psychotherapy procedures; www.commonlanguagepsychotherapy.org), there is no detailed classification available. In the current project, we will use the results of an expert taxonomy of psychotherapy types for depression.[11]

This taxonomy was developed by a group of experts in the field of psychotherapy for depression. They conducted a systematic search for studies on psychological treatments for depression, using broad definitions for psychotherapy. After the identification of randomized trials, they examined which treatments were used in the studies. Treatments used in five or more studies were included in the definition of the psychotherapies. This approach resulted in seven major types of psychotherapy for depression (4.1).

3.4.5 Types of comparators

The selected comparators were:

- Research question 1: usual care, waiting list, no treatment (no pharmacotherapy), placebo pill, placebo treatment. Light therapy or other types of psychotherapy, not defined as a main type of psychotherapy, were not considered eligible as a comparator
- Research question 2: pharmacotherapy (antidepressants)
- Research question 3: main psychotherapy intervention or antidepressants alone

3.4.6 Outcomes

The primary outcome was treatment response. Treatment response was defined as every positive outcome achieved, such as whether a patient met criteria for remission or was free from relapse or recurrence. A sustained response was defined as a treatment response that was continued during and after maintenance treatment. Other outcomes were condition-related outcomes (depression rating scales such as the Hamilton Depression Rating Scale, Beck Depression Inventory), quality of life, work-related outcomes, and safety/tolerability.

Only outcomes at six months or longer after randomization were considered for inclusion. This cut off was chosen because remission is defined as the absence of a depressive disorder three months after the end of therapy, and because it was assumed that most psychotherapies will last around three months. A longer cut off did not seem feasible as few studies have a longer follow up period. Outcomes were extracted for different time periods (six months, one year, two years, three years, and over three years).

3.4.7 Power calculations

We conducted a power calculation according to the procedures described by Borenstein et al. 2009.[12] We hoped to find a sufficient number of studies to be able to identify an effect size of 0.24 (corresponding with an OR of 1.5), which can be seen as a threshold for clinical relevance.[13] These calculations indicated that we would need to include at least 19 studies with a mean sample size of 50 (25 participants per condition), to be able to detect an effect size of d=0.24 (conservatively assuming a medium level of between-study variance, τ^2, a statistical power of 0.80, and a significance level, alpha, of 0.05). Alternatively, we would need 12 studies with 80 participants to detect an effect size of d=0.24, or 10 studies with 100 participants.

3.5 Search strategy and study selection

The systematic literature search was conducted in the bibliographic databases of Medline (PubMed.com), PsycInfo (Ebsco), Embase (embase.com) and the Cochrane library (cochranelibrary.com) from database inception to 19/6/2013. Detailed search strategies are given in the Appendix. This search strategy was combined with a filter for systematic reviews provided by PubMed (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html) and a filter for RCTs as recommended in the Cochrane Handbook.[14] Search strategies for other databases were built accordingly. References of selected studies were searched to identify additional relevant studies.

We used a filter for studies on psychotherapy that was developed for a database of trials on psychotherapy for adult depression.[15] Because there are more than 250 types of psychotherapy with multiple names, it is not possible to include all names of all types of psychotherapy in the search string. We solved this by using an expert taxonomy of psychotherapy types for depression.[11] Furthermore, we also checked the database of randomized trials on psychotherapy for depression described above. For this database we checked the references of other systematic reviews and meta-analyses of main psychological treatments of depression (including systematic reviews of client-centred therapies). This database is updated every year and newly identified studies are continuously added.

The results of the searches were entered in Endnote. Duplicate publications were removed. Two researchers independently examined titles and abstracts (EK and YS, supervised by PC). Studies that possibly met inclusion criteria according to one of the two researchers were retrieved full-text. Full-text papers were examined by the same two researchers, independently from each other. In case of disagreement, consensus was sought. If needed, the opinion of a third researcher (PC) was sought. A document with the reasons for excluding articles based on full text review is available upon request.

3.6 Quality appraisal

The following instruments were used in order to assess study quality:

- Systematic reviews, meta-analyses: Amstar checklist[16]
- Randomised controlled trials (effectiveness): the Cochrane Risk of Bias tool[14]

Both instruments are described in the Appendix. Two reviewers assessed study quality independently (EK and YS, supervised by PC). Differences of opinion were resolved through discussion. If needed, the opinion of a third researcher (PC) was sought.

3.7 Data extraction, description and analysis

The following data were extracted from systematic reviews and meta-analyses into an evidence table:

- Reference, search date, searched databases, language restrictions, inclusion criteria (study types, restrictions), number and type of included studies, total number of patients in the systematic reviews, quality appraisal included studies, setting (community, clinical, other), population characteristics, intervention(s) and comparator(s), length of follow up, outcomes at different time points of follow up, sponsoring, conflicts of interest

Data extracted from RCTs:

- Reference, years of inclusion, country
- Patient characteristics: number included, type of recruitment (community; clinical; other); target group (adults in general, specific target group, such as older adults, women with postpartum depression, comorbid somatic disorder, etc)
- Therapy characteristics: type of psychotherapy (according the operationalization given in Appendix 1), treatment format (individual, group, guided self-help), number of treatment sessions (continuous variable), type of pharmacotherapy, category of pharmacotherapy (SSRI, TCA, SNRI, MAOI, other/mixed/protocol).
- Control characteristics: type of control, number of contact moments
- Data on the follow up period: most studies in this field have only used naturalistic follow up. Therefore, for each study we reported how long the follow up period lasted, but also whether there was regular therapeutic contact with a therapist, data on naturalistic help-seeking during follow up, and medication use during follow up. In some studies, outcome data are only reported for patients who responded to treatment in the acute treatment phase, while others report outcomes for the full, intention-to-treat sample. Only intention to treat data were selected

One reviewer (EK) extracted data; a second reviewer (PC) checked the extracted data.

Systematic reviews were described in text and tables. They were not analysed further nor used as the basis of further analysis as the identified systematic reviews answered this guideline´s research questions only partly, by e.g. focussing on subgroups of patients or psychotherapy. Thus, selected reviews served as background information and as a base for comparison of this guideline´s finding with the existing literature, but they were not used in drawing conclusions.

For RCTs, the primary focus was on dichotomous outcomes, but if no dichotomous outcomes were available or if too few studies reported dichotomous outcomes, data were described in text. Otherwise effect sizes were calculated and meta-analyses performed.

3.7.1 Calculation of effect sizes

For each comparison (psychotherapy versus control; psychotherapy versus pharmacotherapy; psychotherapy versus combined; pharmacotherapy versus combined) the odds ratio (OR) of a positive outcome, based on dichotomous results, such as remission and response, or the proportion of patients that no longer met criteria for a depressive disorder according to a diagnostic interview was calculated. If no dichotomous outcomes were reported, the standardized mean difference (SMD) was calculated as the difference in mean scores divided by the pooled standard deviation. It was transformed into the OR according to the procedures given by Borenstein et al.[12] For dichotomous outcomes all randomized patients were taken as the denominator and reported outcomes in completers were taken as the numerator. This was not possible in studies reporting only continuous outcomes in completer samples and thus, these studies were removed in sensitivity analyses.

3.7.2 Meta-analysis

To calculate pooled relative risks, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). Because considerable heterogeneity was expected among the studies, the random effects model was used in order to pool the studies.

As a test of homogeneity of effect sizes, the I^2-statistic was calculated which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity.[17] 95% confidence intervals (CI) were calculated around I^2 [18] using the non-central chi-squared-based approach within the heterogi module for Stata.[19] The Q-statistic was calculated, and reported when significant.

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's[20] trim and fill procedure, which yields an estimate of the effect size after the publication bias has been taken into account (as implemented in Comprehensive Meta-analysis, version 2.2.021). Egger's test of the intercept was conducted in order to quantify the bias captured by the funnel plot and test whether it was significant.[21]

Tests for publication bias may not be valid in case of significant heterogeneity. If high levels of heterogeneity were identified, the method recently developed by Ioannidis et al. was used to determine whether the number of studies reporting a significant result is higher than expected,[22] as another indication for publication bias.

Moderator and subgroup analyses were planned when sufficient studies were available.

3.8 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence.[23] According to GRADE, we classified the quality of evidence into four categories: high, moderate, low, and very low. The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across all studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level. The rating was then downgraded if needed, based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[24]

Observational studies are by default considered low level of evidence. However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   - Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least two studies, with no plausible confounders): upgrade one level
   - Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade two levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: the presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 3. Grading was done by two reviewers independently (YS and EK). Differences of opinion were resolved through discussion. If no consensus could be reached the opinion of another reviewer was decisive (PC). The reasons for up- or downgrading the evidence are stated in the GRADE profiles in the Appendix. Final conclusions were drawn according to the evidence on effectiveness and harms and the quality of this evidence. The phrasing of the conclusions reflects the quality of the evidence according to GRADE; in addition, the quality level (high, moderate, low or very low) is given in parenthesis after each conclusion.

Table 1 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality for RCTs	Factors that may increase the quality for observational studies	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 3 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention.

Quality element	Reasons for downgrading
	Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

3.9 Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by a small working group (KCE experts and GDG president). This first draft was circulated to the guideline development group two weeks prior to the face-to-face meetings (10 December 2013 and 9 May 2014). Recommendations were changed if important new evidence supported this change. A second set of recommendations was then prepared and once more circulated to the guideline development group for final approval.

The strength of each recommendation was assigned using the GRADE system (see Appendices). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences of the patients, and estimated cost (resource utilization).

4 RESULTS RESEARCH QUESTION ONE

4.1 Systematic review

One systematic review was included on maintenance treatment.[25] However, this systematic review did not adequately answer the research question addressed by the present review. Additionally, one review was suggested by a GDG expert at the last expert meeting.[a] None of the studies in this review met the inclusion criteria for the three research questions. Consequently, the results and recommendation are based on the included RCTs, while the included systematic review is used mainly as background information. A flow chart of the search and selection process is presented in the Appendix. Characteristics and outcomes of the included systematic review are shown in Table 4 and further details, including the quality appraisal, can be found in the Appendix. No systematic review was identified that compared acute phase psychotherapy to control groups.

4.1.1 Characteristics of included SR: MBCT vs. control groups

One SR examined acute phase mindfulness based cognitive therapy (MBCT) compared to treatment as usual (TAU) or pill placebo. The authors included RCTs in which the patients met criteria for recurrent MDD in remission according to the DSM-5, DSM-IV, DSM-III-R, DSM-III, Feighner or RDC. However, the primary aim of this review was to examine the effects of maintenance MBCT exclusively.

4.1.2 Results of included SR: maintenance MBCT vs. control groups

Results derived from the meta-analysis of Piet et al. (2011) showed that maintenance MBCT resulted in a better reduction of depressive symptoms in comparison with TAU or pill placebo at six months post-randomization, corresponding to a relative risk reduction of 34% in favour of MBCT (RR: 0.66; 95%CI 0.53 to 0.82, p<0.001)[25] (Table 4).

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[a] Review of Elliot et al. 2013 26. Elliott R, Watson, J., Greenberg, L.S., Timulak, L., & Freire, E. Research on humanistic-experiential psychotherapies. In M.J. Lambert (Ed.), Bergin & Garfield's. Handbook of psychotherapy and behavior change 6th ed. New York: Wiley. ©Wiley; 2013. p. 495-538.

Table 4 – Characteristics of the included SR: maintenance MBCT vs. control groups

Study	Number of studies included ≥ 6 months follow up	Comparison	Results
Piet et al. 2011[25]	5 RCTs	MBCT vs. TAU or placebo	• Relapse RR: 0.66 (95%CI=0.53-0.82, p<0.001), corresponding to a relative risk reduction of 34% in favour of MBCT

CI: Confidence Interval; MBCT: Mindfulness Based Cognitive Therapy; MDD: Major Depressive Disorder; RCTs: Randomized Controlled Trials; RR: Risk Ratio; TAU: Treatment As Usual

4.2 RCTs

39 RCTs were selected for inclusion (23 RCTs on acute phase treatment[27-49] and 16 RCTs on maintenance treatment[50-65]). A flow chart of the study selection process is given in the Appendix (Chapter 3).

4.2.1 Characteristics of included RCTs: psychotherapy (acute phase) vs. control groups

Across the 23 included RCTs on acute phase treatment,[27-49] outpatients were recruited mainly through clinical samples (n=19),[29-31, 33-38, 40-49] while three studies recruited their participants through the community,[27, 28, 31] and one study through both clinical and community referrals.[32] The included studies were conducted in five different countries: Brazil (n=1),[29] the Netherlands (n=2),[43, 47] Sweden (n=1),[31] the United Kingdom (n=10)[27, 28, 32-34, 40-42, 44, 49] and the United States (n=9).[30, 35-39, 45, 46, 48]

All included studies had a naturalistic follow up with a duration of six to 60 months. All randomized participants were included at the follow up assessment, regardless of whether they responded to acute treatment or not. The included RCTs examined six types of psychotherapy: acceptance and commitment therapy, behavioural activation, cognitive behavioural therapy (CBT), interpersonal psychotherapy, psychodynamic therapy or problem solving therapy, with a duration ranging between six to 20 sessions. The majority of the trials provided psychotherapy individually, while one trial conducted group sessions. The control groups used were the following: life style intervention, no further assessment, no scheduled treatment, no specific antidepressant medication (ADM), no standardized control condition, pill placebo, TAU, or waiting list. Characteristics of the included RCTs are presented in Table 5 and further details can be found in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 5 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. control groups

Studies	Recruitment	Incl.	Acute phase PT	N sessions	Continuation phase PT	N patients	Control group	N patients	FU (months)	Outcome	Country
Burns et al. 2013[27]	Com.	All	CBT & TAU	12	No	18	TAU	18	8	Depressive symptoms (CIS-R), QoL (EQ-5D)	UK
Cooper et al. 2003[28]	Com.	All	• CBT • PDT	NR	No	• 43 • 50	TAU	52	60	Remission (SCID)	UK
Duarte et al. 2009[29]	Clinical sample	All	CBT	NR	NR	41	TAU	44	9	Depressive symptoms (BDI)	BR
Elkin et al.1989[30] (Shea et al. 1992)	Clinical sample	All	• CBT • IPT	18	No	• 59 • 61	Placebo & CM	62	18	Recovery (DSM-IV), no relapse (RDC)	US
Folke et al. 2012[31]	Com.	All	ACT	6 (1 individual, 5 group)	No	18	Non standardized control	17	18	Depressive symptoms (BDI), work related outcomes, QoL (WHOQOL brief version)	SE
Kay-Lambkin et al. 2009[32]	Clinical & com. sample	All	• Therapist delivered CBT • Computer delivered CBT	NR	No	• 35 • 32	No further treatment	30	12	Improvement (BDI<17)	UK
Kessler et al. 2009[33]	Clinical sample	All	CBT	10	No	149	WL	148	8	Recovery (BDI<10), QoL (EQ-5D)	UK
Laidlaw et al. 2008[34]	Clinical sample	All	CBT	17	No	21	TAU	23	6	Meeting diagnostic criteria for depression (DSM-IV)	UK
Lustman et al. 1998[35]	Clinical sample	All	CBT	10	No	25	Non-specific ADM	26	6	Remission (BDI≤9), improvement (decrease of ≥50% in BDI scores)	US
Miranda et al. 2003[36]	Clinical sample	All	CBT	8	No	88	TAU	89	12	Depressive symptoms (HRSD)	US

Studies	Recruitment	Incl.	Acute phase PT	N sessions	Continuation phase PT	N patients	Control group	N patients	FU (months)	Outcome	Country
(Miranda 2006[66])											
Mohr et al. 2011[37]	Clinical sample	All	T-CBT	16	No	41	TAU	44	6	Remission (DSM-IV)	US
O'Mahen et al. 2013[38]	Clinical sample	All	CBT	12	No	30	TAU	25	6	Depressive symptoms (BDI)	US
Pagoto et al. 2013[39]	Clinical & com. sample	All	BA	10	No	78	LI	83	12	Response (decrease of ≥50% in BDI and HRSD); remission (BDI <10, HRSD<7)	US
Power et al. 2012[40]	Clinical sample	All	• CBT • IPT	16	No	• 65 • 64	TAU	28	6	Depressive symptoms (BDI)	UK
Qiu et al. 2013[41]	Clinical sample	All	BA	10	No	31	WL	31	6	Depressive symptoms (HRSD), QoL (FACT-B)	UK
Scott et al. 1997[42]	Clinical sample	All	CBT	NR	No	24	TAU	24	12	Depressive symptoms (BDI, HRSD)	UK
Smit et al. 2006[43] (Conradi et al. 2007)	Clinical sample	All	CBT & DRP	10-12	No	44	TAU	72	6	Relapse/recurrence (2 consecutive weeks of depression started within recovery: 2-7 consecutive weeks without depression	NL
Strong et al. 2008[44]	Clinical sample	All	PST & TAU	10	Yes, 8 booster sessions	101	TAU	99	12	Depressive symptoms (SCL-20)	UK
Swartz et al. 2008[45]	Clinical sample	All	IPT	NR	Yes, additional sessions if needed	26	TAU	21	9	Depressive symptoms (BDI, HRDS)	US
Teasdale et al. 1984[46]	Clinical sample	All	CBT	20	Yes, 1 at six weeks after the acute phase treatment	17	TAU	17	6	Remission (BDI<14)	US

Studies	Recruitment	Incl.	Acute phase PT	N sessions	Continuation phase PT	N patients	Control group	N patients	FU (months)	Outcome	Country
Van Schaik et al. 2006[47] (Bosmans et al. 2007[67])	Clinical sample	All	IPT	10	No	69	TAU	74	12	Remission (MADRS<10), response (decrease>50% in MADRS score), recovery (absence of a PRIME-MD diagnosis), QoL (QALY NL)	NL
Weissman et al. 1981[48]	Clinical sample	All	IPT	16	No	13	Non scheduled treatment	16	12	Depressive symptoms (HRSD)	US
Wiles et al. 2013[49]	Clinical sample	All	CBT & TAU	12	Yes, up to 6 session if needed	234	TAU	235	12	Response (50% reduction in BDI scores), remission (BDI<10), QoL (SF-12 mental and physical subscale)	UK

Abbreviations: ACT: Acceptance and Commitment Therapy; BA: Behavioural Activation; BDI: Beck Depression Inventory; BR: Brazil; CH: Switzerland; CIS-R: Clinical Interview Schedule Revised version; CM: Clinical Management; Com: Community; CBT: Cognitive Therapy; DRP: Depression Recurrence Prevention; DSM: Diagnostic and Statistical Manual of Mental Disorders; EQ-5D: EuroQol- 5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast; HRSD: Hamilton Rating Depression Scale; IPT: Interpersonal Psychotherapy; LI: Lifestyle Intervention; MADRS: Montgomery Asberg Depression Rating Scale; MBCT: Mindfulness Based Cognitive Therapy; MDD: Major Depressive Disorder; min.: minutes; NL: The Netherlands; NR: Not Reported; PDT: Psychodynamic Therapy; PST: Problem Solving Therapy; QoL: Quality of Life; RDC: Research Diagnostic Criteria; SCID: Structural Clinical Interview for DSM disorders; SCL-20: Symptom Checklist-20; SF: Short Form health survey; TAU: Treatment As Usual; T-CT: Telephone based Cognitive Therapy; UK: United Kingdom; US: United States; WHOQOL: World Health Organization Quality of Life?; WL: Waiting List

4.2.2 Characteristics of included RCTs: maintenance psychotherapy vs. control groups

Outpatients were recruited from both clinical and community samples[51, 55, 58, 62-64] in six out of the 16 included maintenance RCTs. Five RCTs recruited their participants through clinical samples[50, 52, 53, 60, 68] , one trial through the community [56] and four RCTs did not report their way of recruitment.[54, 57, 59, 65] The included studies were conducted across nine different countries: Belgium (n=1),[55] Canada (n=2),[62, 64] Germany (n=1),[63] Italy (n=2),[52, 53] the Netherlands (n=1),[50] Sweden (n=1),[56] Switzerland (n=1),[51] the United Kingdom (n=1),[60] and the United States (n=6).[54, 57-59, 61, 65] Patients entered into either maintenance psychotherapy or into control groups and were observed extensively from six to 72 months of follow up. The types of maintenance psychotherapy used were: CBT, interpersonal psychotherapy, or mindfulness based cognitive therapy. The types of controls used were: assessment only, clinical management, clinical management and pill placebo, no specified control condition, placebo or TAU. The maintenance psychotherapeutic interventions consisted of eight to 20 sessions that took place either weekly/biweekly or in a period of 14 weeks to eight months. In some cases booster sessions conducted at an interval of four to six months followed the initial sessions. Study characteristics are presented in Table 6, and more details can be found in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 6 – Characteristics of included RCTs: maintenance psychotherapy vs. control groups

Studies	Recruitment	Maintenance psychotherapy	N sessions	N patients	Control group	N patients	Duration (months)	Outcome	Country
Bockting et al. 2005[50] ; Bockting et al. 2009[69]	Clinical sample	CBT & TAU	8 sessions of group CBT	88	TAU	84	66	Relapse/recurrence (SCID)	NL
Bondolfi et al. 2010[51]	Com.& clinical sample	MBCT & TAU	8 sessions of MBCT and 4 booster sessions at 3 months intervals during follow up	31	TAU	29	14	Relapse (SCID)	CH
Fava et al. 1994[52] Note: companion paper with Fava et al. 1996[70] , Fava et al. 1998[71]	Clinical sample	CBT	10 sessions for at least 3 but not more than 5 months	20	CM	20	72	Relapse (RDC)	IT
Fava et al. 1998b[53] (Fava et al. 2004[72])	Clinical sample	CBT	10 weekly sessions	20	CM	20	72	Relapse (RDC)	IT
Frank et al. 1990[54] Note: Companion with Karp et al. 2004[73]	NR	IPT	12 weekly sessions followed by 4 biweekly sessions depending on clients´ progress	26	MC & placebo	23	36	Recurrence (HRSD≥15), survivors (participant who continued in remission HRSD<15; Raskin<7)	US
Godfrin et al. 2010[55]	Com.& clinical sample	MBCT & TAU	8 sessions over 8 weeks	52	TAU	54	14	Relapse (DSM-IV-TR), QoL (QLDS), adverse events (hospitalization)	BE
Hollandare et al. 2011[56]	Com. sample	iCBT	10 CBT modules over 10 weeks	42	Control (not specified)	42	6	Relapse, (MADRS-S≥19), remission (MADRS-S≤6), QoL (WHOQOL-BRIEF)	SE
Jarrett et al. 2000[57]	NR	CBT	10 sessions the first 2 months followed by 6 monthly sessions	6	Placebo	4	18	Relapse (RDC)	US

Studies	Recruitment	Maintenance psychotherapy	N sessions	N patients	Control group	N patients	Duration (months)	Outcome	Country
Jarrett et al. 2013[58]	Com.& clinical sample	CBT	4 biweekly sessions followed by six monthly sessions	86	Placebo	69	32	Relapse (DSM- IV)	US
Klein et al. 2004[59]	NR	CBASP	13 sessions	42	Assessment only	40	12	Recurrence (HRSD-24≥16; DSM-IV)	US
Ma et al. 2004[60]	Clinical sample	MBCT	8 weekly sessions	37	TAU	38	12	Relapse/Recurrence (DSM-III-R)	UK
Schulberg 1996[61]	Clinical sample	IPT	4 monthly sessions	93	TAU	92	8	Depressive symptoms (BDI)	US
Segal et al. 2010[62]	Com. & clinical sample	MBCT	8 weekly sessions	26		30	28	Relapse (HRSD≥16; SCID)	CA
Stangier et al.2013[63]	Com. & clinical sample	CBT	16 sessions over 8 months	90	Manualized psychoeducation	90	12	Relapse (LIFE, DSM-IV)	DE
Teasdale et al. 2000[64]	Com. & clinical sample	MBCT	8 weekly 2h group training sessions	76	TAU	69	15	Relapse/recurrence (meeting DSM-III-R criteria for major depressive episode)	CA
Vittengl et al. 2009[65] Note: Companion with Jarrett et al. 2001[74]	NR	CBT	20 sessions over 12-14 weeks period	41	Assessment control	43	16	Remission (PSRs≥6, DSM-IV), recovery (PSRs≥35 DSM-IV)	US

Abbreviations: BE: Belgium; CA: Canada; CBASP: Cognitive Behavioural Analysis of Psychotherapy; CH: Switzerland; CM: Clinical Management; CBT: Cognitive Behavioural Therapy; CBT: Cognitive Behavioural Therapy; DE: Germany; HRSD: Hamilton Rating Scale for Depression; iCBT: internet based Cognitive Behavioural Therapy; IPT: Interpersonal Psychotherapy; IT: Italy; LIFE: Longitudinal Interval Follow-Up Evaluation; MBCT: Mindfulness Based Cognitive Therapy; NL: The Netherlands; PSRs: Psychiatric Status Ratings; QLDS: QoL in Depression Scale; QoL: Quality of Life; SCID: Structural Clinical Interview for DSM-IV; SE: Sweden; TAU: Treatment As Usual; US: United States; WHOQOL: World Health Organization Quality of Life

4.2.3 *Results of included RCTs: psychotherapy vs. control groups in adults with MDD, acute phase treatment*

Table 7 presents the results of the meta-analyses comparing psychotherapy with control groups in adults with MDD (acute phase treatment). Forest plots of all meta-analyses are given in the Appendix. Twenty-two studies with 2388 participants examined the comparison between acute phase psychotherapy (without treatment continuation) and no treatment control groups at six months or longer post-randomization. Psychotherapy resulted in better treatment response compared to control groups at six months or longer post–randomization (OR=1.96, 95%CI 1.50 to 2.55, p<0.001). Heterogeneity was moderate (I^2=53.72%, 95%CI 28 to 70%, p<0.001). There was some indication of publication bias. With Duval and Tweedie's Trim and Fill procedure showing a decreased adjusted value (OR 1.79, 95%CI 1.28 to 2.30). However, the adjusted valued was still significant (p<0.001) after controlling for publication bias while the Egger's test was not significant. Eleven studies with 1583 participants compared the outcomes of acute phase psychotherapy versus control groups at 1 year or longer post-randomization. Acute phase psychotherapy and ADM discontinuation resulted in a better response to treatment compared to control groups (OR=1.59, 95%CI 1.14 to 2.21, p<0.05) after one year follow up. Heterogeneity between the studies was moderate (I^2=54.76, 95%CI 17 to 75%, p<0.05). There were no indications for publications bias.

Seven studies with 645 participants assessed remission/recovery by a clinical interview at six months or longer post-randomization. Acute phase psychotherapy did not differ significantly in patients remission/recovery (diagnosed by a clinical interview) compared to control groups at six months or longer post-randomization. Similar results were observed for remission/recovery at one year or longer post-randomization, across three studies with 391 participants that examined this comparison; again there were no significant differences between the two conditions.

Seven studies with 884 participants reported on quality of life. Acute phase psychotherapy resulted in a larger improvement of quality of life compared to control groups at six months or longer post-randomization (Cohen's d=0.26, 95%CI 0.12 to 0.39, p<0.001). Heterogeneity between the studies was zero, with a broad 95%CI of 0 to 71%, however. There were no indications for publication bias. A similar pattern of results was observed at one year or longer post-randomization across five studies with 567 participants. Psychotherapy resulted in superior effects compared to control groups (Cohen's d=0.19, 95%CI 0.03 to 0.36, p<0.001) after one year of follow up. Heterogeneity was zero but with a broad 95%CI of 0 to 90% (Table 8).

Work related outcomes were presented only by the study of Folke et al. 2012.[31] They found that 3 out of 18 patients in the psychotherapy group and 2 out of 16 patients in the control group were declared fit and employed; 3 out of 18 patients in the psychotherapy group and 4 out of 16 patients in the control group were declared fit and unemployed; 8 of 18 patients in the psychotherapy group and 9 of 16 patients in the control group had a disability pension; and finally 4 of 18 patients in the psychotherapy group and 1 of 16 patients in the control group were on continued sick-leave and were unemployed.

Regarding safety and adverse events, Strong et al. 2008[44] reported that during follow up there were 11 cancer-related deaths and one death by suicide in the TAU group vs. seven cancer-related deaths in the problem solving therapy & TAU group. Finally, Weissman et al. 1981[48] mentioned that one patient assigned to interpersonal psychotherapy and two patients assigned to non-scheduled treatment were hospitalized.

Table 7 – Meta-analysed outcomes: psychotherapy vs. control groups in adults with MDD, acute phase treatment

Outcome	N	OR	95%CI	I²	95%CI
Response at 6 months or longer post-randomization	22	1.96**	1.50 to 2.55	53.72%	28 to 70
Response at 1 year or longer post-randomization	11	1.59*	1.14 to 2.21	54.76%	17 to 75
Remission/recovery (diagnosed by clinical interview) at 6 months or longer post-randomization	7	1.28	0.85 to 1.91	33.78%	0 to 69
Remission/recovery (diagnosed by clinical interview) at 12 months or longer post-randomization	3	1.04	0.52 to 1.96	35.93%	0 to 76

p<0.05;p<0.001*

Abbreviations: CI: Confidence Intervals; N: Number of studies OR: Odds Ratio;

Table 8 – Meta-analysed outcomes: quality of life after psychotherapy vs. control groups in adults with MDD, acute phase treatment

Outcome	N	Cohen's d	SE	95%CI	I²	95%CI
Quality of life at 6 months or longer post-randomization	7	0.26**	0.06	0.12 to 0.39	0%	0 to 71
Quality of life at 1 year or longer post-randomization	3	0.20*	0.08	0.03 to 0.36	0%	0 to 90

p<0.05;p<0.001*

Abbreviations: CI: Confidence Intervals; N: Number of; OR: Odds Ratio; SE: Standard Error

4.2.4 Results of included RCTs: psychotherapy vs. control groups in adults who had had MDD, maintenance treatment

Table 9 shows the results of the comparison between maintenance psychotherapy and control groups. Forest plots of meta-analyses are given in the Appendix. Sixteen studies with 1453 participants compared the effects of maintenance psychotherapy versus control groups at six months or longer post-randomization. Maintenance psychotherapy resulted in a better sustained response to treatment, compared to control conditions after six months or longer follow up in patients who had had MDD (OR=2.37, 95%CI 1.78 to 3.14, p<0.001). The heterogeneity was low (I^2=30%, p<0.001) with a 95%CI of 0 to 62%. There was some indication for publication bias. Using Duval and Tweedie's Trim and Fill the point estimated changed to OR=2.04 (95%CI 1.49 to 2.80), and the Egger's test was also significant (p<0.05).

Six RCTs with 466 participants evaluated the difference in sustained response to maintenance psychotherapy compared to control groups at two years or longer post-randomization. Results of the meta-analyses indicated that maintenance psychotherapy outperformed control groups in patients´ sustained response to treatment at two years or longer post-randomization (OR=2.19, 95%CI 1.17 to 4.09, p<0.014). The heterogeneity was moderate (I^2=42, 95%CI 0 to 77%, p<0.05). Publication bias was observed for this comparison as well with the imputed Duval and Tweedie's estimate OR=1.59 (95%CI 0.76 to 3.30), however, the Egger's test was not significant.

Eleven studies with 946 participants assessed no relapse according to a diagnostic interview at six months or longer post-randomization. Psychotherapy outperformed control comparison conditions (OR=3.34, 95%CI 1.60 to 3.41, p<0.001). Heterogeneity between the studies was moderate (I^2=39.80, 95%CI 0 to 70%, p<0.001). There was some indication for publication bias. The imputed Duval and Tweedie's estimate was OR=1.80 (95%CI 1.16 to 2.77) and the Eggers test was significant (p<0.05).

Similar results were obtained for no relapse rates at two years or longer post-randomization across five studies. Psychotherapy significantly outperformed control groups (OR=2.46, 95%CI 1.26 to 4.82, p<0.05). Heterogeneity between the studies was moderate (I^2=47.71, 95%CI 0 to 81%, p<0.001). However, there was some indication of publication bias. Using Trim and Fill the imputed point estimate was OR=1.66 (95%CI 1.13 to 2.45) but Egger's test was not significant (p>0.05).

Only the study of Godfrin et al. 2010[55] reported on quality of life. They found that at 14 months, patients from the MBCT & TAU group had a mean score of 9.13 (SD=7.84; n=52) on the Quality of Life in Depression Scale, while patients from the TAU group had a slightly better mean score of 10.90 (SD=8.69, n=54).

No studies reported on work related outcomes and only two studies reported on adverse events. Godfrin et al. 2010[55] stated that 2.6% of patients from the MBCT & TAU group were hospitalized, while no such incidence was reported for the TAU group. Finally Stangier et al. 2013[63] referred that two patients died by suicide (one after discontinuing CBT and one after completing manualized psychoeducation).

Table 9 – Meta-analysed outcomes: psychotherapy vs. control groups in adults who had had MDD and responded to acute phase treatment, maintenance treatment

Outcome	N	OR	95%CI	I^2	95%CI
Sustained response at 6 months or longer post-randomization	16	2.37**	1.78 to 3.14	30.47%	0 to 62
Sustained response at 2 years or longer post-randomization	6	2.19*	1.17 to 4.09	42.34%	0 to 77
No relapse (diagnosed by a clinical interview) at 6 months or longer post-randomization	11	3.34**	1.60 to 3.41	39.80%	0 to 70
No relapse (diagnosed by a clinical interview) at 12 months or longer post-randomization	5	2.46*	1.26 to 4.82	47.71%	0 to 81

p<0.05;p<0.001*
Abbreviations: CI: Confidence Intervals; N: Number of studies; OR: Odds Ratio

4.3 Conclusions: Main psychotherapy interventions only vs. no treatment

- There is limited evidence that psychotherapy results in a better acute phase treatment response compared to control groups, at 6 months or longer after the start of treatment, in adult patients with MDD (low level of evidence).
- There is limited evidence that psychotherapy results in a better acute phase treatment response compared to control groups, at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- There is limited evidence that psychotherapy results in a better quality of life compared to control groups (in acute phase and maintenance treatment), at 6 months or longer and at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- It is plausible that maintenance treatment with psychotherapy results in a better sustained response compared to control groups at 6 months or longer and at 2 year or longer after the start of maintenance treatment, in adult patients who had had MDD and who responded to acute phase treatment (moderate level of evidence).

5 RESULTS RESEARCH QUESTION TWO

5.1 Systematic reviews

Three systematic reviews were included, all on acute phase treatment.[75-77] None of them answered the research question in full, and thus conclusions and recommendations are not based on these reviews but on a primary analysis of RCTs (see below). The three reviews are described here as background information (what is known at present about the long-term effects of psychotherapy), and for comparative purposes with the present guideline.

No systematic reviews on maintenance treatment were identified. An overview of the search and selection process is given in the Appendix. Characteristics and outcomes of the three reviews are presented in

Table 10 and more details can be found in the Appendix (Chapter 5).

5.1.1 Characteristics of included SRs: psychotherapy vs. ADM

The three reviews evaluated acute phase psychotherapy compared to ADM.[75-77] Among the examined types of psychotherapy were CBT, interpersonal psychotherapy or psychodynamic counselling delivered either face to face or by a computerized program. They included RCTs with participants meeting criteria for MDD according to the DSM5, DSM-IV, DSM-III-R, DSM-III, Feighner or RDC. However, the primary aim of two[75, 77] of the three included reviews was to examine the short-term effects of psychotherapy compared to ADM. Consequently, these reviews presented long-term effects as a secondary analysis only, and in one case, consisted

of a small numbers of included trials.[75] Only the systematic review of Cuijpers et al.[76] focused primarily on long-term effects. However, Cuijpers et al.[76] focused exclusively on the effects of CBT in comparison with ADM. As a result, none of the included reviews adequately answered the research question.

5.1.2 Results of included SRs: psychotherapy vs. ADM

Bortolotti et al.[75] found that psychotherapy resulted in an almost equal reduction of depressive symptoms compared to ADM, six months post-randomization (d=0.03, 95%CI -0.21 to 0.26, p=0.52). Gloaguen et al.[77] analysed eight studies comparing psychotherapy with ADM and found that 29.5% of patients relapsed (defined as a BDI<10) after psychotherapy, compared to 60% of patients after ADM. Finally, Cuijpers et al.[76] examined the long-term treatment response to CBT vs. ADM as a treatment for MDD. The results, based on eight studies, showed that acute phase CBT resulted in a better treatment response compared to ADM discontinuation at six months or longer post-randomization (OR=2.61, 95%CI 1.58 to 4.31, p<0.001).

Table 10 – Characteristics and outcomes of the included SRs: psychotherapy vs. ADM

Studies	N studies incl. with a follow up ≥ 6 months	Comparison	Results
Bortolotti et al. 2008[75]	3	PST, IPT, CBT, counselling vs. ADM	• Depressive symptoms Cohen's d=0.03 (95%CI -0.21 to 0.26; p=0.52)
Gloaguen et al. 1998[77]	8	CBT vs. ADM	Relapse (BDI<10 effect sized were calculated by Olkin d • CBT: 29.5% • ADM: 60% • No statistical tests were reported
Cuijpers et al. 2013[76]	9	CBT vs. ADM	• Acute phase CBT vs. ADM discontinuation: response OR=2.61, 95%CI 1.58 to 4.31, p<0.001 • Acute phase CBT vs. ADM continuation response OR=1.62, 95%CI 0.97 to 2.72 p<0.1

Abbreviations: ADM: Antidepressant Medication; BDI: Beck Depression Inventory; CI: Confidence Intervals; CBT: Cognitive Behavioural Therapy; Incl.: Inclusion; IPT: Interpersonal Psychotherapy; MDD: Major Depressive Disorder; N: Number; OR: Odds Ratio; PST: Problem Solving Therapy; PTD: Psychodynamic Therapy

5.2 RCTs

22 RCTs were selected for inclusion.[36, 48, 54, 57, 58, 61, 62, 78-92] Fifteen RCTs were on acute phase treatment[36, 48, 78-86, 89-92] and seven RCTs were on maintenance treatment.[54, 57, 58, 61, 62, 87, 88] An overview of the search and selection process is given in the Appendix (Chapter 3).

5.2.1 Characteristics of included RCTs: psychotherapy (acute phase) vs. ADM

In the 15 studies on acute phase treatment,[36, 48, 78-86, 89-92] 8 studies included outpatients recruited through clinical samples,[36, 48, 78, 80, 82, 89, 91, 92] and seven studies recruited both clinical and community samples.[79, 81, 83-86, 90] RCTs were conducted in five different countries: Canada (n=1),[90] the Netherlands (n=2),[80, 86] Romania (n=1),[79] the United Kingdom (n=2),[78, 89] and the United States (n=9).[36, 48, 81-85, 91, 92] The majority of the studies had a naturalistic follow up with a duration ranging from six months to two years. Eight studies only followed up on participants who responded to acute treatment,[78, 80-84, 90, 92] while seven studies included all of the initially randomized participants.[36, 48, 79, 85, 86, 89, 91] The six types of psychotherapy examined by the included studies were behavioural activation, CBT, interpersonal psychotherapy, problem solving therapy, psychodynamic psychotherapy, or rational emotive behavioural therapy. The duration of the psychotherapeutic treatments ranged from eight to 24 individual sessions in a period of six to 16 weeks. During follow-up two studies offered three to four booster session of psychotherapy, usually at an interval of one month between sessions.[78, 79, 83] The remaining trials did not offer additional psychotherapeutic treatment sessions after the acute treatment phase.

The antidepressant medications used were amitriptyline, citalopram, clomipramine, fluoxetine, fluvoxamine, imipramine hydrochloride, nortriptyline, paroxetine, sertraline, or venlafaxine. In five studies participants continued to receive ADM during follow up,[36, 79, 80, 83, 90] in nine studies ADM was tapered or discontinued after the acute phase treatment [48, 78, 82, 84-86, 89, 91, 92] ; and in one study patients had the option to continue or to stop ADM.[81] Characteristics of the included studies are given in Table 11 and more details can be found in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 11 – Characteristics of the included RCTs: psychotherapy (acute phase) vs. ADM

Studies	Recruitment	Incl.	Acute phase PT	N sessions	Continuation phase PT	N patients	Acute phase ADM	Contin. phase ADM	N patients	FU (months)	Outcome	Country
Blackburn et al. 1986[78]	Clinical sample	Resp.	CBT	23	4 booster sessions	15	Amitriptyline or clomipramine	No	10	24	Depressive symptoms (CES-D, BDI); Relapse (HRSD≥8)	UK
David et al. 2008[79]	Com. & clinical sample	All	• CBT • REBT	20	3 booster sessions	• 56 • 57	Fluoxetine	Yes	57	6	Remission (HRSD<7), relapse (according to DSM)	RO
Dekker et al. 2013[80]	Clinical sample	Resp.	PDT	16	No	59	SNRI venlafaxine	Yes	44	6	Depressive symptoms (HRSD)	NL

Studies	Recruitment	Incl.	Acute phase PT	N sessions	Continuation phase PT	N patients	Acute phase ADM	Contin. phase ADM	N patients	FU (months)	Outcome	Country
Dobson et al. 2008[81]	Com. & clinical sample	Resp.	• CBT • BA	24	No	• 30 • 27	Paroxetine	Both	28	12	Relapse (HRSD≥14), PSR≥5)	US
Evans et al. 1992[82]	Clinical sample	Resp.	CBT	20	No	10	Imipramine	No	10	24	Relapse (BDI≥16)	US
Hollon et al. 2005[83]	Com. & clinical sample	Resp.	CBT	20	3 booster sessions	35	Paroxetine	Yes	34	12	Relapse (HDRS-17≥14)	US
Kovacs et al. 1981[84]	Com. & clinical sample	Resp.	CBT	20	No	18	Imipramine	No	17	12	Remission (BDI<16)	US
Mohr et al. 2001[85]	Com. & clinical sample	All	CBT	16	No	20	Sertaline	No	21	6	Depressive symptoms (BDI)	US
Moradveisi et al. 2013[86]	Com. & clinical sample	All	BA	16	No	50	Sertaline	No	50	49	Remission (HRSD≤7; BDI≤10)	NL
Miranda et al. 2003[93]	Clinical sample	All	CBT	8	No	88	Paroxetine	Yes	90	12	Depressive symptoms (HRSD)	US
Mynors-Wallis et al. 2000[89]	Clinical sample	All	• PST (GP) • PST (nurse)	6	No	39	Fluvoxamine	No	41	52	Recovery (HRSD-17≤7)	UK
Segal et al. 2006[90]	Com. & clinical sample	Resp.	CBT	20	No	59	Paroxetine hydrochloride	Yes	40	18	Relapse (according to DSM-IV)	CA
Shea et al. 1992[91]	Clinical sample	All	• CBT • IPT	18	No	• 59 • 61	Imipramine	No	57	18	Recovery (DCM-IV), no relapse (RDC)	US
Simons et al. 1986[92]	Clinical sample	Resp.	CBT	20	No	19	Nortriptyline	No	16	12	Responders (BDI<10)	US
Weissman et al. 1981[48]	Clinical sample	All	IPT	16	No	13	Amitriptyline	No	15	12	Depressive symptoms (HRSD)	US

Abbreviations: ADM: Antidepressant Medication; BA: Behavioural Activation; BDI: Beck Depression Inventory; Com: Community; CBT: Cognitive Behavioural Therapy; DD: Disorder Diagnosis; DSM: Diagnostic and Statistical Manual; FU: Follow up; GP: General Practitioner; HRSD: Hamilton Rating Scale for Depression; Incl.: Inclusion; IPT: Interpersonal Psychotherapy; MDD: Major Depressive Disorder; N: Number; NL: Netherlands; PSR: Psychiatric Status Rating; PS: Problem Solving Therapy; PTD: Psychodynamic Psychotherapy; RCD: Research Diagnostic Criteria; REBT: Rational Emotive Behavioural Therapy; Resp.: Responders; RO: Romania; UK: United Kingdom; US: United States

5.2.2 *Characteristics of included RCTs: maintenance psychotherapy vs. ADM*

Participants were outpatients recruited mainly from clinical samples in the seven maintenance RCTs.[54, 57, 58, 61, 62, 87, 88] One study recruited participants from both clinical and community samples,[58] while two studies did not specify the way of recruitment.[54, 57] One RCT was conducted in Canada,[62] two in the United Kingdom,[87, 88] and four United States.[54, 58, 61, 94] After acute treatment, participants who responded positively entered into maintenance therapies of either psychotherapy or ADM and were observed extensively.

The three types of psychotherapy used were CBT, interpersonal psychotherapy and MBCT. The number, interval, and duration of the psychotherapeutic maintenance treatments varied across studies. The time span of the maintenance therapy ranged between eight weeks to 12 months and the number of sessions varied from six to 20. In one study, the maintenance phase started with weekly sessions and continued biweekly and monthly thereafter,[87] while in another trial the frequency of the psychotherapeutic sessions was based on the degree of participants' response.[54] The remaining trials provided weekly sessions. The antidepressant agents used were amitriptyline, citalopram hydrobromide, fluoxetine, imipramine, nortriptyline hydrochloride, paroxetine or phenelzine.

Study characteristics are presented in Table 12, and in further details can be found in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 12 – Characteristics of the included RCTs: maintenance psychotherapy vs. ADM

Studies	Recruitment	Maintenance psychotherapy	N sessions	N patients	Maintenance ADM	N patients	Duration (months)	Outcome	Country
Blackburn et al. 1997[87]	Clinical sample	• CBT (in acute phase patients received CBT) • CBT (in acute phase patients received ADM)	3 sessions during the 1st month, 2 sessions during the 2nd month, 1 monthly session thereafter	• 27 • 22	Amitriptyline or fluoxetine	26	24	Depressive symptoms (HRSD; BDI)	UK
Frank et al. 1990[54]	NR	IPT	12 weekly sessions followed by 4 biweekly sessions depending on clients progress	26	Imipramine	28	36	Recurrence (HRSD≥15), survivors (participants who continued in remission HRSD<15; Raskin<7)	US
Jarrett et al. 2000[57]	NR	CBT	10 sessions the first 2 months, followed by 6 monthly sessions	6	Phenelzine	6	18	Relapse (RDC)	US
Jarrett et al. 2013[58]	Com. & clinical sample	CBT	4 biweekly sessions followed by 6 monthly sessions	86	Fluoxetine	86	32	Relapse (DSM-IV)	US
Kuyken et al. 2008[88]	Clinical sample	MBCT	8 sessions during 8 weeks	61	In line with British National Formulary	62	15	Relapse/recurrence (DSM-IV)	UK
Schulberg et al. 1996[61]	Clinical sample	IPT	4 monthly sessions	93	Nortriptyline	91	8	Depressive symptoms (BDI)	US
Segal et al. 2010[62]	Com. & clinical sample	MBCT	8 weekly sessions	26	Citalopram hydrobromide	28	18	Relapse (HRSD≥16; SCID)	CA

Abbreviations: ADM: Antidepressant Medication; BDI: Beck Depression Inventory; CA: Canada; Com: Community; CBT: Cognitive Behavioural Therapy; DSM: Diagnostic and Statistical Manual; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; MBCT: Mindfulness based Cognitive Therapy; N: Number; RCD: Research Diagnostic Criteria; SCID: Structured Clinical Interview for DSM Disorders; UK: United Kingdom; US: United States

5.2.3 *Results of included RCTs: psychotherapy vs. ADM in adults with MDD, acute phase treatment*

Table 13 shows the results of the meta-analyses comparing psychotherapy with ADM in adults with MDD (acute phase treatment). Forest plots of all meta-analyses are presented in the Appendix. Nine studies with 501 participants compared the outcomes of acute phase psychotherapy (without continuation treatment) versus ADM (which was discontinued at some point during the follow-up period) at six months or longer post-randomisation. Psychotherapy resulted in a better treatment response compared to ADM after six months or longer post-randomization (OR=1.88, 95%CI 1.11 to 3.18, $p<0.05$). Heterogeneity was moderate ($I^2=49\%$, $p<0.05$) but with a broad 95%CI of 1-74%. Six studies with 612 participants examined the outcomes of acute phase psychotherapy (without continuation treatment) versus ADM (which was continued during the full follow-up period) on participants' response to treatment at six months follow up or longer. There was no evidence that psychotherapy or ADM continuation resulted in superior outcomes.

Only three studies with 315 participants examined the comparison between acute phase psychotherapy and ADM continuation at follow up longer than one year. No significantly different results were observed between the two conditions. However, the comparison between acute phase psychotherapy and ADM discontinuation resulted in a better response to treatment in favour of psychotherapy (OR=1.91, 95%CI 1.07 to 3.42, $p<0.05$) after one year follow up. Heterogeneity between the studies was moderate ($I^2=53.64\%$, $p<0.05$) however the 95%CI was broad (8 to77%).

No studies reported on quality of life or work related outcomes, and only three studies reported on adverse events. David et al. 2008 reported that ten patients experienced adverse effects: 9/49 patients receiving ADM (one patient had panic attacks, two patients had anxiety and insomnia, one patient experienced crying and anger, two patients had restlessness and three had insomnia), 0/52 following rational emotive behavioural therapy and 1/50 following CBT experienced insomnia.[79] Moradveisi et al. 2013 referred that three patients dropped out due to medication side effects,[86] Weissman et al. 1981 reported that three patients (one followed psychotherapy and two receiving ADM) were hospitalized.[48] No suicides were reported.

Table 13 – Meta-analysed outcomes: psychotherapy vs. ADM in adults with MDD, acute phase treatment

Outcome	N	OR	95%CI	I^2	95%CI
Response to psychotherapy vs. ADM (no continuation) at six months or longer post-randomization	9	1.88	1.11 to 3.18*	49%	1 to 74%
Response to psychotherapy vs. ADM (+ continuation) at six months or longer post-randomization	6	1.30	0.90 to 1.88	20%	0 to 63%
Response to psychotherapy vs. ADM (no continuation) at 1 year or longer post-randomization	8	1.91	1.07 to 3.42*	53%	8 to 77%
Response to psychotherapy vs. ADM (+ continuation) at 1 year or longer post-randomization	7	1.63	0.99 to 2.69	0%	0 to 85%

**p<0.05*
Abbreviations: CI: ADM: Antidepressant Medication; Confidence Intervals; N: Number of studies; NNT: Numbers Needed to Treat; OR: Odds Ratio

5.2.4 Results of included RCTs: psychotherapy vs. ADM in adults who had had MDD, maintenance treatment

Table 14 presents the results of the comparison between maintenance psychotherapy and maintenance antidepressants. Forest plots of all meta-analyses are presented in the Appendix. Seven studies with 646 participants compared the effects of maintenance psychotherapy to those of maintenance ADM at eight months follow up or longer. Results indicated that maintenance psychotherapy and maintenance ADM did not differ significantly from each other. Further, at two years follow up maintenance psychotherapy did not differ significantly from ADM across four studies with 285 participants.

No studies reported on quality of life or work related outcomes, and only one study reported on adverse events. Jarrett et al. 2013 stated that during maintenance two patients from each condition (ADM, CBT) were hospitalized for worsening depression and/or suicidal ideation. No suicides were reported.

Table 14 – Meta-analysed outcomes: psychotherapy vs. antidepressants in adults who had had MDD and responded to acute phase treatment, maintenance treatment

Outcome	N	OR	95%CI	I^2	95%CI
Sustained response at 8 months or longer post-randomization	7	1.05	0.76 to 1.45	0%	0 to 68%
Sustained response at 2 years or longer post-randomization	4	0.86	0.51 to 1.49	0%	0 to 89%

Abbreviations: ADM: Antidepressant Medication; CI: Confidence Intervals; N: Number of studies; OR: Odds Ratio

5.3 Conclusions: Main psychotherapy interventions only vs. antidepressants

- There is limited evidence that psychotherapy results in a better acute phase treatment response compared to ADM (without continuation), at 6 months and at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- There is limited evidence that psychotherapy results in an equal response to treatment, compared to ADM (continuation), at 6 months and at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- It is plausible that maintenance treatment with psychotherapy results in an equally sustained response, compared to maintenance treatment with ADM at 8 months or longer after the start of maintenance treatment, in adult patients who had MDD and who responded to acute phase treatment with either psychotherapy or ADM (high level of evidence).
- There is limited evidence that maintenance treatment with psychotherapy results in an equally sustained response, compared to maintenance treatment with ADM, at 2 years or longer after the start of maintenance treatment, in adults patients who had MDD and responded to acute phase treatment with either psychotherapy or ADM (low level of evidence).

6 RESULTS RESEARCH QUESTION THREE

6.1 Systematic reviews

No systematic review was identified for the examined comparisons.

6.2 RCTs

Twenty-two RCTs[48, 54, 78, 89, 92, 95-111] were selected for inclusion (15 RCTs on acute phase treatment [44, 74, 85, 88, 91-101] and seven RCTs on maintenance treatment[54, 106-111]). A flow chart of the study selection process is given in the Appendices.

6.2.1 Characteristics of included RCTs: combined psychotherapy and ADM (acute phase) vs. psychotherapy

Across all seven included studies patients were recruited through clinical samples.[48, 78, 89, 92, 95-97] The included RCTs were conducted in three different countries: the Netherlands (n=1),[96] the United Kingdom (n=2)[78, 89] and the United States (n=4).[48, 92, 95, 97] The duration of follow up ranged from six to 24 months. The majority of the studies included all randomized participants at the follow up assessment, regardless of whether they responded to acute phase treatment. However, two studies only included responders to acute phase treatment in their follow up.[92, 97] The types of psychotherapy examined were: CBT, interpersonal psychotherapy, psychodynamic supportive therapy and problem solving therapy with a duration of six to 23 sessions. All included trials provided psychotherapy individually. The antidepressant agents used were the following: amitriptyline hydrochloride, fluvoxamine, imipramine hydrochloride, nortriptyline or paroxetine. Characteristics of the included studies are given in Table 15 and in further detail in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 15 – Characteristics of the included RCTs: combined psychotherapy and ADM (acute phase) vs. psychotherapy

Studies	Recruitment	Incl.	Acute phase combined therapy	N sessions	Cont. phase combined therapy	N patients	Acute phase PT	Contin. phase PT	N patients	FU (months)	Outcome	Country
Beck et al. 1985[95]	Clinical sample	All	CBT & amitriptyline hydrochloride	20	No	15	CBT	No	18	6, 12	Depressive symptoms (BDI ; HRSD)	US
Blackburn et al. 1986[78]	Clinical sample	All	CBT & amitriptyline or clomipramine	23	4 booster sessions	16	CBT	Yes	15	24	Relapse (HRSD≥8; BDI≥9)	UK
De Jonghe et al. 2004[96] Companion with Koppers et al. 2011[112]	Clinical sample	All	PDST & nortriptyline or SSRI	16	No	101	PDST	No	107	6	Remission (HRSD≤7) Recurrence (CIDI)	NL
Hollon et al. 1992[97] ; Evans et al. 1992[82]	Clinical sample	Resp.	CBT & imipramine hydrochloride	20	No	13	CBT	No	10	24	Relapse (BDI≥16)	US
Mynors-Wallis et al. 2000[89]	Clinical sample	All	PS & fluvoxamine or paroxetine	6	No	35	• PS (GP) • PS (nurse)	No	• 39 • 41	13	Recovery (HRSD-17≤7)	UK
Simons et al. 1986[92]	Clinical sample	Resp.	CBT & nortriptyline	20	No	18	CBT	No	19	12	Response (BDI<10)	US
Weissman et al. 1981[48]	Clinical sample	All	IPT & amitriptyline hydrochloride	16	No	18	IPT	No	13	12	Depressive symptoms (HRSD)	US

Abbreviations: BDI: Beck Depression Inventory; BDT: Brief Dynamic Therapy; CIDI: Composite International Clinical Interview; Contin: continuation; CBT: Cognitive Behavioural Therapy; FU: Follow Up; GP: General Practitioner; HRSD: Hamilton Rating Scale for Depression; Incl: included; IPT: Interpersonal Psychotherapy; IT: Italy; N: Number; NL: Netherlands; PDST: Psychodynamic Supportive Therapy; PS: Problem Solving; PT: Psychotherapy; Resp: responders; SSRI: Selective Serotonin Reuptake Inhibitor; UK: United Kingdom; US: United States

6.2.2 Characteristics of included RCTs: combined psychotherapy and ADM (acute phase) vs. ADM

The majority of the included RCTs recruited their participants through clinical samples (n=12),[48, 78, 89, 92, 97-100, 102-105] while one RCT recruited patients through both clinical and community referrals.[101] Eleven out of the 13 trials recruited outpatients, while two studies included inpatients.[102, 103] The studies were conducted across nine different countries: Germany (n=1),[103] Italy (n=3)[98, 100, 101] the Netherlands (n=1),[105] the United Kingdom (n=3),[78, 89, 99] and the United States (n=5).[48, 92, 97, 102, 104] The length of follow up was six to 48 months. Three studies followed only participants who had responded to acute phase treatment and the remaining trials included all randomized patients at follow up. Six types of psychotherapy were examined by the included studies: brief dynamic therapy, CBT, interpersonal psychotherapy, psychodynamic supportive therapy, problem solving therapy or rationale emotive therapy with a duration ranging between six to 29 sessions. Psychotherapy was provided individually in all trials. The antidepressant agents used were the following: amitriptyline hydrochloride, fluoxetine, fluvoxamine, imipramine hydrochloride, nortriptyline, paroxetine or sertraline. Characteristics of the included studies are presented in Table 16 and in and further detail in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 16 – Characteristics of the included RCTs: combined psychotherapy and ADM (acute phase) vs. ADM

Studies	Recruitment	Incl.	Acute phase combined therapy	N sessions	Continuation phase combined therapy	N patients	Acute phase ADM	Contin phase ADM	N patients	FU (months)	Outcome	Country
Bellino et al. 2006[98]	Clinical sample	All	IPT & fluoxetine	NR	No	20	Fluoxetine	No	19	6	Depressive symptoms (HRSD), QoL (SAT-P)	IT
Blackburn et al. 1986[78]	Clinical sample	All	CBT & amitriptyline or clomipramine	23	4 booster sessions	16	Amitriptyline or clomipramine	Yes	10	24	Relapse (HRSD≥8; BDI≥9)	UK
De Jonghe et al. 2001[105]	Clinical sample	All	PDST & nortriptylin or SSRI	16	No	83	Nortriptylin or SSRI	No	84	6, 9	Depressive symptoms (HRSD), QoL (QLDS)	NL
Hollon et al. 1992[97] Note : companion with Evans et al. 1992[82]	Clinical sample	Resp.	CBT & imipramine hydrochloride	20	No	13	Imipramine hydrochloride	No	10	24	Relapse (BDI≥16)	US
Macaskill et al. 1996[99]	Clinical sample	Resp.	RET & lofepramine	29	No	10	Lofepramine	No	10	6	Depressive symptoms (HRSD; BDI)	UK
Maina et al. 2009[100]	Clinical sample	Resp.	BDT & paroxetine	15-30	No	65	Paroxetine	No	83	6, 48	Remission (HRSD≤7)	IT
Maina et al. 2010[101]	Com. & clinical sample	All	BDT & fluvoxamine	10-16	Continuation of fluvoxamine	25	Fluvoxamine	No	29	12	Remission (HRSD≤7), success (CGI:1-2)	IT
Miller et al. 1989[102]	Inpatients	All	CBT & amitriptyline or desipramine	25	No	28	Amitriptyline or desipramine	No	17	6, 12	Relapse (BDI≥16; HRSD≥17), remission	US

											(HRDS≤7; BDI≤9),	
Mynors-Wallis et al. 2000[89]	Clinical sample	All	PS & fluvoxamine or paroxetine	6	No	35	Fluvoxamine or paroxetine	No	36	13	Recovery (HRSD-17≤7)	UK
Schramm et al. 2007[103]	Inpatients	All	IPT & sertraline or amitriptyline	65	No	65	Sertraline or amitriptyline	No	65	12	Relapse (HRSD≥15, psychiatric status ratings score of ≥5), sustained response (50% of symptoms reduction on HRSD), recovery (HRSD≤7)	DE
Simons et al. 1986[92]	Clinical sample	Resp.	CBT & nortriptyline	20	No	18	Nortriptyline	No	16	12	Response (BDI<10)	US
Sirey et al. 2005[104]	Clinical sample	All	CBT & ADM (not specified)	6	Telephone calls at 8 and 10 weeks after randomization	21	ADM (not specified)	No	24	6	Response (HRSD≤10	US
Weissman et al. 1981[48]	Clinical sample	All	IPT & amitriptyline hydrochloride	16	No	18	Amitriptyline hydrochloride	No	15	12	Depressive symptoms (HRSD)	US

Abbreviations: ADM: Antidepressant Medication; BDI: Beck Depression Inventory; BDT: Brief Dynamic Therapy; Com: community; Contin: continuation; CBT: Cognitive Behavioural Therapy; DBT: Dialectical Behaviour Therapy; DE: Germany; FU: Follow UP; HRSD: Hamilton Rating Scale for Depression; Incl: included; IPT: Interpersonal Psychotherapy; IT: Italy; N: number; NL: Netherlands; PDST: Psychodynamic Supportive Therapy; PS: Problem Solving; PT: Psychotherapy; QLDS: Quality of Life in Depression Scale; QoL: Quality of Life; Resp.: Responders; RET: Rationale Emotive Therapy; SAT-P: Satisfaction Profile; SSRI: Selective Serotonin Reuptake Inhibitor; UK: United Kingdom; US: United States

6.2.3 Characteristics of included RCTs: maintenance combined psychotherapy and ADM vs. maintenance psychotherapy

Only one study examined the effects of maintenance psychotherapy combined with ADM compared to maintenance psychotherapy.[54] Frank et al. 1990 compared maintenance imipramine with maintenance interpersonal psychotherapy combined with imipramine. They recruited their participants through a clinical sample and the study was conducted in United States. The length of follow up was 36 months and the sessions were provided weekly initially, subsequently biweekly and finally monthly[54] (Table 17).

Table 17 – Characteristics of the included RCTs: combined maintenance psychotherapy and ADM vs. maintenance psychotherapy

Studies	Recruitment	Acute phase combined therapy	N sessions	N patients	PT	N patients	FU (months)	Outcome	Country
Frank et al. 1990[54]	Clinical sample	IPT & imipramine	2 weekly sessions followed by 8 months biweekly sessions and then monthly	25	IPT	26	36	Recurrence (HRSD≥15), survivors (participants who continued in remission HRSD<15; Raskin<7)	US

Abbreviations: FU: Follow Up; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; N: Number; PT: Psychotherapy; US: United States

6.2.4 Characteristics of included RCTs: maintenance combined psychotherapy and ADM vs. maintenance ADM

Outpatients were recruited from clinical samples in five[54, 108-111] out of the seven included maintenance RCTs. One RCT recruited their participants through community samples[106] and one RCT did not report the way of recruitment.[113] Two studies were conducted in the United Kingdom[109, 111] and five studies were conducted in the United States.[54, 106-108, 110] Patients entered into either maintenance psychotherapy combined with ADM or into maintenance ADM groups and were followed from six to 24 months. The types of maintenance psychotherapy examined: CBT, interpersonal psychotherapy or social skills training. The antidepressant agents used were: amitriptyline hydrochloride, fluoxetine, imipramine or paroxetine. The maintenance psychotherapeutic interventions consisted of six to 20 sessions that were conducted either weekly/biweekly or monthly. Study characteristics are given in Table 18, and more details can be found in the evidence tables (Chapter 5) and in the GRADE Summary of Findings tables (Chapter 6) in the Appendix.

Table 18 – Characteristics of the included RCTs: combined maintenance psychotherapy and ADM vs. maintenance ADM

Studies	Recruitment	Acute phase combined therapy	N sessions	N patients	Acute phase PT	N patients	FU (months)	Outcome	Country
Frank et al. 1990[54]	Clinical sample	IPT & imipramine	12 weekly sessions followed by 4 biweekly sessions depending on clients progress	25	Imipramine	28	36	Recurrence (HRSD≥15), survivors (participants who continued in remission HRSD<15; Raskin<7)	US
Hersen et al. 1984[106]	Com. sample	SS & amitriptyline	6-8 sessions over six months	21	Amitriptyline	14	6	Depressive symptoms (BDI; HRSD; REDS)	US
Reynolds et al. 1999[113]	NR	IPT & paroxetine	16 weeks of continuation treatment	28	Paroxetine	35	12	QoL(Quality of well being scale)	US
Reynolds et al. 2006[108]	Clinical sample	IPT & paroxetine	1 session/week over 2 years	28	Paroxetine	35	24	Recurrence (DSM-IV)	US
Paykel et al. 1999[109]	Clinical sample	CBT & amitriptyline	16 sessions during 20 weeks plus 2 booster sessions approximately 6 and 14 weeks later	80	Amitriptyline	78	17	Relapse (DSM-III-R)	UK
Perlis et al. 2002[110]	NR	CBT & fluoxetine	12 weekly sessions followed by 7 biweekly	66	Fluoxetine	66	6	Relapse (HRSD≥15)	US
Wilkinson et al. 2009[111]	Clinical sample	CBT & fluoxetine or amitriptyline	NR	22	Fluoxetine or amitriptyline	23	6, 12	Recurrence (MADRS≥10; BDI≥12)	UK

Abbreviations: ADM: Antidepressant Medication; BDI: Beck Depression Inventory; Com: community; CBT: Cognitive Behavioural Therapy; DSM: Diagnostic and Statistical Manual of Mental Disorders; FU: Follow Up; HRSD: Hamilton Rating Scale for Depression; IPT: Interpersonal Psychotherapy; IT: Italy; MADRS: Montgomery Asberg Depression Rating Scale; N: number; NR: Not Reported; QoL: Quality of Life; RCD: Research Diagnostic Criteria; SS: Social Skills training; UK: United Kingdom; US: United States

6.2.5 *Results of included RCTs: combined psychotherapy and ADM vs. psychotherapy in adults with MDD, acute phase treatment*

Table 19 shows the results of the meta-analyses comparing combined acute phase therapy with acute phase psychotherapy in adults with MDD.

Seven studies with 302 participants examined the comparison between acute phase combined psychotherapy with ADM and acute phase psychotherapy at six months and at one year or longer post-randomization. Acute phase combined therapy did not differ significantly in patients´ response to treatment, compared to acute phase psychotherapy at six months and one year or longer post-randomization. Heterogeneity between studies was zero (95%CI 0 to 71%, p<0.05). There were no indications for publication bias.

No studies reported on quality of life, adverse events or work related outcomes.

Table 19 – Meta-analysed outcomes: combined psychotherapy and ADM vs. psychotherapy in adults with MDD, acute phase treatment

Outcome	N	OR	95%CI	I^2	95%CI
Response at 6 months and at 1 year or longer post-randomization	7	1.30	0.76 to 2.22	0%	0 to 71

Abbreviations: CI: Confidence Intervals; N: Number of studies; OR: Odds Ratio

6.2.6 *Results of included RCTs: combined psychotherapy and ADM vs. ADM in adults with MDD, acute phase treatment*

Table 20 presents the results of the comparison between acute phase combined psychotherapy with ADM and acute phase ADM at six months or longer post-randomization. Combined psychotherapy with ADM (acute phase) resulted in a better treatment response compared to acute phase ADM after six months or longer post-randomization (OR=2.72, 95%CI 1.83 to 4.04, p<0.001) across twelve studies with 662 participants. Heterogeneity between studies was low (I^2=15.92%, 95%CI 0 to 59%, p<0.001). There was some indication of publication bias. Duval and Tweedie's Trim and Fill procedure indicated that three studies were missing. The imputed estimate was 2.31 (95%CI 1.47 to 3.62). However, Egger's Test was not significant (p>0.05). Similar results were observed for the same comparison after one year or longer post-randomization across eight studies with 391 participants. Combined acute phase therapy outperformed acute phase ADM (OR=2.72, 95%CI 1.50 to 4.95, p<0.05). Heterogeneity was low (I^2=17.34%, 95%CI 0 to 60%, p<0.001). Using Duval and Tweedie's Trim and Fill procedure a decreased adjusted value was obtained (OR 2.02, 95%CI 1.04 to 3.92), while the Egger's test was not significant.

Two studies on inpatients were excluded in a sensitivity analysis. Acute phase combined psychotherapy with ADM resulted in better response to treatment compared to acute phase ADM at six months or longer post-randomization in outpatients with MDD (OR 2.98, 95%CI 1.89 to 4.70, p<0.001). Heterogeneity was low (I^2=22.45%, 95%CI 0 to 62%, p<0.001). There was indication of publication bias. Using Trim and Fill the imputed value estimate was 2.44 (95%CI 1.47 to 4.07) while Egger's test was not significant. A similar pattern of results was observed at one year or longer post-randomization. Combined therapy outperformed ADM in treatment response of outpatients with MDD (OR 2.89, 95%CI 1.23 to 6.81). Heterogeneity was moderate (I^2=39.15%, 95%CI 0 to 76%, p<0.05). Duval and Tweedie's Trim and Fill procedure indicated a possibility for publication bias and produced an imputed estimate of 1.76 (95%CI 0.71 to 4.34), however, Egger's test was not significant.

Two studies reported on quality of life. Bellino et al. 2006 found that at six months or longer post-randomization patients who followed combined therapy had better mean scores compared to patients who follow ADM on SAT-P psychological functioning (psychotherapy & ADM: 69, standard deviation (SD)=11.7, n=20; ADM: 57.2, SD=14.7, n=19), work scores (psychotherapy & ADM: 56, SD=31.2, n=20; ADM: 54.4, SD=14.6, n=19) and social functioning (psychotherapy & ADM: 68.5 SD=12.5, n=20; ADM: 51.7, SD=10.9, n=19). However, the same study showed that the ADM group had better outcomes compared to combined therapy on SAT-P physical functioning (psychotherapy & ADM: 59.5, SD=16.7, n=20; ADM: 62.8, SD=11.9, n=19) as well as on sleep, food and free time scores (psychotherapy & ADM: 56.4, SD=20.7, n=20; ADM: 64.5, SD=14.9, n=19) at six months or longer post-randomization. Additionally, De Jonghe et al. 2001 found that combined therapy resulted in an overall better quality of life rated on the Quality of Life in Depression Scale, compared to ADM alone after six months or longer post-randomization (psychotherapy & ADM: 25.44; SD=7.59, n=80; ADM: 19.58, SD=9.29, n=81).

Three studies reported on adverse events. Zobel et al. 2011 (companion paper with Schramm et al. 2007) reported that there were no significant differences between treatment groups regarding rehospitalization or suicides attempts. Miller et al. 1989 found that 3/22 patients treated with combined therapy and 2/9 treated with ADM were rehospitalized, while 6/22 patients who followed combined therapy and 2/9 who followed ADM alone experienced substantial suicidal ideation at one year or longer post-randomization. Weissman et al. 1981 found that 0/18 patients in the combined treatment group and 2/15 in the ADM alone group rehospitalized. No studies reported on work related outcomes.

Table 20 – Meta-analysed outcomes: combined psychotherapy with ADM vs. ADM in adults with MDD, acute phase treatment

Outcome	N	OR	95%CI	I²	95%CI
Response at 6 months or longer post-randomization	12	2.72**	1.83 to 4.04	15.92%	0 to 59
Response at 1 year or longer post-randomization	8	2.72*	1.50 to 4.96	17.34%	0 to 60
Response at 6 months or longer post-randomization (inpatients excluded)	10	2.98**	1.89 to 4.70	22.45%	0 to 62
Response at 1 year or longer post-randomization (inpatients excluded)	6	2.89*	1.23 to 6.81	39.15%	0 to 76

** p<0.05; **p<0.001*

Abbreviations: CI: Confidence Intervals; N: Number of studies; OR: Odds Ratio

6.2.7 *Results of included RCTs: combined psychotherapy with ADM vs. psychotherapy in adults who had had MDD, maintenance treatment*

Only one study with 128 participants examined the comparison between combined maintenance psychotherapy with ADM and maintenance psychotherapy at six months or longer post-randomization. Frank et al. 1990 found that combined maintenance therapy resulted in fewer recurrence rates and in a greater number of survivors compared to psychotherapy alone, at one and at two years or longer post-randomization. More details can be found in the evidence tables in the Appendix. No studies reported on quality of life, work related outcomes and safety or adverse events.

6.2.8 *Results of included RCTs: combined psychotherapy with ADM vs. ADM in adults who had had MDD, maintenance treatment*

Table 21 shows the results of the comparison between maintenance combined psychotherapy and ADM at six months or longer post-randomization derived from seven studies with 518 participants. Combined maintenance psychotherapy with ADM resulted in better treatment sustained response compared to ADM at six months or longer post–randomization (OR=1.62, 95%CI 1.07 to 2.44, p<0.05). Heterogeneity was zero (95%CI 0 to 71%, p<0.05). There was no indication of publication bias.

Five studies with 351 participants compared the outcomes of combined maintenance psychotherapy with ADM versus ADM at one year or longer post-randomization. Combined maintenance psychotherapy with ADM resulted in a better sustained response to treatment in comparison with ADM (OR=1.84, 95%CI 1.13 to 2.99, p<0.05) after one year or longer post-randomization. Heterogeneity between the studies was low (I²=5.16%, 95%CI 0 to 80%, p<0.05). There was no indication of publication bias.

Only Reynolds et al. 2006 presented quality of life outcomes. They found that at one year, patients from the interpersonal psychotherapy & ADM group had a mean of 0.54 (SD=0.14) rated on Quality of well-being scale compared to patients from ADM who had a mean of 0.54 (SD=0.13).

Regarding safety and adverse events, Reynolds et al. 1999 reported that during one-year follow-up 2/25 patients in the ADM group experienced adverse effects. No other studies reported on adverse outcomes.

Table 21 – Meta-analysed outcomes: combined psychotherapy with ADM vs. ADM in adults who had had MDD and responded to acute phase treatment, maintenance treatment

Outcome	N	OR	95%CI	I^2	95%CI
Sustained response at 6 months or longer post-randomization	7	1.62*	1.44 to 2.27	0%	0 to 71
Sustained response at 1 year or longer post-randomization	5	1.84*	1.13 to 2.99	5.16%	0 to 80

**p<0.05*

Abbreviations: CI: Confidence Intervals; N: Number of studies; OR: Odds Ratio

6.3 Conclusions: Main psychotherapy interventions combined with antidepressants vs. main psychotherapy intervention or antidepressants only

- There is limited evidence that combined psychotherapy with ADM results in an equal acute phase treatment response compared to psychotherapy at 6 months and at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- There is limited evidence that combining psychotherapy with ADM results in a better acute phase treatment response compared to ADM alone, at 6 months or longer after the start of treatment, in adult patients with MDD (low level of evidence).
- There is limited evidence that combined psychotherapy with ADM results in a better acute phase treatment response compared to ADM alone, at 1 year or longer after the start of treatment, in adult patients with MDD (very low level of evidence).
- There is limited evidence that maintenance treatment with combined psychotherapy and ADM results in a better sustained response compared to maintenance psychotherapy alone, at 6 months and at 1 year or longer after the start of treatment, in adult patients who had had MDD and who responded to acute phase treatment (low level of evidence).
- There is limited evidence that maintenance treatment with combined psychotherapy and ADM results in a better sustained response compared to maintenance with ADM alone, at 6 months or longer after the start of treatment, in adult patients who had had MDD and who responded to acute phase treatment (low level of evidence).
- It is plausible that maintenance treatment with combined psychotherapy and ADM results in a better sustained response compared to maintenance with ADM alone, at 1 year or longer after the start of treatment, in adult patients who had had MDD and who responded to acute phase treatment (moderate level of evidence).

6.4 Discussion

The aim of the present systematic review was threefold; firstly, to examine the long-term efficacy of the main psychotherapeutic interventions in treatment of adults with major depression. Secondly, to identify to what extent there is a difference between the long-term efficacy of psychotherapy and antidepressive agents in adults with major depression. Finally, whether there is any advantage to combine both treatments in adults with major depression in the long-term.

Results based on GRADE indicated that there is limited evidence that psychotherapy results in a better acute phase treatment response compared to control groups, at six months or longer after the start of treatment, in adult

patients with MDD. Also, there is limited evidence that this treatment response is maintained at one year or longer after the start of treatment. Moreover, there is limited evidence that psychotherapy results in a better quality of life compared to control groups, at six months and at one year or longer after randomization. Finally, the results illustrated that in adult patients who had had MDD and who responded to acute phase treatment it is plausible that maintenance treatment with psychotherapy results in a better sustained response compared to control groups at six months and at two years or longer after the start of maintenance treatment,

As for the second aim, results based on GRADE showed that at six months or longer after the start of treatment there was limited evidence that psychotherapy resulted in better acute phase treatment response compared to ADM (without continuation) and an equal response to treatment compared to ADM (continuation) in adults patients with MDD. Further, with respect to maintenance treatment the results illustrated that it was plausible that maintenance psychotherapy resulted in an equally sustained response compared to maintenance ADM at eight months after the start of the maintenance treatment. Finally, there was limited evidence that maintenance psychotherapy resulted in an equally sustained response compared to maintenance ADM at two years after the beginning of the maintenance treatment.

Regarding the third aim, results based on GRADE indicated that there was limited evidence that combined psychotherapy with ADM resulted in an equal acute phase treatment response compared to psychotherapy at six months and at one year or longer after the start of treatment, in adult patients with MDD. Further, there was limited evidence that combined psychotherapy with ADM resulted in a better acute phase treatment response compared to ADM alone, at six months or at one year or longer after the start of treatment. As for the maintenance studies, there was limited evidence that maintenance combined psychotherapy with ADM resulted in a better sustained response compared to maintenance psychotherapy, at 6 months and at one year or longer after the start of treatment, in adult patients who had had MDD and who responded to acute phase treatment. Moreover, there was limited evidence that maintenance combined psychotherapy with ADM resulted in a better sustained response compared to maintenance ADM, at six months or longer after the start of treatment. The same comparison resulted in plausible better sustained response in favour of combined therapy after one year post-randomization.

The finding that maintenance psychotherapy outperformed control groups at six months and at one year or longer after the start of treatment is in line with previous literature. Piet et al. 2011[25] examined the effects of maintenance MBCT compared to TAU and pill placebo in patients with recurrent MDD in remission. They found higher effects on relapse prevention in favour of maintenance MBCT. However, with respect to acute phase treatment no systematic review was identified.

The result that acute phase psychotherapy outperformed ADM (without continuation) at six months or longer post-randomization is in line with the results presented in the meta-analysis of Cuijpers et al. 2013.[76] That review showed that acute phase CBT resulted in better response to treatment compared to ADM (without continuation) at six months or longer in adult patients with MDD. Similar to the present review, results were presented by Cuijpers et al. 2013[76] for the comparison between acute phase CBT and ADM (continuation). At six months or longer CBT had an equal response to treatment compared with ADM. Further, the present results are in accordance with findings of Gloaguen et al. 1998[77] which indicated that on long-term (six months or longer) follow-up there were greater relapse rates for ADM compared to psychotherapy for adults with MDD. Finally, the results of the present study failed to replicate the findings of Bortolotti et al. 2008[75] who found that ADM resulted in an almost equal outcome (reduction of depressive symptoms) compared to psychotherapy after six months post-randomization. However, Bortolotti et al. 2008[75] based their results on only three studies and did not distinguish between ADM with continuation and ADM with discontinuation. To our knowledge, there are no systematic reviews, which adequately examined (had adequate number of studies in order to perform subgroup analyses) the long-term effects of maintenance psychotherapy compared to maintenance ADM. Regarding the third research question, no previous systematic review was identified.

The present study has several ***strengths.*** The included studies targeted outpatients with MDD and thus, the results of the present review refer to a ***highly homogeneous*** population. Additionally, the results of the present systematic review are based on a direct comparison between acute/maintenance phase psychotherapy/combined treatment and control

groups or acute/maintenance phase ADM. Finally, critical outcomes on quality of life were presented for the first comparison (psychotherapy vs. control groups) of the present review.

However, the present results should be interpreted with caution due to several ***limitations.*** Firstly, with respect to the first research question the control groups were diverse. For instance, treatment as usual may refer to the prescription of antidepressant medication, or to a low intensity intervention, while in most cases it is very poorly described. A separate analysis of trials using placebo control was not possible since only one trial within acute phase treatment studies and one trial within maintenance treatment used placebo as control condition. Furthermore, in all three research questions, most of the included trials used CBT as a psychotherapeutic intervention. Therefore, differences between ***different*** types of psychotherapy could not be examined and the generalizability of the present findings to all types of psychotherapy is restricted. Similarly, a distinction between patients with a first episode of depression vs. patients with a relapse was not possible, though treatment approaches may differ. There were, however, no specific studies on patients with a first episode, and a meta-regression analysis on the percentage of patients with a first episode in each study was also not feasible because most studies did not report this in a coherent way. Finally, the outcome was specified to treatment response since the included studies did not provide enough information on outcomes assessed by clinical interview. In the case of the second and third research question, outcomes on quality of life were not or hardly available, nor were there enough studies that provided outcomes assessed by clinical interview. Very few studies reported on work related outcomes. Additionally, information on adverse or safety effects was very limited with only three out of 38 trials in the first research question, four out of 22 trials in the second research question and three out of 23 trials in the third research question reporting on adverse effects.

The fact that RCTs randomise persons that voluntary participate in the study may cause a selection bias limiting the generalizability of the results. Patient preferences may influence treatment results and at the same time influence the chance that they participate in the trial, e.g. patients with a strong preference for antidepressants would not easily accept to be included in an RCT with a control arm without anti-depressants or comparing psychotherapy with a waiting list control group. Similar influence of preferences may also be true for patients with an aversion to antidepressants or for patients with an aversion to or a preference for psychotherapy. RCTs that try to assess the influence of patient preferences, as described in section 7.4, suffer from similar problems.

Additionally, the RCTs were performed in Western countries and therefore results might not be generalizable to patients who grew up in other parts of the world e.g. various immigrant groups.

To conclude, the present review demonstrated that there is limited evidence that acute phase psychotherapy outperforms control groups at six months or longer after the start of treatment, and that it is plausible that maintenance psychotherapy outperforms control groups. There was limited evidence for the effectiveness of acute phase psychotherapy on quality of life compared to control groups at six months or longer after the start of treatment. Additionally, this review showed that there is limited evidence that in adult patients with MDD acute phase psychotherapy results in a better response compared to acute ADM at six months or longer after the start of treatment. It is plausible that maintenance psychotherapy results in an equally sustained response compared to maintenance ADM at eight months or longer after the start of maintenance treatment. Finally, as for the acute phase combined therapy, there is limited evidence that it results in better response to treatment compared to ADM. As for the maintenance combined therapy, there is limited evidence that it results in a better sustained response to treatment compared to ADM at six months post-randomization, however, this difference is plausible at one year or longer after the start of maintenance treatment. None of the other examined comparisons resulted in different or plausible results between the examined conditions. Further research to address outcomes such as quality of life or adverse events, and to examine more types of psychotherapy, is warranted.

7 OTHER CONSIDERATIONS

7.1 Balance between benefits and harms

7.1.1 Side effects associated with anti-depressants

There is a variety of classes of antidepressants, with varying profile concerning side effects and risks. Moreover, within these classes, side effects differ. This fact, combined with the fact that we have insufficient information on what antidepressants are prescribed for which conditions, makes it difficult to give an overall estimation of the burden related to side effects and balance them in relation to psychotherapy. A brief summary of the main side effects and risks associated with antidepressants, extracted from the NICE guideline on depression from 2010[1] is provided below:

The oldest and generally cheapest antidepressants are the tricyclic antidepressants (TCAs). TCAs cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, and sweating), sedation and postural hypotension. These side effects necessitate starting with a low dose and increasing slowly. All TCAs except lofepramine are toxic in overdose, with seizures and arrhythmias being of particular concern.

The selective serotonin reuptake inhibitors (SSRIs) are, in comparison with TCAs, associated with less anticholinergic side effects and are less likely to cause postural hypotension or sedation. The most problematic side effects of this class of drugs are nausea, diarrhoea and headache. Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes precipitating many significant drug interactions.

Monoamine inhibitor oxidase (MAOIs) exerts their therapeutic effect by binding irreversibly to monoamine oxidase, the enzyme responsible for the degeneration of monoamine neurotransmitters such as noradrenaline (NA) and serotonin. All MAOIs have the potential to induce a hypertensive crisis if foods containing tyramine (which is also metabolised by monoamine oxidase) are eaten or if drugs that increase monoamine neurotransmission are co-prescribed. These foods and drugs must be avoided for at least 14 days after discontinuing MAOIs. Reversible inhibitors of monoamine oxidase (RIMAs) have a much lower likelihood of causing a hypertensive crisis, and dietary restrictions are usually not required.

For all three classes, there is evidence of a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment, but the effect on effective suicides is unclear.

Antidepressants are not addictive but can cause discontinuation symptoms. Discontinuation symptoms can be broadly divided into six groups; affective (for example irritability), gastrointestinal (for example nausea), neuromotor (for example ataxia), vasomotor (for example sweating), neurosensory (for example paresthesia), and other neurological (for example dreaming).

7.1.2 Side-effects associated with psychotherapy

Side effects of psychotherapies have hardly been examined systematically. It is suggested that psychotherapies potentially could result in deterioration in some depressed patients, and that some psychotherapies could increase the risk for other mental disorders (for example psychotic decompensation in depressed patients with personality disorders), and, furthermore, increase the risk of suicide. Unfortunately, these issues are hardly ever examined in psychotherapy trials, and whether such negative effects really occur cannot be verified empirically.[114] It is known that some psychological interventions overall have negative effects in comparison to control groups. Randomized trials have shown for example that debriefings after traumatic incidences increase the risk for developing a post-traumatic stress disorder compared to people who do not receive debriefing.[115, 116] It has also been shown that group therapy for antisocial problems in adolescents may lead to more antisocial problems when compared to adolescents who do not receive this therapy.[117] These are, however, negative effects on a group level. It is also possible that interventions have an overall positive effect, but have negative effects on a specific individual. As indicated, this has not been examined sufficiently to draw any conclusions about that.

7.2 Quality of the evidence

There was very low level of evidence that maintenance treatment with combined psychotherapy and ADM had superior effect (resulted in a better sustained response) compared to maintenance psychotherapy alone, at 6 months and at 1 year or longer after the start of treatment. Similarly, there was very low level of evidence that psychotherapy has comparative short-term effects as ADM, but superior effect at the longer term.There was moderate level of evidence that psychotherapy and ADM is superior to ADM alone.

7.3 Costs (resource allocation)

While antidepressants are reimbursed for patients with a depression, psychotherapy currently lacks recognition and is not reimbursed in Belgium. There are recent policy indications that this might change. Given the results of the medical evidence summary, it seems relevant to consider the balance between cost and benefits of psychotherapy for major long-term depression.

7.4 Patient values and preferences

Evidence-based practice involves conscientious decision-making, based not only on efficacy and effectiveness, but also on patient characteristics and preferences. On depression specifically, there has been an increase in research to determine patient preferences for the various treatment types, including psycho- and pharmacotherapy.

Clinical practice guidelines, including the American Psychiatric Association guidelines for the treatment of depression,[118] place emphasis on accommodating patient preferences and suggest that, when possible, providers should attempt to take these into consideration when recommending a course of treatment.

For this guideline, a comprehensive search for systematic reviews and meta-analysis on patient preferences for the treatment of depression was performed between 10 December 2013 and 15 January 2014. Databases searched included PubMed, OVID Medline, The Cochrane Library, Embase and Psychinfo. For detailed search strategies please see the Appendix. One recent review of reviews[119] and one recent meta-analysis were included.[120]

A review of reviews, published in July 2013,[119] asks whether treatment for depression should be based more on patient preferences. The authors reviewed:

- studies examining the effect of patient treatment preferences on treatment course and outcomes
- studies on which treatment options patients tend to prefer
- studies on which factors might affect these preferences

Finally, the review discusses the clinical implications of the research findings.

Ad a)

The review finds that a variety of study designs (including RCTs, partially randomized preference trials, RCTs with patient preference arms and collaborative care studies), in a variety of settings (with primary care as the most common) is used to assess the relationship between preference, treatment process and outcome. The authors conclude that the results of these studies are mixed, with the majority of studies reporting no relationship between treatment preferences and outcome, and a few reporting a positive relationship. Notably, the studies also have insufficient statistical power to detect such differences. However, while there is limited evidence supporting a direct relationship between patient preferences and outcome, there is "somewhat more evidence that preferences may have an indirect effect, through factors such as engagement or alliance ratings, adherence, attrition and satisfaction". That being said, the authors find the results are mixed for these indirect measures as well.

Ad b)

A number of studies (mainly surveys) in both clinical and lay populations look at attitudes towards, and acceptability of various treatment options for depression. Regarding attitudes, people surveyed are often concerned about potential side-effects of antidepressants and may believe antidepressants are addictive. Concerns about psychotherapy may be more related to time commitment and cost. Regarding acceptability, when surveyed about treatment preferences, people generally prefer psychotherapy over antidepressants. However, a number of studies also find that patient often endorse non evidence-based treatments, including

self-help books, herbal supplements, relaxation or talking to friends. Some of these studies suggest that people may have negative attitudes towards mental health professionals in general.

In addition, a recent meta-analysis[120] aims to provide an estimate of the proportion of patients preferring psychological treatment relative to medication for psychiatric disorders. For all psychiatric disorders (depression, anxiety and general mental illness) the proportion of adult patients preferring psychological treatment was 0.75 (95%CI: 0.69 – 0.80) which was significantly higher than equivalent preference (p<.001), the proportion that would indicate equal preference for psychological and pharmacological treatment. Within the 22 studies that examined the treatment of depression only, the proportion of patient preferring psychological treatment revealed a mean 0.70 (95 % CI: 0.62 – 0.77). The study also found that in all psychiatric populations younger patients (p=.05) and women (p<0.01) were significantly more likely to choose psychotherapy.

Ad c)

Factors that have been examined in relation to treatment preferences include demographic variables (age, race, sex) and other potentially contributing factors i.e. depression severity, previous treatment experience and etiology beliefs. Contrary to the results in the meta-analysis one study reported in the review[121] found that regarding age, older adults with depression have been found to prefer psychotherapy (behavioral interventions) over pharmacotherapy. Regarding sex, males may be more accepting of antidepressants than females while females have been found to be more likely to prefer counseling.

Finally, one study,[122] found that higher depression severity is found to be associated with a less positive attitude towards antidepressants while it, contrarily in another study,[123] is found to be associated with a preference for medication and with a greater preference to receive treatment by professionals in general. Regarding the effect of previous treatment experience, the authors found the evidence to be conflicting with some studies reporting a positive association between previous experience with one type of treatment, and preference for the same treatment types; while others found the opposite result. Finally, beliefs about the causes of depression and treatment knowledge may influence treatment preferences as well, such that patients may prefer treatments that are congruent with their etiological beliefs.[119]

The authors of the review[119] conclude that, considering that various forms of treatments (including various psycho- and pharmacotherapies) have demonstrated equivalence in efficacy, patient preferences may be an important factor when choosing the best treatment option. However, more research is needed to determine the true effect of preferences on treatment course, and the potential interaction of treatment preferences with factors including depression severity, setting, patient and provider characteristics and cost. Contrarily, the meta-analysis states that patient preferences are associated with improved retention and outcomes. However, the meta-analysis largely bases this information on a systematic review on trials with predominantly musculoskeletal disorders and might as such not be directly comparable with patients having depression.

Finally, the review concludes that studies tend to find a preference for psychotherapy over pharmacotherapy, and a preference for treatment in a primary care setting.[119]

8 RECOMMENDATIONS

8.1 Psychotherapy alone, or in combination with antidepressants

Recommendations	Strength of Recommendation	Level of Evidence
Psychotherapy* combined with anti-depressant medication is the preferred treatment option for patients with a major depression both in the acute phase and the continuation phase.	Weak	Very Low
If a patient with a major depression does not want combined treatment (i.e. if the patient prefers to start with only one type of treatment) psychotherapy* could be a first choice, because psychotherapy* is at least as effective as antidepressants in the short term and superior to antidepressants in the long-term. This recommendation might not apply to patients with a severe major depressive disorder having psychotic symptoms.	Weak	Very Low
Antidepressant medication only should be avoided as a treatment option for major depression in the symptomatic phase, because the combination of psychotherapy* and antidepressants has superior effect in the long-term.	Strong	Moderate

The effect is currently only sufficiently studied for **cognitive behavioural therapy (CBT)*

Considerations linking evidence to recommendations.

Factor	Comment
Balance between clinical benefits and harms	In preparation of the final GDG meeting draft recommendations were prepared by KCE researchers and circulated to the GDG group in advance. Each of the three recommendations were discussed, and each GDG member were given time to comment on the recommendation as it was stated, and to suggest changes to the wording of the recommendation. The recommendations are a result of agreement within the GDG group (no formal consensus method utilized). Regarding the first recommendation the GDG collectively endorsed, that this recommendation should state that combined therapy is preferred over anti-depressant medication alone, because of its proven superior effect in the long-term. The GDG made this a weak recommendation based on low level of evidence on combination therapy, because the evidence that adding psychotherapy to ADM is superior to ADM but that the evidence that adding ADM to psychotherapy is beneficial is much weaker or non-existent. However, one group member argued that it should be specified that this had not been proven for all psychotherapies, and that the effect currently only sufficiently is studied for CBT. Another group member did not agree with this specification, and as a result decided to have her name removed from the list of authors. Since the rest of the group agreed with this specification an asterisk* was added to the word “psychotherapy” with an explanation stated below. Regarding the second recommendation the GDG, based on the available evidence found, collectively agreed that, if a patient with a major depression does not want combined treatment (i.e. if the patient prefers to start with only one type of treatment)

Factor	Comment
	psychotherapy could be a first choice, because psychotherapy is at least as effective as antidepressants in the short term and superior to antidepressants in the long-term. Regarding the third recommendation the GDG argued that antidepressants alone should be avoided as a treatment option in the symptomatic phase. This is because the evidence that adding psychotherapy to ADM is superior to ADM but that the evidence that adding ADM to psychotherapy is beneficial is much weaker or non-existent. Therefore the GDG felt that a supplementary recommendation to avoid ADM monotherapy was useful and justified and that the evidence was sufficient to classify it as moderate. Additionally, the GDG argued that this recommendation should be stated strongly because some patients who are offered combination treatment continue medication treatment but discontinue psychotherapy and that this leads to a high risk of relapse. It was a general comment to all recommendations that it is a shortcoming of this review that no mentioning is made with respect to severity of the depression, and that the recommendations likely could have had more clinical relevance had this distinction been made. Side-effects of anti-depressants are diverse and depend on the type of anti-depressant used. Although there are statistics in Belgium on general consumption of different types of antidepressants, it is unclear what the consumption pattern is for major depression, as a large proportion of the anti-depressants may be prescribed for minor or misdiagnosed depression. Side-effects of antidepressants are partly reflected in decreased compliance in the RCTs; this is only evident on the condition that the results are analysed on an intention to treat basis. Side-effects of psychotherapies have hardly been examined systematically. It is suggested that psychotherapies potentially could result in deterioration in some depressed patients, and that some psychotherapies could increase the risk for other mental disorders (for example psychotic decompensation in depressed patients with personality disorders), and, furthermore, increase the risk of suicide. Unfortunately, these issues are hardly ever examined in psychotherapy trials, and whether such negative effects really occur cannot be verified empirically. As deterioration is partly accounted for in the effect measure this is unlikely to alter the balance benefit harm.
Quality of evidence	The evidence ranged from Very Low to Moderate. Based on discussions on the assigned level of evidence in the GRADE tables, the GDG argued that population indirectness was present because a number of the RCTs mixed patients with a first episode of depression with patients with a recurrent episode. Consequently, the level of evidence was lowered from Low to Very Low in the recommendations affected (first and second recommendation). However, in the third recommendation it should be noted that we did not downgrade all the studies for indirectness. The maintenance studies mainly included patients with a recurrent depression (usually patients with a third or more episode) and it was agreed that it was not appropriate to downgrade, even though we do not have information on the severity of depression for this group either. It was discussed whether to further lower the quality (for indirectness) based on the fact that pregnant women were excluded from studies, but it was decided not to do so because this is a general issue with the design of RCTs.

Factor	Comment
	The vast majority of studies found were on cognitive behavioural therapy (CBT) and it was decided to clarify in the recommendations (as a footnote) that the effect currently only has been sufficiently studies for CBT. Additionally, a subgroup analysis on the CBT studies alone was added to the appendices. It was not feasible to do subgroup analyses on other types of psychotherapy due to an insufficient number of studies. The GDG agreed that the advice given in the second recommendation, that if a patient with a major depression does not want combined treatment, psychotherapy* only could be a first choice might not apply to patients with a severe major depression having psychotic symptoms (ICD 10 code F.32.3). These patients should, according to the GDG, first and foremost receive pharmacological management for their psychotic symptoms. In order to avoid that the patients were treated with psychotherapy as monotherapy, this consideration was consequently added to the second recommendation. Additionally, the GDG considered that patients in acute danger of suicide should not start a new treatment with psychotherapy, and should remain in hospital until the acute phase is over. None of the included studies examined this particular patient population. It was not deemed necessary to explicitly state this consideration in the recommendations. Although it is unclear if the antidepressants in the studies and those used in Belgium are the same, there is no compelling evidence that one antidepressant is more effective than the other, so this form of indirectness was not taken into account.
Costs (resource allocation)	The GDG argued that it is difficult to make recommendations without a cost-effectiveness analysis.
Patients values and preferences	The evidence supporting a direct relationship between patient preferences and outcome was very limited and not sufficiently strong to generate influence when the GDG formulated the recommendations. Although recent literature suggest that patients generally tend to prefer psychological treatment to anti-depressant the clinical benefits of psychotherapy in the long-term were the determinant factor for the formulation of recommendation # 2. From the literature review on patient preferences, there is no evidence to support a recommendation on routine variation in treatment strategy based on for example age, sex or race.

9 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

9.1 Stakeholder involvement

9.1.1 Consensus on recommendations

In order to assess the agreement with the recommendations and the anticipated facilitators and barriers to implementation of the recommendations, we conducted a survey amongst the stakeholders and afterwards met with the stakeholders at a face-to-face meeting (June 5th, 2014) to further discuss and elaborate on these matters. Amongst the stakeholders included were the patient organization “Psytoyens”.

The result of the survey showed that a very high proportionof the stakeholders agreed with the recommendations (16/18, 14/18 and 16/18 for the three recommendations, respectively). A graphical representation of the stakeholder responses for each survey question can be found in the Appendix (see Appendices Chapter 9, section 9.1). The survey allowed for the stakeholders to provide their comments independently to each of the recommendations in advance.

During the stakeholder meeting each recommendation and all comments received were discussed and the stakeholders were given time to raise any concerns they had regarding the recommendations. The main concern raised centered on the applicability of the recommendations to patients with a moderate or a severe depression and whether the recommendation not to use antidepressants for these patients was correct. There was consensus that all the recommendations were applicable to patients with a mild depression. However, since this study did not distinguish between severe, moderate and mild depression, it was decided to keep the recommendations so they were aligned with the results of the literature review. Additionally, some stakeholders did not agree that it was stated that the effect of psychotherapy currently only is sufficiently studied for cognitive behavioural therapy (CBT). There was, however, no group consensus to remove this fact. In conclusion the stakeholder meeting did not result in any concrete changes to the recommendations originally proposed.

Additionally, representatives from the patient organization Psytoyens, at their own initiative, translated our survey and conducted it amongst their members. The result of this survey also showed a high agreement level. The results can be found in the appendices (see Appendices Chapter 9, section 9.2)

9.1.2 Facilitators and barriers as identified by stakeholders

The main facilitators and barriers for implementation of the recommendations identified by the stakeholders (in the survey and the face-to-face meeting) are grouped by domain in the table below:

Domain	Facilitators	Barriers
Importance of primary care	• General practitioners (GPs) are key persons in diagnosing and treating depression, can facilitate access to psychotherapy and medication, can help ensure good follow-up	• Diagnosis might not be accurate • The access to psychotherapy is limited, might favour prescription of medication in primary care • Role of nurses in primary care is not clearly defined
Change resistance (patients and providers)	• Public information/public campaigns • Recognition and reimbursement of psychotherapy • Involvement of patients' associations	• "Habits of physicians" • Perception that psychotherapy requires too much time • Pressure from pharmaceutical industry
Human resources	• Recognition and reimbursement of psychotherapy • Clearer definition of the role of a clinical psychologist in treatment of depression • Increase number of cognitive behavioural therapists	• Lack of well trained professionals • Lack of skilled psychiatrists in affective disorders • Lack of well-trained physicians (incl. GPs) • Some psychotherapists have inadequate training and/or lack of experience to deal with depressed patients • Lack of training in 'good clinical practice guidelines' in Universities and in continuous medical education
Organisation/Collaboration	• Development of networks for specialised professionals • Creation of excellence centres for diagnosis/treatment of severe/difficult affective disorders (including treatment resistant depression)	• Current lack of sound collaboration between professionals including GPs and psychotherapists • Financial barriers due to lack of reimbursement for psychotherapy • Complex health system in terms of communication

9.2 Dissemination and implementation

This guideline is intended to be used by the concerned professional associations: general practitioners, psychiatrists, association of psychiatric nurses, organizations of psychotherapists/psychologists. In order to facilitate this process all members of the guideline development group and the stakeholder group will receive the final documents, and the synthesis with the aim to be disseminated within their respective associations. Additionally, the scientific synthesis is being transformed by a communication specialist into a text that should be easily understandable by clinicians, including those clinicians who might be less familiar with EBM. Furthermore, the publication on EBMPracticeNet will likely facilitate the access to all clinicians potentially interested.

The following aspects may, according to KCE, hamper the implementation of the recommendations:

- The scope of the guideline, and in particular the fact that the guideline does not cover diagnostic. It is well known that a number of patients are labelled as having a major depression without fulfilling the criteria (false positives) and therefore receive a treatment they do not need. On the other hand, a number of truly depressed patients do not receive a depression diagnosis and consequently might not receive the treatment they actually need;
- Although a law regarding the recognition and regulation of psychotherapy in Belgium was published in may 2014 and should take effect in september 2016, it is unclear how and when it will be implemented and to what degree it will provide the necessary guarantees concerning quality and protection of the patient in the field, as the concrete modalities for implementation still need to be determined. A Federal Council for psychotherapy will be established that should advice on these issues. Consequently, there are for the moment no qualifications needed for a person to call himself a psychotherapist, and the quality of the psychotherapy is not guaranteed.
- A major barrier for implementation of this guideline is the fact that for major depression, psychotherapy is currently not reimbursed in Belgium.

9.3 Monitoring the quality of care

Monitoring the quality of care cannot be performed by an analysis of administrative databases as psychotherapy is not registered for the moment in Belgium.

Instead specific surveys are needed by researchers or scientific societies in order to assess whether if the recommendations are followed, and in particular whether patients use psychotherapy for the treatment of depression and when they do which type of psychotherapy they use, the duration of the treatment and whether this is used in combination with antidepressants.

9.4 Guideline update

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

APPENDICES

APPENDIX 1. DEFINITIONS OF TYPES OF PSYCHOTHERAPY FOR ADULT DEPRESSION[11]

Cognitive–behavior therapy (CBT): In CBT, therapists focus on the impact a patient's present dysfunctional thoughts have on current behavior and future functioning. CBT is aimed at evaluating, challenging, and modifying a patient's dysfunctional beliefs (cognitive restructuring). In this form of treatment, the therapist mostly emphasizes homework assignments and outside-of-session activities. Therapists exert an active influence over therapeutic interactions and topics of discussion, use a psychoeducational approach, and teach patients new ways of coping with stressful situations. We distinguished two main types of CBT: (a) CBT in which cognitive restructuring is the core element of the treatment and (b) CBT in which cognitive restructuring is an important component, but in which at least two other components (such as behavioral activation, social skills training, relaxation, or coping skills) also have a prominent place. One example of this approach is the Coping with Depression course (Lewinsohn et al. 1984[124]). Within the first subtype, we distinguished two variants. Variant a1: The manual developed by Beck et al. (1979)[125] is the most widely used manual for CBT (which includes a module on behavioral activation; see below). Variant a2: In several studies, cognitive restructuring is used as a treatment (with or without a module on behavioral activation), but no explicit reference is made to Beck et al.'s manual.[125]

Nondirective supportive therapy (SUP): We defined nondirective therapy as any unstructured therapy without specific psychological techniques other than those common to all approaches, such as helping people to ventilate their experiences and emotions and offering empathy. It is not aimed at solutions or acquiring new skills. It is based on the assumption that relief from personal problems may be achieved through discussion with others. These nondirective therapies are commonly described in the literature as either counseling or supportive therapy. We distinguished two main types of SUP: (a) SUP explicitly referring to the work of Rogers (1967),[126] this is a specific form of nondirective therapy in which reflection is an important therapeutic technique to elicit feelings, and (b) this subtype included the

SUP interventions that were not explicitly referring to the work of Rogers, but met the definition of SUP.

Behavioral activation therapy (BA): We considered an intervention to be activity scheduling when the registration of pleasant activities and the increase of positive interactions between a person and his or her environment were the core elements of the treatment. Social skills training could be a part of the intervention. Although this intervention was developed by Lewinsohn et al. (1976),[127] we also included studies that used the principles of this intervention but did not refer directly to the work of Lewinsohn et al. Some studies referred to the behavioral activation component included in the manual for CBT by Beck et al. (1979).[125] This component of CBT is based on similar principles.

Psychodynamic therapy (DYN): The primary objective in (short-term) psychodynamic therapy is to enhance the patient's understanding, awareness, and insight about repetitive conflicts (intrapsychic and intrapersonal). An assumption in DYN is that a patient's childhood experiences, past unresolved conflicts, and historical relationships significantly affect a person's present life situation. In this form of treatment, the therapist concentrates on the patient's past, unresolved conflicts, and historical relationships and the impact these have on a patient's present functioning. Furthermore, in DYN the therapists explore a patient's wishes, dreams, and fantasies. The time limitations and the focal explorations of the patient's life and emotions distinguish DYN from psychoanalytic psychotherapy.

Problem-solving therapy (PST): We defined PST as a psychological intervention in which the following elements had to be included: definition of personal problems, generation of multiple solutions to each problem, selection of the best solution, the working out of a systematic plan for this solution, and evaluation as to whether the solution has resolved the problem. There are several subtypes of PST, such as PST according to Nezu (1986)[128] and Mynors-Wallis et al. (1995).[129]

Interpersonal psychotherapy (IPT): IPT is a brief and highly structured manual-based psychotherapy that addresses interpersonal issues in depression to the exclusion of all other foci of clinical attention (http://www.interpersonalpsychotherapy.org). IPT has no specific theoretical origin, although its theoretical basis can be seen as coming from the work of Sullivan, Meyer, and Bowlby. The current form of the treatment was developed by the late Gerald Klerman and Myrna Weissman in the 1980s.[130]

Social skills training (SST): SST is a form of behavior therapy in which clients are taught skills that help in the building and retainment of social and interpersonal relationships. In most versions of SST, patients are trained in assertiveness. This means that the client is taught to stand up for his or her rights by expressing feelings in an honest and respectful way that does not insult people.

REFERENCES

1. National Collaborating Centre for Mental Health cbN. The treatment and management of depression. UK; 2010.
2. Lewinsohn PM, Solomon, A., Seeley, J. R., et al. Clinical implications of 'subthreshold' depressive symptoms. *Journal of Abnormal Psychology*. 2000;**109**:345-51.
3. Gisle L. Sante' Mentale. In: Publique ISdS, editor.; 2008.
4. Bartholomeeusen S, Kim CY, Mertens R, Faes C, Buntinx F. The denominator in general practice, a new approach from the Intego database. *Fam Pract*. 2005 Aug;**22**(4):442-7.
5. Truyers C, Bartholomeeusen S, Buntinx F. Geestelijke gezondheidsproblemen in de huisartsenpraktijken. *Huisarts Nu* 2012;**41**:25-6.
6. Boffin N, Bossuyt N, Declercq T, Vanthomme K, Van Casteren V. Incidence, patient characteristics and treatment initiated for GP-diagnosed depression in general practice: results of a 1-year nationwide surveillance study. *Family Practice*. 2012 Dec;**29**(6):678-87.
7. Waraich P, Goldner, E. M., Somers, J. M., et al. Prevalence and incidence studies of mood disorders: a systematic review of the literature. *Canadian Journal of Psychiatry*. 2004;**49**:124-38.
8. Gezondheidsraad H. PUBLICATIE VAN DE HOGE GEZONDHEIDSRAAD nr. 8571: De impact van psychofarmaca op de gezondheid met een bijzondere aandacht voor ouderen. 2011. p. 1-38.
9. Cuijpers P, Van Straten A, Van Oppen P, Andersson G. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. *Journal of Clinical Psychiatry*. 2008;**69**(11):1675-85.
10. Boffin N, Bossuyt N, Vanthomme K, Van Audenhove C, Van Casteren V. Short-term follow-up of patients diagnosed by their GP with mild depression or first-time moderate depression. Results of a 1-year nationwide surveillance study. *Family Practice*. 2012 Dec;**29**(6):688-95.

11. Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *J Consult Clin Psychol*. 2008 Dec;**76**(6):909-22.
12. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-Analysis: Wiley; 2009.
13. Cuijpers P, Turner EH, Koole SL, van Dijke A, Smit F. What is the threshold for a clinically relevant effect? The case of major depressive disorders. *Depress Anxiety*. in press.
14. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions : Version 5.1.0: The Cochrane collaboration; [updated March 2011].
15. Cuijpers P, van Straten A, Warmerdam L, Andersson G. Psychological treatment of depression: a meta-analytic database of randomized studies. *BMC Psychiatry*. 2008;**8**:36.
16. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;**7**:10.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003 Sep 6;**327**(7414):557-60.
18. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*. 2007 Nov 3;**335**(7626):914-6.
19. Orsini N, Bottai M, Higgins J, Buchan L. HETEROGI: Stata module to quantify heterogeneity in a meta-analysis. 2005.
20. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000 Jun;**56**(2):455-63.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997 Sep 13;**315**(7109):629-34.
22. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials*. 2007;**4**(3):245-53.
23. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;**64**(4):401-6.
24. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013 Feb;**66**(2):151-7.
25. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clin Psychol Rev*. 2011 Aug;**31**(6):1032-40.
26. Elliott R, Watson, J., Greenberg, L.S., Timulak, L., & Freire, E. Research on humanistic-experiential psychotherapies. In M.J. Lambert (Ed.), Bergin & Garfield's. Handbook of psychotherapy and behavior change 6th ed. New York: Wiley. ©Wiley; 2013. p. 495-538.
27. Burns A, O'Mahen H, Baxter H, Bennert K, Wiles N, Ramchandani P, et al. A pilot randomised controlled trial of cognitive behavioural therapy for antenatal depression. *BMC Psychiatry*. 2013;**13**.
28. Cooper PJ, Murray L, Wilson A, Romaniuk H. Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. 1. Impact on maternal mood. *The British Journal of Psychiatry*. 2003;**182**(5):412-9.
29. Duarte PS, Miyazaki MC, Blay SL, Sesso R. Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int*. 2009 Aug;**76**(4):414-21.
30. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch Gen Psychiatry*. 1989 Nov;**46**(11):971-82; discussion 83.
31. Folke F, Parling T, Melin L. Acceptance and Commitment Therapy for Depression: A Preliminary Randomized Clinical Trial for

Unemployed on Long-Term Sick Leave. *Cognitive and Behavioral Practice*. 2012;**19**(4):583-94.

32. Kay-Lambkin FJ, Baker AL, Lewin TJ, Carr VJ. Computer-based psychological treatment for comorbid depression and problematic alcohol and/or cannabis use: a randomized controlled trial of clinical efficacy. *Addiction*. 2009 Mar;**104**(3):378-88.
33. Kessler D, Lewis G, Kaur S, Wiles N, King M, Weich S, et al. Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial *Lancet*. 2009;**9690**:628-34.
34. Laidlaw K, Davidson K, Toner H, Jackson G, Clark S, Law J, et al. A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *Int J Geriatr Psychiatry*. 2008 Aug;**23**(8):843-50.
35. Lustman PJ, Griffith LS, Freedland KE, Kissel SS, Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Annals of Internal Medicine*. 1998;**8**:613-21.
36. Miranda J, Chung JY, Green BL, Krupnick J, Siddique J, Revicki DA, et al. Treating Depression in Predominantly Low-Income Young Minority Women: A Randomized Controlled Trial. *JAMA: Journal of the American Medical Association*. 2003 Jul;**290**(1):57-65.
37. Mohr DC, Carmody T, Erickson L, Jin L, Leader J. Telephone-administered cognitive behavioral therapy for veterans served by community-based outpatient clinics. *J Consult Clin Psychol*. 2011 Apr;**79**(2):261-5.
38. O'Mahen H, Himle JA, Fedock G, Henshaw E, Flynn H. A pilot randomized controlled trial of cognitive behavioral therapy for perinatal depression adapted for women with low incomes. *Depress Anxiety*. 2013 Jul;**30**(7):679-87.
39. Pagoto S, Schneider KL, Whited MC, Oleski JL, Merriam P, Appelhans B, et al. Randomized controlled trial of behavioral treatment for comorbid obesity and depression in women: the Be Active Trial. *Int J Obes (Lond)*. 2013 Nov;**37**(11):1427-34.
40. Power MJ, Freeman C. A randomized controlled trial of IPT versus CBT in primary care: with some cautionary notes about handling missing values in clinical trials. *Clin Psychol Psychother*. 2012 Mar-Apr;**19**(2):159-69.
41. Qiu J, Chen W, Gao X, Xu Y, Tong H, Yeng M, et al. A randomized controlled trial of group cognitive behavioral therapy for Chinese breast cancer patients with major depression. *Journal of Psychosomatic Obstetrics and Gynecology*. 2013;**34**(2):60-7.
42. Scott C, Tacchi MJ, Jones R, Scott J. Acute and one-year outcome of a randomised controlled trial of brief cognitive therapy for major depressive disorder in primary care. *The British journal of psychiatry : the journal of mental science*. 1997:131-4.
43. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, De Graaf R, Beekman A. Costs of nine common mental disorders: implications for curative and preventive psychiatry. *J Ment Health Policy Econ*. 2006;**9**:193 - 200.
44. Strong V, Waters R, Hibberd C, Murray G, Wall L, Walker J, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. *The Lancet*. 2008;**372**(9632):40-8.
45. Swartz HA, Frank E, Zuckoff A, Cyranowski JM, Houck PR, Cheng Y, et al. Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. *American Journal of Psychiatry*. 2008;**165**(9):1155-62.
46. Teasdale JD, Fennell MJ, Hibbert GA, Amies PL. Cognitive therapy for major depressive disorder in primary care. *Br J Psychiatry*. 1984 Apr;**144**:400-6.
47. van Schaik A, van Marwijk H, Ader H, van Dyck R, de Haan M, Penninx B, et al. Interpersonal psychotherapy for elderly patients in primary care. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2006 Sep;**14**(9):777-86.
48. Weissman MM, Klerman GL, Prusoff BA. Depressed outpatients. Results one year after treatment with drugs and/or interpersonal psychotherapy. *Archives of General Psychiatry*. 1981;**38**(1):51-5.
49. Wiles N, Thomas L, Abel A, Ridgway N, Turner N, Campbell J, et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression:

results of the CoBalT randomised controlled trial. *The Lancet*. 2013;**381**(9864):375-84.

50. Bockting CL, Schene AH, Spinhoven P, Koeter MW, Wouters LF, Huyser J, et al. Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. *J Consult Clin Psychol*. 2005 Aug;**73**(4):647-57.
51. Bondolfi G, Jermann F, der Linden MV, Gex-Fabry M, Bizzini L, Rouget BW, et al. Depression relapse prophylaxis with Mindfulness-Based Cognitive Therapy: replication and extension in the Swiss health care system. *J Affect Disord*. 2010 May;**122**(3):224-31.
52. Fava GA, Grandi S, Zielezny M, Canestrari R, Morphy MA. Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *Am J Psychiatry*. 1994 Sep;**151**(9):1295-9.
53. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P. Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. *Arch Gen Psychiatry*. 1998 Sep;**55**(9):816-20.
54. Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, et al. Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry*. 1990 Dec;**47**(12):1093-9.
55. Godfrin KA, van Heeringen C. The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: A randomized controlled study. *Behav Res Ther*. 2010 Aug;**48**(8):738-46.
56. Hollandare F, Johnsson S, Randestad M, Tillfors M, Carlbring P, Andersson G, et al. Randomized trial of Internet-based relapse prevention for partially remitted depression. *Acta Psychiatr Scand*. 2011 Oct;**124**(4):285-94.
57. Jarrett RB, Kraft D, Schaffer M, Witt-Browder A, Risser R, Atkins DH, et al. Reducing relapse in depressed outpatients with atypical features: a pilot study. *Psychother Psychosom*. 2000 Sep-Oct;**69**(5):232-9.
58. Jarrett RB, Minhajuddin A, Gershenfeld H, Friedman ES, Thase ME. Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. *JAMA Psychiatry*. 2013 Nov 1;**70**(11):1152-60.
59. Klein DN, Santiago NJ, Vivian D, Blalock JA, Kocsis JH, Markowitz JC, et al. Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. *Journal of Consulting and Clinical Psychology*. 2004;**72**(4):681-8.
60. Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. *J Consult Clin Psychol*. 2004 Feb;**72**(1):31-40.
61. Schulberg HC, Block MR, Madonia MJ, Scott CP, Rodriguez E, Imber SD, et al. Treating major depression in primary care practice. Eight-month clinical outcomes. Archives of General Psychiatry; 1996. p. 913-9.
62. Segal ZV, Bieling P, Young T, MacQueen G, Cooke R, Martin L, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. *Arch Gen Psychiatry*. 2010 Dec;**67**(12):1256-64.
63. Stangier U, Hilling C, Heidenreich T, Risch AK, Barocka A, Schlosser R, et al. Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: a multicenter prospective randomized controlled trial. *Am J Psychiatry*. 2013 Jun 1;**170**(6):624-32.
64. Teasdale JD, Segal ZV, Williams JMG, Ridgewaya VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology*. 2000;**68**(4):615-23.
65. Vittengl JR, Clark LA, Jarrett RB. Continuation-phase cognitive therapy's effects on remission and recovery from depression. *J Consult Clin Psychol*. 2009 Apr;**77**(2):367-71.
66. Miranda J, Green BL, Krupnick JL, Chung J, Siddique J, Belin T, et al. One-year outcomes of a randomized clinical trial treating depression in low-income minority women. *J Consult Clin Psychol*. 2006 Feb;**74**(1):99-111.

67. Bosmans JE, van Schaik DJ, Heymans MW, van Marwijk HW, van Hout HP, de Bruijne MC. Cost-effectiveness of interpersonal psychotherapy for elderly primary care patients with major depression. *Int J Technol Assess Health Care*. 2007 Fall;**23**(4):480-7.
68. Schulberg HC, Pilkonis PA, Houck P. The severity of major depression and choice of treatment in primary care practice. Journal of Consulting and Clinical Psychology; 1998. p. 932-8.
69. Bockting CL, Spinhoven P, Wouters LF, Koeter MW, Schene AH, Group DS. Long-term effects of preventive cognitive therapy in recurrent depression: a 5.5-year follow-up study. *J Clin Psychiatry*. 2009 Dec;**70**(12):1621-8.
70. Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R. Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *Am J Psychiatry*. 1996 Jul;**153**(7):945-7.
71. Fava GA, Rafanelli C, Cazzaro M, Conti S, Grandi S. Well-being therapy. A novel psychotherapeutic approach for residual symptoms of affective disorders. *Psychol Med*. 1998 Mar;**28**(2):475-80.
72. Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *Am J Psychiatry*. 2004 Oct;**161**(10):1872-6.
73. Karp JF, Buysse DJ, Houck PR, Cherry C, Kupfer DJ, Frank E. Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. *Am J Psychiatry*. 2004 Oct;**161**(10):1877-84.
74. Jarrett RB, Kraft D, Doyle J, Foster BM, Eaves GG, Silver PC. Preventing recurrent depression using cognitive therapy with and without a continuation phase: a randomized clinical trial. Archives of General Psychiatry; 2001. p. 381-8.
75. Bortolotti B, Menchetti M, Bellini F, Montaguti MB, Berardi D. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. *Gen Hosp Psychiatry*. 2008 Jul-Aug;**30**(4):293-302.
76. Cuijpers P, Hollon SD, van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open*. 2013 January 1, 2013;**3**(4).
77. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord*. 1998 Apr;**49**(1):59-72.
78. Blackburn IM, Eunson KM, Bishop S. A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. *Journal of Affective Disorders*. 1986;**10**(1):67-75.
79. David D, Szentagotai A, Lupu V, Cosman D. Rational emotive behavior therapy, cognitive therapy, and medication in the treatment of major depressive disorder: a randomized clinical trial, posttreatment outcomes, and six-month follow-up. *J Clin Psychol*. 2008 Jun;**64**(6):728-46.
80. Dekker J, Van HL, Hendriksen M, Koelen J, Schoevers RA, Kool S, et al. What is the best sequential treatment strategy in the treatment of depression? Adding pharmacotherapy to psychotherapy or vice versa? *Psychother Psychosom*. 2013;**82**(2):89-98.
81. Dobson KS, Hollon SD, Dimidjian S, Schmaling KB, Kohlenberg RJ, Gallop RJ, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. Journal of Consulting and Clinical Psychology; 2008. p. 468-77.
82. Evans MD, Hollon SD, DeRubeis RJ, Piasecki JM, Grove WM, Garvey MJ, et al. Differential relapse following cognitive therapy and pharmacotherapy for depression. *Arch Gen Psychiatry*. 1992 Oct;**49**(10):802-8.
83. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, et al. Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry*. 2005 Apr;**62**(4):417-22.
84. Kovacs M, Rush AJ, Beck AT, Hollon SD. Depressed outpatients treated with cognitive therapy or pharmacotherapy. A one-year follow-up. *Arch Gen Psychiatry*. 1981 Jan;**38**(1):33-9.

85. Mohr DC, Boudewyn AC, Goodkin DE, Bostrom A, Epstein L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *J Consult Clin Psychol*. 2001 Dec;**69**(6):942-9.

86. Moradveisi L, Huibers MJH, Renner F, Arasteh M, Arntz A. Behavioural activation v. antidepressant medication for treating depression in Iran: Randomised trial. *British Journal of Psychiatry*. 2013;**202**(3):204-11.

87. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. The British journal of psychiatry : the journal of mental science; 1997. p. 328-34.

88. Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. Journal of Consulting and Clinical Psychology; 2008. p. 966-78.

89. Mynors-Wallis LM, Gath DH, Day A, Baker F. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ (Clinical research ed); 2000. p. 26-30.

90. Segal ZV, Kennedy S, Gemar M, Hood K, Pedersen R, Buis T. Cognitive Reactivity to Sad Mood Provocation and the Prediction of Depressive Relapse. *Archives of General Psychiatry*. 2006 Jul;**63**(7):749-55.

91. Shea MT, Elkin I, Imber SD, Sotsky SM, Watkins JT, Collins JF, et al. Course of depressive symptoms over follow-up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Arch Gen Psychiatry*. 1992 Oct;**49**(10):782-7.

92. Simons AD, Murphy GE, Levine JL, Wetzel RD. Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. *Arch Gen Psychiatry*. 1986 Jan;**43**(1):43-8.

93. Miranda J, Duan N, Sherbourne C, Schoenbaum M, Lagomasino I, Jackson-Triche M, et al. Improving care for minorities: can quality improvement interventions improve care and outcomes for depressed minorities? Results of a randomized, controlled trial. Health Services Research; 2003. p. 613-30.

94. Jarrett RB, Minhajuddin A, Borman PD, Dunlap L, Segal ZV, Kidner CL, et al. Cognitive reactivity, dysfunctional attitudes, and depressive relapse and recurrence in cognitive therapy responders. Behaviour Research and Therapy; 2012. p. 280-6.

95. Beck AT, Hollon SD, Young JE, Bedrosian RC, Budenz D. Treatment of depression with cognitive therapy and amitriptyline. *Archives of general psychiatry*. 1985 Feb;**42**(2):142-8.

96. de Jonghe F, Hendricksen M, van Aalst G, Kool S, Peen V, Van R, et al. Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. *The British journal of psychiatry : the journal of mental science*. 2004 Jul;**185**:37-45.

97. Hollon SD, DeRubeis RJ, Evans MD, Wiemer MJ, Garvey MJ, Grove WM, et al. Cognitive therapy and pharmacotherapy for depression. Singly and in combination. *Arch Gen Psychiatry*. 1992 Oct;**49**(10):774-81.

98. Bellino S, Zizza M, Rinaldi C, Bogetto F. Combined treatment of major depression in patients with borderline personality disorder: a comparison with pharmacotherapy. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2006 Jun;**51**(7):453-60.

99. Macaskill ND, Macaskill A. Rational-emotive therapy plus pharmacotherapy versus pharmacotherapy alone in the treatment of high cognitive dysfunction depression. *Cogn Ther Res*. 1996;**20**(6):575-92.

100. Maina G, Rosso G, Bogetto F. Brief dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: long-term results. *Journal of affective disorders*. 2009 Apr;**114**(1-3):200-7.

101. Maina G, Rosso G, Rigardetto S, Piat SC, Bogetto F. No effect of adding brief dynamic therapy to pharmacotherapy in the treatment of obsessive-compulsive disorder with concurrent major depression. *Psychotherapy and Psychosomatics*. 2010;**79**(5):295-302.

102. Miller IW, Norman WH, Keitner GI. Cognitive-behavioral treatment of depressed inpatients: six- and twelve-month follow-up. *The American journal of psychiatry*. 1989 Oct;**146**(10):1274-9.
103. Schramm E, van Calker D, Dykierek P, Lieb K, Kech S, Zobel I, et al. An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. *The American journal of psychiatry*. 2007 May;**164**(5):768-77.
104. Sirey JA, Bruce ML, Alexopoulos GS. The Treatment Initiation Program: an intervention to improve depression outcomes in older adults. *The American journal of psychiatry*. 2005 Jan;**162**(1):184-6.
105. de Jonghe F, Kool S, van Aalst G, Dekker J, Peen J. Combining psychotherapy and antidepressants in the treatment of depression. *Journal of affective disorders*. 2001 May;**64**(2-3):217-29.
106. Hersen M, Bellack AS, Himmelhoch JM, Thase ME. Effects of social skill training, amitriptyline, and psychotherapy in unipolar depressed women. *Behav Ther*. 1984;**15**(1):21-40.
107. Reynolds CF, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA : the journal of the American Medical Association; 1999. p. 39-45.
108. Reynolds Iii CF, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, et al. Maintenance treatment of major depression in old age. *New England Journal of Medicine*. 2006;**354**(11):1130-8.
109. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Archives of general psychiatry; 1999. p. 829-35.
110. Perlis RH, Nierenberg AA, Alpert JE, Pava J, Matthews JD, Buchin J, et al. Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. *J Clin Psychopharmacol*. 2002 Oct;**22**(5):474-80.
111. Wilkinson P, Alder N, Juszczak E, Matthews H, Merritt C, Montgomery H, et al. A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. International Journal of Geriatric Psychiatry; 2009. p. 68-75.
112. Koppers D, Peen J, Niekerken S, Van R, Dekker J. Prevalence and risk factors for recurrence of depression five years after short term psychodynamic therapy. *Journal of affective disorders*. 2011 Nov;**134**(1-3):468-72.
113. Reynolds CF, 3rd, Frank E, Dew MA, Houck PR, Miller M, Mazumdar S, et al. Treatment of 70(+)-year-olds with recurrent major depression. Excellent short-term but brittle long-term response. *Am J Geriatr Psychiatry*. 1999 Winter;**7**(1):64-9.
114. Barlow DH. Negative effects from psychological treatments: A perspective. *American Psychologist*. 2010;**65**(1):13-20.
115. McNally RJ. Does early psychological intervention promote recovery from posttraumatic stress? *Psychological Science in the Public Interest (Wiley-Blackwell)*. 2003 11//;**4**(2):45.
116. Mayou RA. Psychological debriefing for road traffic accident victims: Three-year follow-up of a randomised controlled trial. *The British Journal of Psychiatry*. 2000;**176**(6):589-93.
117. Dishion TJ, Andrews DW. Preventing escalation in problem behaviors with high-risk young adolescents: Immediate and 1-year outcomes. *Journal of Consulting and Clinical Psychology*. 1995;**63**(4):538-48.
118. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. *Am J Psychiatry*. 2000 Apr;**157**(4 Suppl):1-45.
119. Winter SE, Barber JP. Should treatment for depression be based more on patient preference? *Patient Preference Adherence*. 2013;**7**:1047-57.
120. McHugh R, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: A meta-analytic review. *Journal of Clinical Psychiatry*. 2013 Jun;**74**(6):595-602.

121. Arean PA. Personalizing behavioral interventions: The case of late-life depression. *Neuropsychiatry*. 2012;**2**(2):135-45.
122. Berkowitz SA, Bell RA, Kravitz RL, Feldman MD. Vicarious experience affects patients' treatment preferences for depression. *PLoS ONE*. 2012;**7**(2).
123. Dobscha SK, Corson K, Gerrity MS. Depression treatment preferences of VA primary care patients. *Psychosomatics*. 2007;**48**(6):482-8.
124. Lewinsohn PM, Antonuccio DO, Steinmetz Breckenridge J, Teri L. The Coping with Depression Course : a Psychoeducational Intervention for Unipolar Depression. Eugene, OR 97440: Castalia Publishing Company; 1984.
125. Beck AT. Cognitive therapy of depression. New York: Guilford Press; 1979.
126. Rogers CR. On becoming a person : a therapist's view of psychotherapy. London: Constable; 1967.
127. Lewinsohn PM, Biglan A, Zeiss AM. Behaviorla treatment of depression. In: Davidson PO, editor. The behavioral management of anxiety, depression and pain. New York: Brunner / Mazel; 1976. p. 197p.
128. Nezu AM. Efficacy of a social problem-solving therapy approach for unipolar depression. *J Consult Clin Psychol*. 1986 Apr;**54**(2):196-202.
129. Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, Tomlinson D. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *BMJ*. 1995 Feb 18;**310**(6977):441-5.
130. Klerman G WM, Rounsaville B, Chevron E. . Interpersonal psychotherapy of depression. New York: Basic Books; 1984.