



Antidepressant medication in comparison with psychological treatment for moderate-severe depressive disorder

SCOPING QUESTION: In adults with moderate-severe depressive disorder, what is the effectiveness and safety of antidepressant medication (ADM) in comparison with psychological treatment?

BACKGROUND

Depressive disorder is a highly prevalent and disabling disorder. Its relative disease burden is pronounced in high- and middle-income countries and it is also a major cause of disease burden in low-income countries (Andrews and Titov, 2007; Kessler et al., 2005; Mathers and Loncar, 2006). It is associated with reduced quality of life, impaired social and personal relationships, disturbed academic and professional life, a variety of physical health problems and elevated economic costs with individual and societal impacts (Andrews and Wilding, 2004; Bijl and Ravelli, 2000; Gustavsson et al., 2011; Ustun et al., 2004). The adverse impact of depressive disorder is on the life of individuals and their families, which underscores the need for treatment. Several studies have examined the effects of pharmacotherapy and several types of psychological treatment on the reduction of depressive symptoms. Both pharmacological and psychological treatments have been found to be effective in treating depressive disorders in adults (Cuijpers et al., 2010; Cuijpers et al., 2008a; Cuijpers et al., 2008b).

The WHO mhGAP programme's existing guidelines recommend that either structured brief psychological treatments (e.g., interpersonal psychotherapy or cognitive behavioural therapy, including behavioural activation) or antidepressant medication (e.g., SSRIsⁱ and tricyclic antidepressants) be considered in adults with moderate-severe depression. Health care workers need to know whether these treatments have different effects, including side-effects, in treating depressive disorder in the short and long term, in order to improve clinical decision-making. The scoping question aims to identify the comparative effectiveness and safety of antidepressant medication in comparison with psychological treatment for adults with moderate-severe depressive disorder.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with moderate-severe depressive disorder
- **Interventions:** Psychological treatment
- **Comparison:** Antidepressant medication
- **Outcomes:**



- **Critical outcomes** - Reduction of symptoms, improved functioning/quality of life, adverse effects of treatment
- **Important outcomes** - Remission (as a categorical variable), treatment drop-out, sustained response

Search strategy

In order to locate relevant systematic reviews, two researchers independently conducted a systematic literature search of existing systematic reviews in the bibliographic databases of Medline, PsycINFO, Embase and the Cochrane Library. Each of these databases were searched until January 2014. Several keywords for psychological treatment and depressive disorder were combined with filters for systematic reviews (Higgins and Green, 2011). The results of the searches were entered into Endnote. Titles and abstracts were examined after duplicate publications were removed. Studies were retrieved and examined in full-text when they showed potential to meet the inclusion criteria. Consensus was sought in cases where the researchers disagreed on inclusion and, if needed, the opinion of a third researcher was sought. A new review was commissioned if no systematic reviews were available. Additionally, relevant systematic reviews were updated.

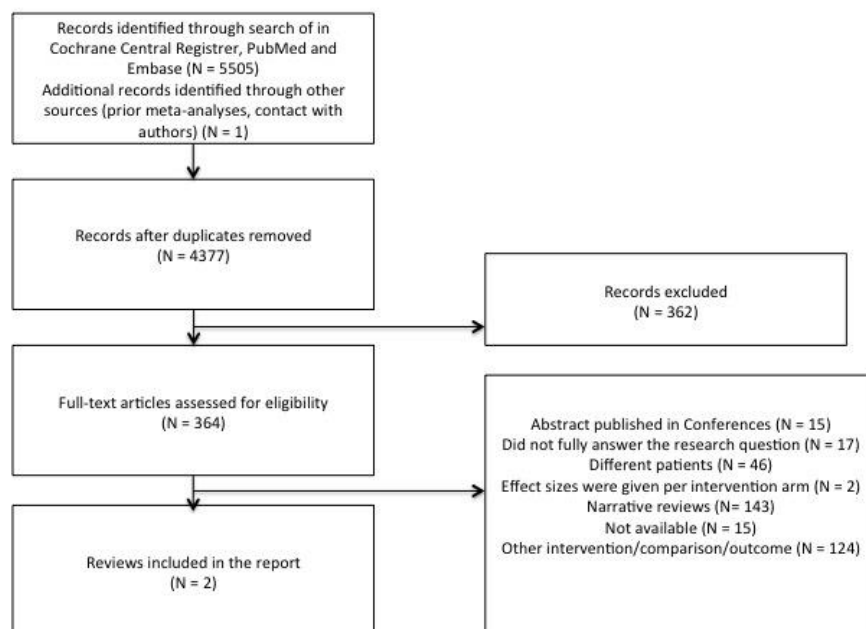
To identify RCTsⁱⁱ, an existing database of randomized trials on psychological treatment for depressive disorder was searched, comprising studies from 1966 with newly identified studies added annually to January 2014 (Cuijpers et al., 2008c). Furthermore, references of other systematic reviews and meta-analyses of the main psychological treatments for depressive disorder were also searched.

Included in GRADE tables or footnotes

The systematic literature search resulted in 5,505 references (MEDLINE: 1,634; Embase: 1, 999; PsycInfo: 721 and Cochrane Library: 1, 150). After removing duplicates, the titles and abstracts of 4,377 reports were examined resulting in the examination of 364 articles in full text. Reasons for exclusion are listed below in the section 'Excluded from GRADE tables and footnotes' on p. 5. Two systematic reviews on the comparison between antidepressant medication and psychological treatments were selected:

- Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds III CF (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. *World Psychiatry*.12(2):137-48.
- Karyotaki E, Smit Y, Cuijpers P, Gillain B, Fairon N, Paulus D, Robays J, Holdt Henninhsen K. Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants. Brussels: Belgian Health Care Knowledge Centre; 2014.

Figure 1. Selection process of systematic reviews





Excluded from GRADE tables and footnote

All excluded results and reasons for exclusion can be found in Appendix 1.

There were 17 reviews that examined several forms of psychological treatments compared to antidepressant medication at post-treatment and at long-term follow up. None of them answered the research questions in full.

Furthermore, two systematic reviews were excluded because the effect sizes were given per intervention arm (rather than per treatment comparison), 143 were excluded because they only presented narrative reviews, 15 articles were not available, 15 were abstracts published in scientific conference, 124 examined other intervention/comparison or they reported different outcomes and 46 included people with different problems

PICO Table

Population: Adults with moderate-severe depressive disorder					
Intervention	Comparison	Outcome	Systematic reviews used for GRADE	Justification for systematic review used	Relevant GRADE table
Acute (without continuation treatment) psychological treatment	Acute (without continuation treatment) antidepressants medication	Reduction in depressive symptoms – POST TREATMENT	Cuijpers et al. (2013)	Short-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 1
		Functioning/quality of life – POST TREATMENT	NO DATA		
		Remission – POST TREATMENT	Cuijpers et al. (2013)	Short-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 1
		Safety/adverse events – POST TREATMENT	Cuijpers et al. (2013)	Short-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 1



		Treatment dropout – POST TREATMENT	Cuijpers et al. (2013)	Short-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 1
Acute (without continuation treatment) psychological treatment	Acute (without continuation treatment) antidepressants medication	Reduction in depressive symptoms – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	Karyotaki et al. (2014)	Long-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 2
		Functioning/quality of life - 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
		Remission – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	Karyotaki et al. (2014)	Long-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 2
		Safety/adverse events – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
		Treatment dropout – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
Acute (without continuation treatment) psychological treatment	Antidepressants medication (acute plus continuation during follow-up)	Reduction in depressive symptoms – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	Karyotaki et al. (2014)	Long-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 3
		Functioning/quality of life - 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
		Remission – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
		Safety/adverse events – 6 MONTHS AND 1 YEAR POST	NO DATA		

		RANDOMIZATION			
		Treatment dropout – 6 MONTHS AND 1 YEAR POST RANDOMIZATION	NO DATA		
Psychological treatment (maintenance treatment)	Antidepressants medication (maintenance treatment)	Sustained response – 6 MONTHS OR LONGER POST RANDOMIZATION	Karyotaki et al. (2014)	Long-term effects of all main types of psychological treatment compared to antidepressants in treatment of adult moderate-severe depressive disorder	Table 4
		Functioning/quality of life - 6 MONTHS OR LONGER POST RANDOMIZATION	NO DATA		
		Remission– 6 MONTHS OR LONGER POST RANDOMIZATION	NO DATA		
		Safety/adverse events – 6 MONTHS OR LONGER POST RANDOMIZATION	NO DATA		
		Treatment dropout – 6 MONTHS OR LONGER POST RANDOMIZATION	NO DATA		

Narrative description of the studies that went into the analysis

Cuijpers et al. (2013) examined the **effects of acute phase psychological treatment compared to antidepressant medication on depressive and anxiety symptoms at post-treatment assessment** in adults with moderate-severe depressive disorder. The authors included in total 67 RCTs (40 and 27 focusing on depressive and anxiety disorders, respectively), from which 32 studies out of 40 depression studies focused on depressive disorder. Types of psychological treatment for depressive disorder examined include cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), psychodynamic (DYN), problem solving therapy (PST) and non-directive counselling. Types of antidepressant medication examined include monoamine oxidase inhibitors (MAOIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other types of antidepressant medication. Results derived from the meta-analysis of Cuijpers et al. (2013) indicated that psychological treatment resulted in a comparable response to treatment compared to pharmacotherapy at the post treatment assessment in people with moderate-severe depressive disorder ($g=0.02$, 95% CI: -0.10 to 0.13; $p>0.05$) (See GRADE Table 1, row 1).

Heterogeneity was moderate ($I^2=46$, 95%CIⁱⁱⁱ: 22 to 63). Furthermore, psychological treatment resulted in equal remission rates, treatment dropout and adverse effects, compared to pharmacotherapy at the post treatment assessment (See GRADE Table 1, rows 3-4, see Appendix 2 for study bibliographies).

Karyotaki et al. (2014) examined the **long-term effects of acute (without continuation treatment) and maintenance psychological treatment compared to antidepressant medication (continuation/no continuation) in treatment response at six months or longer post-randomization** in adults with moderate-severe depressive disorder. The authors included 22 RCTs, 15 on acute phase treatment and 7 on maintenance treatment. The bibliographic details for each of these studies can be found in Appendix 2. Types of psychological treatment examined include behavioural activation (BA), cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), mindfulness-based cognitive therapy (MBCT), problem solving therapy (PST), psychodynamic treatment (DYN) or rational emotive therapy (RET). Types of antidepressant medication (ADM) examined include MAOIs, SNRIs, SSRIs and TCAs. The following comparisons were made:

- (a) The systematic review of Karyotaki et al. (2014) included nine studies that **compared the outcomes of acute phase psychological treatment to antidepressant medication (which was discontinued at some point during the follow-up period) at 6 months or longer post-randomization**. Results indicated that psychological treatment resulted in a better treatment response compared to antidepressant medication after 6 months or longer post-randomization ($OR^{iv}=1.88$, 95%CI 1.11 to 3.18, $p<0.05$; GRADE Table 2, row 1). Heterogeneity was moderate ($I^2=49\%$, $p<0.05$; 95%CI of 1-74%) (15). Similar results were also seen after treatment discontinuation, indicating a better response to treatment in favour of psychological treatment ($OR=1.91$, 95%CI 1.07 to 3.42, $p<0.05$), after a 1 year follow up period (see GRADE Table 2, row 2). Heterogeneity between the studies was moderate ($I^2=53.64\%$, 95%CI: 8 to 77%).
- (b) This systematic review found no differences at 6 months in the results of six studies examining the **comparison between acute phase psychological treatment and antidepressant medication (which was continued during the full follow-up period) on people with moderate-severe depressive disorder response to treatment at six months or longer post-randomization** (see GRADE Table 3, row 1). Results indicate no significant differences between acute phase psychological treatment and antidepressant medication continuation at follow up of longer than 1 year (see GRADE Table 3, row 2).
- (c) Analysis on **remission at 6 months or longer post-randomization** revealed no differences **between psychological treatment and pharmacotherapy discontinuation** (see data GRADE Table 2, row 3). Only two studies reported on remission for the comparison between psychological treatment and pharmacotherapy (continuation) (not included in GRADE tables). David et al. 2008 reported that 24/56 people of CBT group, 25/57 people of rational emotive behavioural therapy group and 19/57 people of antidepressant medication group had remitted at 6 months post-randomization (no significant differences), while Dobson et al. (2008) found no statistically significant differences in remission rates between BA, CBT and antidepressant medication (no continuation). The authors reported that 12/27 people in the BA

group, 10/30 in the CBT and 6/28 people in the antidepressant medication (no continuation) group experienced remission at 1 year after randomization.

- (d) Only three RCTs reported on **adverse events** (not in Grade tables). David et al. 2008 found that significantly more people in the antidepressant medication (continuation) group experienced adverse effects, as compared to people in psychological treatment groups. More specifically, the authors reported that 9/49 people receiving antidepressant medication (continuation) experienced adverse effects (e.g., panic attacks, anxiety, insomnia, crying/anger and restlessness), 0/52 experienced adverse effects following rational emotive behavioural therapy and 1/50 experienced adverse effects following CBT (insomnia). Moradveisi et al. 2013 compared psychological treatment to antidepressant medication (discontinuation) and reported that three people dropped out due to medication side effects; however, this difference was not significant. Weissman et al. 1981 found no significant differences between psychological treatment and antidepressant medication (discontinuation) in adverse effects rates. The authors reported that three people (one followed psychological treatment and two receiving antidepressant medication) were hospitalized. No suicides were reported. Finally, no studies reported on quality of life or work related outcomes.
- (e) With respect to maintenance therapy, Karyotaki et al. (2014) found that **maintenance psychological treatment and maintenance antidepressant medication** did not differ significantly from each other at 8 months or at 2 years or longer post-randomization (see GRADE Table 4, rows 1-2). Only one study reported on adverse events. Jarrett et al. (2013) stated that during maintenance therapy two people from each group (ADM and CBT) were hospitalized for worsening depression and/or suicidal ideation (not included in GRADE tables). However, no suicides were reported. Finally, no studies reported on quality of life or work related outcomes.

GRADE Tables

Table 1. Acute (without continuation treatment) psychological treatment vs. acute (without continuation treatment) antidepressant medication in adults with moderate-severe depressive disorder, post-treatment

Author(s): Eirini Karyotaki, Pim Cuijpers,

Question: In adults with moderate-severe depressive disorder, what is the effectiveness and safety of antidepressant medication (ADM) in comparison with psychological treatment?

Bibliography: Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds III CF (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. World Psychiatry.12(2):137-48.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological treatment	ADM ^v	Relative (95% CI)	Absolute		
Reduction in depressive symptoms to psychological treatment vs. antidepressant medication in adults with moderate-severe depressive disorder												
32	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	No serious imprecision	None	1639	1489	-	SMD ^{vi} 0.02 higher (0.10 lower to 0.13 higher)	⊕⊕○○ LOW	CRITICAL
Remission to psychological treatment vs. antidepressant medication in adults with moderate-severe depressive disorder												
15	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ²	No serious imprecision	Reporting bias ⁴	253/552 (45.8%)	245/553 (44.3%)	OR 0.98 (0.72 to 1.34)	5 fewer per 1000 (from 73 more to 79 fewer)	⊕⊕○○ LOW	IMPORTANT
Functioning/quality of life												
N/A ^{vii}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Safety/adverse events												
8	Randomized trials	Serious ¹	No serious inconsistency	Serious	Serious ³	None	5/250 (2%)	17/309 (5.5%)	OR 0.5 (0.18 to 1.36)	25 fewer per 1000 (from 20 more to 45 fewer)	⊕○○○ VERY LOW	CRITICAL
Treatment dropout												

20	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	Serious ³	None	218/886 (24.6%)	310/878 (35.3%)	OR 0.75 (0.54 to 1.05)	63 fewer per 1000 (from 11 more to 125 fewer)	⊕○○○ VERY LOW	IMPORTANT
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¹ 18/32 RCTs at high risk of bias due to unclear/inadequate sequence generation; 20/32 RCTs at high risk of bias due to unclear/inadequate allocation concealment; 10/32 RCTs at high risk of bias due to unblinded outcome assessment; 9/32 RCTs at high risk of bias due to (the handling of) incomplete data; 6/8 at high risk of bias due to unclear/inadequate sequence generation; 6/8 RCTs at high risk of bias due to unclear/inadequate allocation concealment; 13/20 RCTs at high risk of bias due to unclear/inadequate sequence generation and at high risk of bias due to unclear/inadequate allocation concealment.

² Several different types of psychological treatment have been examined (the same might be reported for antidepressants).

³ 95%CI includes no effect; 95%CI crosses a suggested minimal important difference of an OR of 1.5, or an OR of 0.67, or a SMD of 0.24 (Cuijpers et al., 2014).

⁴ According to 'trim and fill' procedure, 3 studies were missing.

Table 2. Acute (without continuation treatment) psychological treatment vs. antidepressants medication (no continuation of antidepressants during follow up) in adults with moderate-severe depressive disorder. acute phase treatment long-term outcomes

Authors: E Karyotaki and P Cuijpers

Question: In adults with moderate-severe depressive disorder, what is the effectiveness and safety of antidepressant medication (ADM) in comparison with psychological treatment?

Bibliography: Karyotaki E, Smit Y, Cuijpers P, Gillain B, Fairon N, Paulus D, Robays J, Holdt Henninhsen K. Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants. Brussels: Belgian Health Care Knowledge Centre; 2014.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological treatment	ADM	Relative (95% CI)	Absolute		
Response to psychological treatment vs. antidepressant medication (no continuation) at 6 months or longer post-randomization												
9	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	Serious ³	Reporting bias ⁴	201/327 (61.5%)	86/174 (49.4%)	OR 1.88 (1.11 to 3.18)	157 more per 1000 (from 17 more to 494 more)	⊕○○○ VERY LOW	CRITICAL
Response to psychological treatment vs. antidepressant medication (no continuation) at 1 year or longer post-randomization												
8	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	Serious ³	Reporting bias ⁴	201/326 (61.7%)	86/174 (49.4%)	OR 1.91 (1.07 to 3.42)	157 more per 1000 (from 17 more to 275 more)	⊕○○○ VERY LOW	CRITICAL
Remission to psychological treatment vs. antidepressant medication (no continuation) at 6 months and at 1 year or longer post randomization												
5	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	Serious ³	None	140/285 (49.1%)	58/145 (40%)	OR 1.50 (0.87 to 2.54)	100 more per 1000 (from 33 fewer to 229 more)	⊕○○○ VERY LOW	IMPORTANT
Functioning/quality of life												

N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Safety/adverse events												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Treatment dropout												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

¹ 4/9 RCTs and 3/8 RCTs, respectively, are at high risk of bias due to unblinded assessment of all outcomes; part of the outcomes were assessed unblinded in an additional 5/12, 4/8 and 5/5 RCTs; 7/9 RCTs, 6/8 and 5/5 RCTs are at high risk of bias due to (the handling of) incomplete data.

² Several different types of psychological treatment have been examined.

³ 95%CI includes a suggested minimal important difference of an OR of 1.5, or an OR of 0.67, or a SMD of 0.24 (Cuijpers et al., 2014).

⁴ Small studies with a favourable effect for ADM seem to be missing on visual inspection of the funnel plot. Substantial difference in estimated effect sizes using the 'trim and fill' test, with the imputed point estimates are 1.15 (95%CI: 0.64 to 2.06) and 1.07 (0.57 to 2.04), respectively.

Table 3. Acute (without continuation treatment) psychological treatment vs. antidepressants medication (with continuation of antidepressants during follow up) in adults with moderate-severe depressive disorder, acute phase treatment long-term outcomes

Authors: E Karyotaki and P Cuijpers

Question: In adults with moderate-severe depressive disorder, what is the effectiveness and safety of antidepressant medication (ADM) in comparison with psychological treatment?

Bibliography: Karyotaki E, Smit Y, Cuijpers P, Gillain B, Fairon N, Paulus D, Robays J, Holdt Henninhsen K. Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants. Brussels: Belgian Health Care Knowledge Centre; 2014.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological treatment	ADM continuation	Relative (95% CI)	Absolute		
Response to psychological treatment vs. antidepressant medication (plus continuation) at 6 months or longer post-randomization												
6	Randomized trials	Serious ¹	No serious inconsistency	Serious ²	Serious ³	None	160/256 (62.5%)	86/154 (55.8%)	OR 1.30 (0.90 to 1.88)	63 more per 1000 (from 26 fewer to 145 more)	⊕○○○ VERY LOW	CRITICAL
Response to psychological treatment vs. antidepressant medication (plus continuation) at 1 year or longer post-randomization												
3	Randomized trials	Serious ¹	No serious inconsistency	No serious indirectness	Serious ³	None	85/151 (56.3%)	49/102 (48%)	OR 1.63 (0.99 to 2.69)	121 more per 1000 (from 3 fewer to 233 more)	⊕⊕○○ LOW	CRITICAL

Remission to psychological treatment vs. antidepressant medication (plus continuation) at 6 months and at 1 year or longer post randomization												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT
Functioning/quality of life												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Safety/adverse events												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Treatment dropout												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

¹ 3/6 RCTs and 1/3 RCTs, respectively, at high risk of bias due to unblinded assessment of part of the outcomes; 3/6 RCTs and 3/3 RCTs at high risk of bias due to (the handling of) incomplete data.

² Several different types of psychological treatment have been examined.

³ 95%CI includes a suggested minimal important difference of an OR of 1.5, or an OR of 0.67, or a SMD of 0.24(Cuijpers et al., 2014).

Table 4. Psychological treatment vs. antidepressants in adults with moderate-severe depressive disorder, maintenance treatment long-term outcomes

Authors: E Karyotaki and P Cuijpers

Question: In adults with moderate-severe depressive disorder, what is the effectiveness and safety of antidepressant medication (ADM) in comparison with psychological treatment?

Bibliography: Karyotaki E, Smit Y, Cuijpers P, Gillain B, Fairon N, Paulus D, Robays J, Holdt Henninhsen K. Major Depression: Long term efficacy of psychotherapy, alone or in combination with antidepressants. Brussels: Belgian Health Care Knowledge Centre; 2014.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance psychological treatment	Maintenance ADM	Relative (95% CI)	Absolute		
Sustained response to maintenance psychological treatment vs. maintenance antidepressant medication at <u>8 months</u> or longer post-randomization												
7	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ¹	No serious imprecision	None	129/204 (63.2%)	129/210 (61.4%)	OR 1.05 (0.76 to 1.45)	11 more per 1000 (from 67 fewer to 84 more)	⊕⊕⊕○ MODERATE	CRITICAL
Sustained response to maintenance psychological treatment vs. maintenance antidepressant medication at <u>2 years</u> or longer post-randomization												

4	Randomized trials	Serious ²	No serious inconsistency	No serious indirectness	Serious ³	None	69/118 (58.5%)	74/120 (61.7%)	OR 0.86 (0.51 to 1.46)	36 fewer per 1000 (from 166 fewer to 85 more)	⊕⊕⊕ LOW	CRITICAL
Remission to maintenance psychological treatment vs. maintenance antidepressant medication at <u>8 months</u> and at <u>2 years</u> or longer post-randomization												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT
Functioning/quality of life												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	NA	N/A	CRITICAL
Safety/adverse events												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
Treatment dropout												
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

¹ Several different types of psychological treatment have been examined.

² 2/4 RCTs at high risk of bias due to unblinded assessment of all of the outcomes; 1 RCT at high risk of bias due to unblinded assessment of part of the outcomes; 2 RCTs at high risk of bias due to (the handling of) incomplete data.

³ 95%CI includes no effect and crosses a suggested minimal important difference of an OR of 1.5, or an OR of 0.67, or a SMD of 0.24 (Cuijpers et al., 2014).

Additional evidence not mentioned in GRADE tables

In a partially randomized preference trial, Bedi et al. (2000) found non-significant differences between non-directive counselling and antidepressant medication across the eight domains of SF-36. Hollon et al. (1992) did not find any evidence of differentiation in a RCT comparing CBT and antidepressant medication on the Global Assessment Scale (GAS) at post-treatment assessment.

Analysis on remission at follow-up between psychological treatment and pharmacotherapy (with continuation) identified two studies that reported on remission (not included in the GRADE tables).

The RCT led by David et al. (2008) found that 24/56 people of the CBT group, 25/57 people of the REBT group and 19/57 people of the ADM group had remitted at 6 months post-randomization (no significant differences), while Dobson et al. (2008) found no statistically significant differences in remission rates between BA, CBT and ADM (no continuation). The authors reported that 12/27 people in the BA group, 10/30 in the CBT group and 6/28 people in the ADM (no continuation) group experienced remission at 1 year after randomization.

Very few RCTs report on the adverse effects of either antidepressant or psychological treatment when these two forms of interventions are compared directly. In terms of indirect evidence, the side effects of psychotherapies have not been extensively examined systematically. It has been suggested that psychotherapies could result in deterioration (e.g., symptoms worsening, relapse, recurrence or a combination of these) in some depressed patients, and that some psychotherapies could increase risk of other mental disorders (e.g., psychotic decompensation in depressed patients with comorbid personality disorders), as well as increase risk of suicide (Barlow, 2010; Bergin, 1966; Blais et al., 2013; Dimidjian and Hollon, 2010). One trial that examined psychological interventions was stopped because of excessive adverse events in the intervention group (Duggan et al., 2014). However, the adverse effects in psychological treatment have not been systematically examined in trials extensively and further study is needed on the extent to which negative effects occur. Overall, the study of adverse effects of psychological treatment is still in its infancy.

Much is known about the potential adverse side effects of antidepressant medications. Common side effects of SSRIs include agitation, anxiety, nausea, diarrhoea or constipation, loss of appetite and weight loss, dizziness, blurred vision, dry mouth, excessive sweating, insomnia, drowsiness and headaches (Ferguson, 2001). Additional side effects of SSRIs that are thought to be clinically relevant include:

Sexual dysfunction (Clark et al., 2013; Serretti and Chiesa, 2011; Serretti and Chiesa, 2009; Papkostas, 2008)

SSRIs can cause various types of sexual dysfunction, such as anorgasmia, erectile dysfunction, diminished libido, genital numbness and sexual anhedonia (i.e. pleasure-less orgasm). Sexual dysfunction occasionally persists after discontinuing SSRIs. The frequency of this effect is unknown. The mechanism by which SSRIs cause sexual side effects is not well understood; however, research findings suggest that stimulation of postsynaptic 5-HT₂ and 5-HT₃ receptors decreases dopamine and norepinephrine release from the substantia nigra. A number of (non-SSRI) medications are not associated with sexual side effects, such as bupropion, mirtazapine, tianeptine, agomelatine and moclobemide.

Cardiac side-effects (Kogut et al., 2013)

SSRIs do not appear to affect the risk of coronary heart disease (CHD) in those without a previous diagnosis of CHD. A number of large studies of people without known pre-existing heart disease have reported no electrocardiogram (ECG) changes related to SSRI use. The recommended maximum daily dose of citalopram and escitalopram was reduced due to concerns with QT interval ^{viii}prolongation. In overdose, fluoxetine reportedly causes sinus tachycardia, myocardial infarction, junctional rhythms and trigeminy. Some authors have suggested electrocardiographic monitoring in patients with severe pre-existing cardiovascular disease who are taking SSRIs.

Bleeding abnormalities (Anglin et al., 2014)

SSRIs interact with anticoagulants, like warfarin and acetylsalicylic acid. This includes an increased risk of gastrointestinal bleeding and post-operative bleeding. While the relative risk of intracranial bleeding is increased, the absolute risk is very low. SSRIs are also known to cause platelet



dysfunction. This risk is greater in those who are also on anticoagulants, antiplatelet agents and nonsteroidal anti-inflammatory medications (NSAIDs), as well as in those with comorbidities, such as cirrhosis of the liver or liver failure.

Discontinuation syndrome (Harvey and Slabbert, 2014)

SSRIs should not be abruptly discontinued after extended therapy. Instead, they should be tapered over several weeks to minimize discontinuation-related symptoms, which may include nausea, headache, dizziness, chills, body aches, paraesthesia, insomnia and electric shock-like sensations. Paroxetine may produce discontinuation-related symptoms at a greater rate than other SSRIs; however, qualitatively similar effects have been reported for all SSRIs. Fluoxetine presents less discontinuation effects, likely due to its long half-life and the natural tapering effect associated with slow clearance from the body. One strategy for minimizing SSRI discontinuation symptoms is to switch the patient to fluoxetine and then to taper and discontinue the fluoxetine over several weeks.

Overdose

SSRIs appear safer in overdose when compared with traditional antidepressants, such as the tricyclic antidepressants. This relative safety is supported both by case series studies and studies of deaths per number of prescriptions. However, case reports of SSRI poisoning have indicated that severe toxicity can occur and deaths have been reported following massive single ingestions, although this is exceedingly uncommon when compared to the tricyclic antidepressants. Most patients will have mild or no symptoms following moderate overdoses due to the wide therapeutic index of the SSRIs. Serotonin syndrome is the most commonly reported severe effect following SSRI overdose. Serotonin toxicity is another common side effect and is usually associated with very high overdoses or multiple medication ingestion. Other reported significant effects include coma, seizures and cardiac toxicity.

Pregnancy (Howard et al., 2014)

Antidepressant exposure in pregnancy is significantly associated with early gestational age at birth, preterm delivery and with lower Apgar scores at 1 min and 5 min. It is worth noting that some of these associations might be of limited clinical significance. Meta-analyses have previously reported associations with antidepressant exposure and reduced birth weight; however, a 2013 meta-analysis demonstrated no significant association with reduced birth weight when the comparison group was limited to depressed mothers without antidepressant exposure. There exists a consistent significant association between exposure to antidepressant medication during pregnancy and occurrence of clinical signs of respiratory distress and/or poor neonatal adaptation syndrome. Risks to the foetus are very difficult to assess. Many studies are small with biased samples, low-quality study design, little adjustment for important confounders (such as smoking) and an almost invariable absence of adjustment for confounding by indication. Initial reports of risks have frequently not been substantiated or are shown to be smaller once larger studies and meta-analyses have been done. For example, despite early reports, an increased risk of spontaneous abortion associated with exposure to antidepressant medication has not been confirmed and recent population studies have not found associations with antenatal SSRIs and stillbirths or neonatal deaths after adjusting for confounders. Two meta-analyses showed paroxetine exposure is associated with only slightly increased risk of fetal cardiac malformations.



PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Outcomes	Acute (without continuation treatment) psychological treatment vs. acute (without continuation treatment) antidepressant medication <i>(Number of studies, OR or SMD [95% CI], findings and quality)</i>		Acute (without continuation treatment) psychological treatment vs. antidepressant medication (acute plus continuation during follow-up) <i>(Number of studies, OR or SMD [95% CI], findings and quality)</i>	Psychological treatment (maintenance treatment) vs. antidepressant medication (maintenance treatment) <i>(Number of studies, OR SMD [95% CI], findings and quality)</i>
	POST-TREATMENT	LONG-TERM OUTCOMES		
Response	32 studies, SMD 0.02 (-0.10 to 0.13) No difference LOW quality	9 studies (6 months), OR 1.88 (1.11 to 3.18) In favour of psychological treat. VERY LOW quality 8 studies (12 months), OR 1.91 (1.07 to 3.42) In favour of psychological treat. VERY LOW quality	6 studies (6 months), OR 1.30 (0.90 to 1.88) No difference VERY LOW quality 3 studies (12 months), OR 1.63 (0.99 to 2.69) No difference LOW quality	7 studies (8 months), OR 1.05 (0.76 to 1.45) No difference MODERATE quality 4 studies (24 months), OR 0.86 (0.51 to 1.46) No difference LOW quality
Remission	15 studies, OR 0.98 (0.72 to 1.34) No difference LOW quality	5 studies, OR 1.50 (0.87 to 2.54) No difference VERY LOW quality	_____	_____
Functioning	_____	_____	_____	_____
Adverse	8 studies,	_____	_____	_____



events	OR 0.50 (0.18 to 1.36) No difference VERY LOW quality			
Dropouts	20 studies, OR 0.75 (0.54 to 1.05) No difference VERY LOW quality	_____	_____	_____

Evidence to recommendations table

Benefits	<p>Psychological treatment vs. antidepressant medication in adults with moderate-severe depressive disorder, acute phase treatment outcomes immediately post-treatment:</p> <ul style="list-style-type: none"> • There is low quality evidence suggesting that acute phase psychological treatment and antidepressant medication are similarly effective in terms of reduction of depressive symptoms and remission rates at the post-treatment assessment in adults with moderate-severe depressive disorder. <p>Psychological treatment vs. antidepressant medication in adults with moderate-severe depressive disorder, acute phase treatment long-term outcomes:</p> <ul style="list-style-type: none"> • There is very low quality evidence suggesting that acute phase psychological treatment results in a better acute phase treatment response compared to antidepressant medication (with discontinuation) at 6 months and at 1 year or longer post-randomization in adults with moderate-severe depressive disorder. • There is very low quality evidence suggesting that treatment with psychological treatment and antidepressants (with discontinuation) are similarly effective in terms of remission rates at 6 months or longer post-randomization. <p>Psychological treatment vs. antidepressant medication (with continuation of antidepressants during follow up) in adults with moderate-severe depressive disorder, acute phase treatment</p>
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	<p>long-term outcomes:</p> <ul style="list-style-type: none"> • There is very low quality evidence suggesting that acute phase psychological treatment and antidepressant medication (with continuation) are similarly effective in terms of treatment response at 6 months or longer post-randomization in adults with moderate-severe depressive disorder. • There is low-quality evidence that acute phase psychological treatment and antidepressant medication (with continuation) are similarly effective in terms of treatment response at 1 year or longer post-randomization in adults with moderate-severe depressive disorder. <p>Psychological treatment vs. antidepressant medication in adults who had moderate-severe depressive disorder, maintenance treatment long-term outcomes:</p> <ul style="list-style-type: none"> • At 8 months: There is moderate quality evidence suggesting that maintenance psychological treatment and maintenance antidepressant medication are similarly effective in terms of sustained treatment response at 8 months or longer post-randomization in adults who had moderate-severe depressive disorder and who had responded to acute phase treatment with either psychological treatment or antidepressant medication. • At 24 months: There is limited evidence that maintenance treatment with psychological treatment and treatment with antidepressant medication result in a similarly sustained response in adults who had moderate-severe depressive disorder and who had responded to acute phase treatment with either psychological treatment or antidepressant medication at 2 years or longer post-randomization. The confidence estimate is low.
<p>Harms</p>	<p>Psychological treatment vs. antidepressant medication in adults with moderate-severe depressive disorder, post-treatment outcomes:</p> <ul style="list-style-type: none"> • There is a lot of <i>indirect</i> evidence on adverse effects of antidepressants (i.e evidence from studies that do not directly compare antidepressant medication with psychological treatment). Common side effects of SSRIs include agitation, anxiety, nausea, diarrhoea or constipation, loss of appetite and weight loss, dizziness, blurred vision, dry mouth, excessive sweating, insomnia, drowsiness and headaches. Additional clinically relevant side-effects include sexual dysfunction, cardiac and bleeding abnormalities and discontinuation symptoms. There are safety concerns



	<p>related to the use of antidepressants during pregnancy.</p> <ul style="list-style-type: none"> • Very few RCTs report on the adverse effects of either antidepressant medication or psychological treatment when these two forms of interventions are compared directly. • There is very low quality <i>direct</i> evidence that psychological treatment and antidepressant medication result in a similar number of adverse events and in dropout rates at the post-treatment assessment in adults with moderate-severe depressive disorder. • There is an absence of evidence on adverse effects of psychological treatments.
<p>Summary of the of quality of evidence</p>	<p>The evidence from low-income countries is very limited, especially from non-urban or rural settings.</p> <p>Although the quality of the evidence is low to very low, the benefits of either intervention outweigh the harms.</p> <p>Direct comparisons suggest that there are no differences between these interventions, provided that acute phase antidepressant medication is followed by maintenance antidepressant medication.</p> <p>Indirect comparisons suggest that adverse effects are likely more pronounced in antidepressant medications.</p>

<p>Values and preferences</p>	
<p>In favour of preferring one treatment over the other</p>	<p>Psychological treatment, and more specifically CBT, has been found to have an effect without requiring continuation of the therapy. This is not the case with pharmacotherapy. Existing WHO guidelines on pharmacotherapy for moderate-severe depressive disorder strongly recommend 9-12 months continuation of antidepressant medication. Stopping treatment any earlier is associated with an elevated risk of relapse.</p> <p>The systematic review of Karyotaki et al. (2014) examined individual preferences and values in treating moderate-severe depressive disorder with either psychological treatment or pharmacotherapy. The authors reviewed studies examining the effect of individual treatment preferences on treatment course and outcome. Further, the authors examined which treatment options patients tend to prefer and which factors may affect these preferences. The examined studies were all from high-income industrialized</p>



	<p>settings. They reported that in these settings there is no relationship between treatment preferences and outcome, with only a small number of studies reported a positive relationship. Moreover, the results indicated that study participants are often concerned about the potential side-effects of antidepressants, treatment time commitment and increased cost of psychological treatment. With respect to treatment preferences, individuals in these settings generally preferred psychological treatment to antidepressant medication. Finally, older adults and women tended to prefer psychological treatment, while individuals with higher levels of depressive symptoms tended to prefer antidepressant medication.</p> <p>Psychological treatment has a lower risk of medicalizing social problems than pharmacotherapy. It may also provide coping skills to help individuals manage new episodes of psychological distress in settings with perpetual distress.</p> <p>Although in high-income countries most people prefer psychological treatment to pharmacotherapy, this may not be the case across low- and middle-income countries. People in some settings clearly prefer antidepressant medication; for example, in India, as described in an ethnographic report (Nunley, 1996).</p>
Against	The potential of decreasing depressive disorder and its burden while enhancing recovery is an important value applicable to both psychological treatment and antidepressant medication.
Uncertainty or variability?	There may be variability across the world in terms of treatment preferences.
Feasibility (including resource use considerations)	<p>Personnel is required for both pharmacological and psychological treatments, and both specialists and non-specialist staff may be successfully trained to deliver these treatments in low- and middle- income countries (Patel et al., 2010).</p> <p>Many non-specialist health services in the world are understaffed and lack personnel (e.g., nurses, community health workers, etc.) that can undermine capacity to deliver multiple sessions of psychological treatments or continued monitoring of antidepressant medication.</p>



	<p>In low- and middle-income countries, many non-specialist health services, including local pharmacies, often experience interruptions in medication supply.</p> <p>Economic trials show that treatment of depressive disorder is cost-effective compared to no treatment and may increase productivity among workers (WHO, 2013). Given that the two interventions are equally effective, the cost-effectiveness of antidepressant medication vs. psychological treatment will depend on staff and medication costs. These costs vary across countries, therefore it is not possible to make a generalized statement on relative cost-effectiveness of antidepressant medication vs. psychological treatment that can be applied globally (Chisholm et al., 2006).</p> <p>It is worth noting that offering brief psychological treatment is less resource-intensive than offering longer-term psychological treatment. Structured psychological treatments can be manualized and make training and supervision easier than unstructured psychological treatment.</p>
<p>Uncertainty or variability</p>	<p>High variability: Intensity of resource use for each treatment options depends on the context.</p>

Recommendation and remarks

Recommendation

As first-line therapy, health care providers may select psychological treatments (such as behavioural activation [BA], cognitive behavioural therapy [CBT], or interpersonal psychotherapy [IPT]) or antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]). They should keep in mind the possible adverse effects associated with antidepressant medications, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences.

Rationale: Although the quality of the evidence is low to very low, the benefits of either intervention outweigh their harms with no differences between the interventions in direct comparisons. Indirect comparisons suggest that adverse effects are



likely more pronounced with antidepressant medications.

Remarks

Sufficient human resources (e.g., community health workers trained and supervised in delivering psychological treatment) and continuous medication supply need to be made available for psychological and antidepressant treatment, respectively. Health care providers should discuss with help-seekers the pros and cons of either treatment (e.g. including side effects, and time needed) allowing the person to decide which treatment he or she prefers.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low
Balance of benefits versus harms	<input checked="" type="checkbox"/> Benefits clearly outweigh harms for either treatments <input type="checkbox"/> Benefits and harms are balanced <input type="checkbox"/> Potential harms clearly outweigh potential benefits
Values and preferences	<input type="checkbox"/> No major variability <input checked="" type="checkbox"/> Major variability



Resource use	<input type="checkbox"/> Less resource-intensive <input type="checkbox"/> More resource-intensive X Variable: Depends on country, setting and intervention option
Strength	CONDITIONAL

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APPENDIX 1

Studies excluded from GRADE tables and footnotes with reasons for exclusion

REASON FOR EXCLUSION: Did not answer research question in full

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REASON FOR EXCLUSION: Effect sizes were given per intervention arm (rather than per treatment comparison)

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ⁱ Selective serotonin uptake inhibitor (SSRI)

ⁱⁱ Randomized controlled trial (RCT)

ⁱⁱⁱ Confidence interval (CI)

^{iv} Odds ratio (OR)

^v Antidepressant medication (ADM)

^{vi} Standardized mean difference (SMD)

^{vii} Not applicable (N/A)

^{viii} Measure of time between start of the Q-wave and end of the T-wave (QT interval).