Depression module – evidence profile DEP4: Antidepressant medicine in comparison with psychological treatment for moderate-severe depressive disorder

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

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World Health Organization

Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1. Background

Depression is a highly prevalent and recurrent mental disorder (Kessler, R. C., & Bromet, 2013). It has a great negative impact on the quality of life and functioning of the individuals, and it is associated with high societal and economic costs (Bloom et al., 2011; Ferrari et al., 2010; World Health Organization [WHO], 2008). By 2030, depression is predicted to be one of the leading causes of disability and premature mortality worldwide (Mathers & Loncar, 2006). Reducing the burden of depression by developing evidence-based interventions is now a major global priority (World Bank Group & WHO, 2016). Different types of antidepressant medication and psychological interventions have been found to be effective in the treatment of depression (Cipriani et al., 2018; Cuijpers et al., 2021), being both therapies recommended as first-line treatments (Nathan & Gorman, 2015; Fletcher, Leaman, McSloy, & Leng, 2020). Research on the differential effectiveness between psychotherapy, pharmacotherapy, and their combination suggests better outcomes for combined treatment, as well as more acceptability for psychotherapy (Cuijpers et al. 202; Karyotaki et al., 2016).

An increasing number of trials assessing the relative effectiveness and safety of antidepressants and psychotherapies is being published every year, and recent meta-analyses using more precise techniques (e.g., network analyses) provide evidence about the relative effectiveness of antidepressant medications that should be considered in clinical guidelines. In the current report, we aimed to present the results of a systematic review of meta-analyses covering the relative efficacy and safety of antidepressants, psychotherapy, and their combination for depression. Focusing on Tricyclic Antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI), and brief and structured psychotherapies, we evaluated the relative effectiveness and safety of these therapies and their combination in a wide range of outcomes, including symptom reduction, suicide-related outcomes, adverse effects, improvements in functioning, remission, treatment drop-out, and sustained response.

2. Methodology

Evidence from recent meta-analyses comparing the effectiveness and safety of pharmacotherapy, psychotherapy and their combination for adults with depressive episode or disorders was summarized.

2.1. PICO Question

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

Population (P): Adults with moderate-severe depressive disorder and/or elevated depressive symptoms
Intervention (I): Psychological treatment (e.g. behavioural activation, cognitive behavioural therapy, and interpersonal psychotherapy); Antidepressant medication (TCAs or SSRIs); Combined psychological treatment and antidepressant medication (TCAs or SSRIs)
Comparator (C): head to head comparison
Outcomes (O):

List critical outcomes:

- **Critical outcome 1:** Reduction of symptoms
- **Critical outcome 2** Improved functioning/quality of life
- **Critical outcome 3:** Adverse effects

List important outcomes:

- **Important outcome 1:** Remission (as a categorical variable)
- **Important outcome 2:** Treatment drop-out
- **Important outcome 3:** Sustained response

2.2. Search strategy

Existing systematic reviews were identified by conducting searches in the following bibliographic databases:

- PubMed
- PsycINFO
- Embase
- Cochrane reviews
- Global Index Medicus

The search strings were designed in collaboration with a Medical Information Specialist at the Vrije Universiteit Amsterdam. We designed the search strings by combining blocks with free and index terms indicative for 1) Depression (*Type of Participants*), 2) Antidepressants (TCA and SSRIs) (*Types of interventions*), 3) Psychotherapies (brief) (*Types of interventions)*, and 4) terms related to systematic reviews and meta-analyses (*Type of studies*). In line with the WHO guideline methodology, indicating that evidence obtained for the development of guidelines should be as recent as possible (World Health Organization, 2014), the period of the searches covered from 1 January 2019 until 31 January 2022. No restrictions were applied for language.

2.3. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases were assessed for eligibility by examining their titles and abstracts, based on the inclusion and exclusion criteria developed a priori. Studies were included if they were (i) Systematic reviews of randomized controlled trials (RCTs). (ii) Had adult participants (>18 years) with a primary diagnosis of depression as established by a diagnostic interview or elevated symptoms of depression according to cut off scores on self-report scales. (iii) Compared the effectiveness or safety between antidepressant medications (ADM), psychological interventions and combined treatment (ADM + psychotherapy) (iv) Reported outcomes regarding mental health symptoms, adverse effects, quality of life and functioning, drop out, remission and sustained response. We excluded studies that had participants with secondary depression (due to medical conditions/illness, trauma, etc), bipolar disorder, psychotic depression, and treatment resistant depression. The full text of articles found to be potentially relevant based on their titles and abstracts were retrieved and examined, considering the same inclusion criteria in the second stage of study selection. Data from eligible studies were extracted into pre-defined templates that include the general characteristics of the study, population, intervention, comparator, and outcomes. When there was an overlap between studies (i.e. they evaluated the same antidepressant medications, in similar target populations, and reported the same outcomes), we selected the meta-analysis based on the following criteria and in the following order: (i) Recency (more recent publication covering a more recent search period) (ii) number of included RCTs, (iii) broadness of the review (covering multiple antidepressants and groups of antidepressants compared to pill placebo and/or treatment as usual, with a wide range of outcomes) (iv) AMSTAR ratings

Two reviewers (AA and MC/CM) independently assessed the eligibility of the studies identified and extracted data from study reports. Discrepancies between the reviewers were resolved through discussions. The search strategy and results reporting the databases searched, the strategy used to search each database, the total number of citations retrieved from each database, and the reasons for excluding some publications after reviewing the full text have been carefully documented. The flow of articles throughout the search and up to the final cohort of included studies is shown in Figure 1, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage.

2.4. Selection and coding of identified records

Rayyan and Endnote were used for the management of references. Rayyan was used during the first two stages of the project, involving the selection of studies based on titles, abstracts, and full texts. Endnote was used to store the references and pdfs of the included studies for the remaining stages of the project. Data

extraction was conducted in excel files with a predefined format which was designed by the involved reviewers. A wide range of study level data regarding date of searches, target population characteristics, type of intervention and control, average length of interventions, total number of participants, mean age, proportion of women and risk of bias were extracted. All data was collected by two independent reviewers and discrepancies were resolved through discussions.

2.5. Quality assessment

The quality of the included systematic reviewers was assessed with the **AMSTAR quality appraisal tool 2**. Two independent researchers (AA and MC/CM) applied the AMSTAR-2 checklist to the included studies, and any disagreements were discussed with a third researcher.
The certainty of the evidence was assessed using **GRADE** (Grading of Recommendations, Assessment, Development and Evaluations). When available, we extracted the GRADE assessments from the meta-analysis. When the GRADE assessment was not available, we assessed it ourselves examining the following criteria:

- **Risk of bias (RoB):** We extracted the RoB ratings from the individual studies included in the meta-analyses (when available). We calculated the percentage of trials rated at low, high, and unclear risk of bias. Based on this information, and in order to take consistent decisions across the available evidence, we rated the RoB GRADE item using a decision tree. This decision tree can be accessed in the appendix.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics: I2, which indicates the percentage of heterogeneity between effect sizes, and its 95% confidence interval (95% CI). When the 95% CI of the I^2 is not reported, we computed it and used it in our judgements. We judged inconsistency as serious when I^2 was over 75% and its 95% CI substantially overlaps with the category of considerable heterogeneity (above 75%). Substantial overlap was estimated with the median of the 95% CI. If the 95% CI was not available or could not be calculated, we rated it as serious if heterogeneity was larger than 50% (category of substantial heterogeneity). If I^2 was not reported and could not be calculated, we rated it as serious.
- **Indirectness**: Direct evidence was derived from research that directly compares the interventions which we are interested in, delivered to the participants in which we are interested, and that measures the outcomes important to patients. We rated for each particular comparison how indirect the reviewed evidence was in terms of population, intervention, and outcomes.
- **Imprecision**: We rated this item based on a standard power calculation (α 0.05 and β 0.20) for detecting an effect size of 0.2, which requires a sample size of 400 participants in total. We judged as serious for all analyses that included less than 400 participants. Analyses including less than 100 participants was rated as very serious. A rating of serious was given when the number of participants included in the analyses was not available.
- **Other considerations**: For this item we explored publication bias. We rated it as serious if there was evidence for publication bias in the meta-analyses, based on statistical tests. However, we did not downgrade the evidence if a meta-analysis did not investigate it.

2.6. Analysis of subgroups or subsets

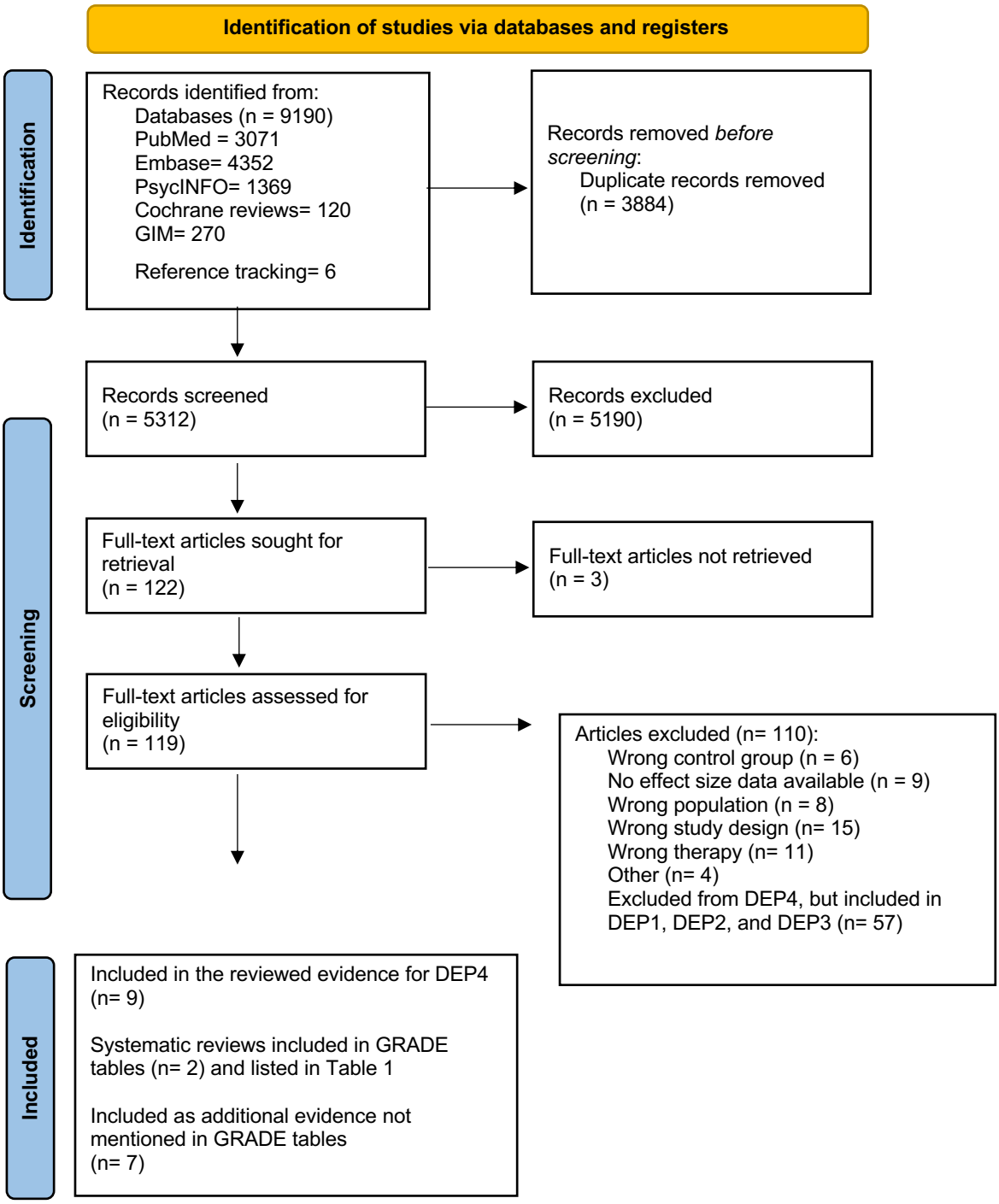
Since we reviewed existing systematic reviews, we considered the subgroups or subsets that were available in the included meta-analyses. The subgroups of interest were:

- Severity of depression: e.g., moderate, and severe depression

3. Results

3.1. Systematic reviews and/or studies identified by the search process

Figure 1: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only



GIM: Global Index Medicus

3.2. Included In GRADE tables/footnotes

CUIJPERS, P., NOMA, H., KARYOTAKI, E., VINKERS, C. H., CIPRIANI, A. & FURUKAWA, T. A. 2020. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry,* 19**,** 92-107.

FURUKAWA, T. A., SHINOHARA, K., SAHKER, E., KARYOTAKI, E., MIGUEL, C., CIHAROVA, M., BOCKTING, C. L. H., BREEDVELT, J. J. F., TAJIKA, A., IMAI, H., OSTINELLI, E. G., SAKATA, M., TOYOMOTO, R., KISHIMOTO, S., ITO, M., FURUKAWA, Y., CIPRIANI, A., HOLLON, S. D. & CUIJPERS, P. 2021. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. *World Psychiatry,* 20**,** 387-396.

3.3. Excluded from GRADE tables/footnotes

CUIJPERS, P., OUD, M., KARYOTAKI, E., NOMA, H., QUERO, S., CIPRIANI, A., ARROLL, B. & FURUKAWA, T. A. 2021. Psychologic Treatment of Depression Compared With Pharmacotherapy and Combined Treatment in Primary Care: A Network Meta-Analysis. *Ann Fam Med,* 19**,** 262-270.

FOURNIER, J. C., FOR, , N. R., WANG, Z., LI, Z., IYENGAR, S., DERUBEIS, R. J., SHELTON, R., AMSTERDAM, J., JARRETT, R. B., VITTENGL, J. R., SEGAL, Z., DIMIDJIAN, S., SHEA, M. T., DOBSON, K. S. & HOLLON, S. D. 2022. Initial Severity and Depressive Relapse in Cognitive Behavioral Therapy and Antidepressant Medications: An Individual Patient Data Meta-analysis. *Cognitive Therapy and Research*.

KAPPELMANN, N., REIN, M., FIETZ, J., MAYBERG, H. S., CRAIGHEAD, W. E., DUNLOP, B. W., NEMEROFF, C. B., KELLER, M., KLEIN, D. N., ARNOW, B. A., HUSAIN, N., JARRETT, R. B., VITTENGL, J. R., MENCHETTI, M., PARKER, G., BARBER, J. P., BASTOS, A. G., DEKKER, J., PEEN, J., KECK, M. E. & KOPF-BECK, J. 2020. Psychotherapy or medication for depression? Using individual symptom meta-analyses to derive a Symptom-Oriented Therapy (SOrT) metric for a personalised psychiatry. *BMC Med,* 18**,** 170.

LEICHSENRING, F., STEINERT, C., RABUNG, S. & IOANNIDIS, J. P. A. 2022. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. *World Psychiatry,* 21**,** 133-145.

MACHMUTOW, K., MEISTER, R., JANSEN, A., KRISTON, L., WATZKE, B., HÄRTER, M. C. & LIEBHERZ, S. 2019. Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults. Cochrane Database Syst Rev, 5, Cd012855.

ROSS, E. L., VIJAN, S., MILLER, E. M., VALENSTEIN, M. & ZIVIN, K. 2019. The Cost-Effectiveness of Cognitive Behavioral Therapy Versus Second-Generation Antidepressants for Initial Treatment of Major Depressive Disorder in the United States: A Decision Analytic Model. Ann Intern Med, 171, 785-795.

ROSS, E. L., VIJAN, S., MILLER, E. M., VALENSTEIN, M. & ZIVIN, K. 2019. The Cost-Effectiveness of Cognitive Behavioral Therapy Versus Second-Generation Antidepressants for Initial Treatment of Major Depressive Disorder in the United States: A Decision Analytic Model. Ann Intern Med, 171, 785-795.

Table 1: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
1	**Psychotherapy compared to pharmacotherapy in adults with depressive disorders**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of psychotherapy compared to pharmacotherapy on depressive symptoms in adults diagnosed with depression
		Improved quality of life and functioning	-	No available recent meta-analytic evidence on this outcome (N/A)
		Adverse effects (Study drop out)	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the adverse effects of psychotherapy compared to pharmacotherapy on depressive symptoms in adults diagnosed with depression
		Remission	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on psychotherapy compared to pharmacotherapy on remission depressive symptoms in adults diagnosed with depression
		Sustained response	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on psychotherapy compared to pharmacotherapy on sustained response in adults diagnosed with depression
2	**Combined therapy (psychotherapy + pharmacotherapy) compared to psychotherapy alone in adults with depressive disorders**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to psychotherapy alone on depressive symptoms in adults diagnosed with depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the adverse effects of of combined therapy compared

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
				to psychotherapy alone on depressive symptoms in adults diagnosed with depression
		Remission	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on of combined therapy compared to psychotherapy alone on remission depressive symptoms in adults diagnosed with depression
		Sustained response	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on of combined therapy compared to psychotherapy alone on sustained response in adults diagnosed with depression
3	**Combined therapy (psychotherapy + pharmacotherapy) compared to pharmacotherapy alone in adults with depressive disorders**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to pharmacotherapy alone on depressive symptoms in adults diagnosed with depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the adverse effects of combined therapy compared to pharmacotherapy alone on depressive symptoms in adults diagnosed with depression
		Remission	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on of combined therapy compared to pharmacotherapy alone on remission depressive symptoms in adults diagnosed with depression
		Sustained response	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on of combined therapy compared to pharmacotherapy alone on sustained response in adults diagnosed with depression

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
4	**Psychotherapy compared to pharmacotherapy in adults with depressive disorders (subgroup: moderate depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of psychotherapy compared to pharmacotherapy on depressive symptoms in adults with moderate baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)
		Remission	-	(N/A)
		Sustained response	-	(N/A)
5	**Combined therapy (psychotherapy + pharmacotherapy) compared to psychotherapy alone in adults with depressive disorders (subgroup: moderate depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to psychotherapy alone on depressive symptoms in adults with moderate baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)
		Remission	-	(N/A)
		Sustained response	-	(N/A)
6	**Combined therapy (psychotherapy + pharmacotherapy) compared to pharmacotherapy alone in adults with depressive disorders (subgroup: moderate depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to pharmacotherapy alone on depressive symptoms in adults with moderate baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)
		Remission	-	(N/A)

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
		Sustained response	-	(N/A)
7	**Psychotherapy compared to pharmacotherapy in adults with depressive disorders (subgroup: severe depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of psychotherapy compared to pharmacotherapy on depressive symptoms in adults with severe baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)
		Remission	-	(N/A)
		Sustained response	-	(N/A)
8	**Combined therapy (psychotherapy + pharmacotherapy) compared to psychotherapy alone in adults with depressive disorders (subgroup: severe depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to psychotherapy alone on depressive symptoms in adults with severe baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)
		Remission	-	(N/A)
		Sustained response	-	(N/A)
9	**Combined therapy (psychotherapy + pharmacotherapy) compared to pharmacotherapy alone in adults with depressive disorders (subgroup: severe depression)**	Reduction in mental health symptoms	Cuijpers et al., 2020	Most recent high-quality meta-analysis available on the effectiveness of combined therapy compared to pharmacotherapy alone on depressive symptoms in adults with severe baseline depression
		Improved quality of life and functioning	-	(N/A)
		Adverse effects (Study drop out)	-	(N/A)

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
		Remission	-	(N/A)
		Sustained response	-	(N/A)
10	**Psychotherapy -> psychotherapy compared to pharmacotherapy -> pharmacotherapy in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of psychotherapy followed by psychotherapy maintenance therapy compared to pharmacotherapy followed by pharmacotherapy maintenance therapy on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of psychotherapy followed by psychotherapy maintenance therapy compared to pharmacotherapy followed by pharmacotherapy maintenance therapy on depressive symptoms in adults with depression
11	**Combined -> combined compared to psychotherapy -> psychotherapy in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of combined therapy followed by combined maintenance therapy compared to psychotherapy followed by psychotherapy maintenance therapy on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of combined therapy followed by combined maintenance therapy compared to psychotherapy followed by psychotherapy maintenance therapy on depressive symptoms in adults with depression
12	**Combined -> combined compared to pharmacotherapy ->**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of combined therapy followed by combined maintenance therapy compared

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
	pharmacotherapy in adults with depressive disorders			to pharmacotherapy followed by pharmacotherapy maintenance therapy on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of combined therapy followed by combined maintenance therapy compared to pharmacotherapy followed by pharmacotherapy maintenance therapy on depressive symptoms in adults with depression
13	**Combined -> combined compared to pharmacotherapy -> combined in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of combined therapy followed by combined maintenance therapy compared to pharmacotherapy followed by combined maintenance therapy on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of combined therapy followed by combined maintenance therapy compared to pharmacotherapy followed by combined maintenance therapy on depressive symptoms in adults with depression
14	**Psychotherapy -> naturalistic follow up compared to pharmacotherapy -> naturalistic follow up in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of psychotherapy with a naturalistic follow up compared to pharmacotherapy with a naturalistic follow up on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of psychotherapy with a naturalistic follow up compared to pharmacotherapy

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
				with a naturalistic follow up on depressive symptoms in adults with depression
15	**Combined -> naturalistic follow up compared to psychotherapy -> naturalistic follow up in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of combined therapy with a naturalistic follow up compared to psychotherapy with a naturalistic follow up on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of combined therapy with a naturalistic follow up compared to psychotherapy with a naturalistic follow up on depressive symptoms in adults with depression
16	**Combined -> naturalistic follow up compared to pharmacotherapy -> naturalistic follow up in adults with depressive disorders**	Sustained response	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained effectiveness of combined therapy with a naturalistic follow up compared to pharmacotherapy with a naturalistic follow up on depressive symptoms in adults with depression
		Acceptability (all cause drop out)	Furukawa et al., 2021	Most recent high-quality meta-analysis available on the sustained acceptability of combined therapy with a naturalistic follow up compared to pharmacotherapy with a naturalistic follow up on depressive symptoms in adults with depression

Note. For Furukawa et al., 2021, the symbol "->" distinguishes between the acute phase treatment and the maintenance treatment (or naturalistic follow-up)

3.2. Narrative description of studies that contributed to GRADE analysis[1]

Cuijpers et al., 2020: No network meta-analysis has examined the relative effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression, while this is a very important clinical issue. We conducted systematic searches in bibliographical databases to identify randomized trials in which a psychotherapy and a pharmacotherapy for the acute or long-term treatment of depression were compared with each other, or in which the combination of a psychotherapy and a pharmacotherapy was compared with either one alone. The main outcome was treatment response (50% improvement between baseline and endpoint). Remission and acceptability (defined as study drop-out for any reason) were also examined. Possible moderators that were assessed included chronic and treatment-resistant depression and baseline severity of depression. Data were pooled as relative risk (RR) using a random-effects model. A total of 101 studies with 11,910 patients were included. Depression in most studies was moderate to severe. In the network meta-analysis, combined treatment was more effective than psychotherapy alone (RR=1.27; 95% CI: 1.14-1.39) and pharmacotherapy alone (RR=1.25; 95% CI: 1.14-1.37) in achieving response at the end of treatment. No significant difference was found between psychotherapy alone and pharmacotherapy alone (RR=0.99; 95% CI: 0.92-1.08). Similar results were found for remission. Combined treatment (RR=1.23; 95% CI: 1.05-1.45) and psychotherapy alone (RR=1.17; 95% CI: 1.02-1.32) were more acceptable than pharmacotherapy. Results were similar for chronic and treatment-resistant depression. The combination of psychotherapy and pharmacotherapy seems to be the best choice for patients with moderate depression. More research is needed on long-term effects of treatments (including cost-effectiveness), on the impact of specific pharmacological and non-pharmacological approaches, and on the effects in specific populations of patients.

Furukawa et al., 2021: Major depression is often a relapsing disorder. It is therefore important to start its treatment with therapies that maximize the chance of not only getting the patients well but also keeping them well. We examined the associations between initial treatments and sustained response by conducting a network meta-analysis of randomized controlled trials (RCTs) in which adult patients with major depression were randomized to acute treatment with a psychotherapy (PSY), a protocolized antidepressant pharmacotherapy (PHA), their combination (COM), standard treatment in primary or secondary care (STD), or pill placebo, and were then followed up through a maintenance phase. By design, acute phase treatment could be continued into the maintenance phase, switched to another treatment or followed by discretionary treatment. We included 81 RCTs, with 13,722 participants. Sustained response was defined as responding to the acute treatment and subsequently having no depressive relapse through the maintenance phase (mean duration: 42.2±16.2 weeks, range 24-104 weeks). We extracted the data reported at the time point closest to 12 months. COM resulted in more sustained response than PHA, both when these treatments were continued into the maintenance phase (OR=2.52, 95% CI: 1.66-3.85) and when they were followed by discretionary treatment (OR=1.80, 95% CI: 1.21-2.67). The same applied to COM in comparison with STD (OR=2.90, 95% CI: 1.68-5.01 when COM was continued into the maintenance phase; OR=1.97, 95% CI: 1.51-2.58 when COM was followed by discretionary treatment). PSY also kept the patients well more often than PHA, both when these treatments were continued into the maintenance phase (OR=1.53, 95% CI: 1.00-2.35) and when they were followed by discretionary treatment (OR=1.66, 95% CI: 1.13-2.44). The same applied to PSY compared with STD (OR=1.76, 95% CI: 0.97-3.21 when PSY was continued into the maintenance phase;

[1]Please note that this section includes the abstracts as taken directly from the publications.

OR=1.83, 95% CI: 1.20-2.78 when PSY was followed by discretionary treatment). Given the average sustained response rate of 29% on STD, the advantages of PSY or COM over PHA or STD translated into risk differences ranging from 12 to 16 percentage points. We conclude that PSY and COM have more enduring effects than PHA. Clinical guidelines on the initial treatment choice for depression may need to be updated accordingly

3.3. Grading the Evidence

GRADE Table 1: Psychotherapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Psychotherapy [a] compared to pharmacotherapy [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Reduction in depressive symptoms – Cuijpers, 2020										
50	RCT	very serious [g]	not serious	not serious	not serious	publication bias strongly suspected [d]	3646	SMD **0.04** [CI -0.09 to 0.16]	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
59	RCT	very serious [g]	not serious	not serious	not serious	none	5933	RR **0.99** [CI 0.92 to 1.08]	⊕⊕◯◯ LOW	CRITICAL
Improved QAL and functioning – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects – Acceptability (Study drop out) – Cuijpers, 2020										
58	RCT	very serious [h]	not serious	not serious	serious [e]	publication bias strongly suspected [d]	NR	RR **1.17** [CI 1.02 to 1.32]	⊕◯◯◯ VERY LOW	CRITICAL
Remission – Remission - Cuijpers, 2020										
47	RCT	very serious [g]	not serious	not serious	not serious	none	4913	RR **1.01** [CI 0.93 to 1.10]	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Sustained Response – Long term effect (6-12 months) - Cuijpers, 2020										
NR	RCT	very serious [h]	serious [f]	not serious	serious [e]	NR	NR	RR **0.85** [CI 0.74 to 0.98]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Relative Risk; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference; **QAL:** Quality of life

Interpretation of outcomes:
Reduction in depressive symptoms – Above 0 favours psychotherapy; below 0 favours pharmacotherapy.
Treatment response – above 1 favours psychotherapy; below 1 favours pharmacotherapy
Acceptability (Study drop out) – above 1 favours psychotherapy; below 1 favours pharmacotherapy
Remission – above 1 favours psychotherapy; below 1 favours pharmacotherapy
Sustained response – below 1 favours psychotherapy; above 1 favours pharmacotherapy

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder. The mean age of the participants and the proportion of women were not reported.
d. Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.
e. This has been rated as serious because the number of participants included in the analyses was not available.
f. Estimates of heterogeneity are not available for this analysis in the meta-analysis, and this seriously affects the certainty of the evidence.
g. Vast majority of the studies had a high risk of bias (high risk > 60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.
h. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.

GRADE Table 2: Combined therapy compared to psychotherapy alone in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to psychotherapy alone in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Reduction in depressive symptoms – Cuijpers, 2020										
19	RCT	very serious [f]	not serious	not serious	not serious	none	1646	SMD **0.30** [CI 0.14 to 0.45]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
19	RCT	very serious [f]	not serious	not serious	not serious	none	1966	RR **1.27** [CI 1.14 to 1.39]	⊕⊕◯◯ LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects – Acceptability (Study drop out) – Cuijpers, 2020										
18	RCT	very serious [g]	not serious	not serious	serious [d]	none	NR	RR **1.06** [CI 0.89 to 1.26]	⊕◯◯◯ VERY LOW	CRITICAL
Remission – Remission - Cuijpers, 2020										
15	RCT	very serious [f]	not serious	not serious	not serious	none	1326	RR **1.22** [CI 1.08 to 1.39]	⊕⊕◯◯ LOW	IMPORTANT
Sustained Response – Long term effect (6-12 months) - Cuijpers, 2020										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
NR	RCT	very serious [g]	serious [e]	not serious	serious [d]	NR	NR	RR **0.84** [CI 0.71 to 0.99]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Relative Risk; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference; **QAL:** Quality of life

Interpretation of outcomes:
Reduction in depressive symptoms – Above 0 favours combined therapy; below 0 favours psychotherapy.
Treatment response – above 1 favours combined therapy; below 1 favours psychotherapy.
Acceptability (Study drop out) – above 1 favours combined therapy; below 1 favours psychotherapy
Remission – above 1 favours combined therapy; below 1 favours psychotherapy.
Sustained response – below 1 favours combined therapy; above 1 favours psychotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder. The mean age of the participants and the proportion of women were not reported.
d. This has been rated as serious because the number of participants included in the analyses was not available.
e. Estimates of heterogeneity are not available for this analysis in the meta-analysis, and this seriously affects the certainty of the evidence.
f. Vast majority of the studies had a high risk of bias (high risk > 60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.
g. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.

GRADE Table 3: Combined therapy compared to pharmacotherapy alone in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to pharmacotherapy alone in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Reduction in depressive symptoms – Cuijpers, 2020										
41	RCT	very serious [g]	not serious	not serious	not serious	publication bias strongly suspected [d]	2993	SMD **0.33** [CI 0.20 to 0.47]	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
46	RCT	serious [h]	not serious	not serious	not serious	publication bias strongly suspected [d]	3933	RR **1.25** [CI 1.14 to 1.37]	⊕◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects – Acceptability (Study drop out) – Cuijpers, 2020										
41	RCT	very serious [i]	not serious	not serious	serious [e]	none	NR	RR **1.23** [CI 1.05 to 1.45]	⊕◯◯◯ VERY LOW	CRITICAL
Remission – Remission - Cuijpers, 2020										
25	RCT	serious [j]	not serious	not serious	not serious	none	3014	RR **1.23** [CI 1.09 to 1.39]	⊕⊕⊕◯ MODERATE	IMPORTANT
Sustained Response – Long term effect (6-12 months) - Cuijpers, 2020										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
NR	RCT	very serious [i]	serious [f]	not serious	serious [e]	NR	NR	RR **0.72** [CI 0.62 to 0.83]	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Relative Risk; **RCTs**: Randomized Controlled Trials; **SMD:** Standard Mean Difference; **QAL:** Quality of life

Interpretation of outcomes:

Reduction in depressive symptoms – Above 0 favours combined therapy; below 0 favours pharmacotherapy.
Treatment response – above 1 favours combined therapy; below 1 favours pharmacotherapy.
Acceptability (Study drop out) – above 1 favours combined therapy; below 1 favours pharmacotherapy.
Remission – above 1 favours combined therapy; below 1 favours pharmacotherapy.
Sustained response – below 1 favours combined therapy; above 1 favors pharmacotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder. The mean age of the participants and the proportion of women were not reported.
d. Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.
e. This has been rated as serious because the number of participants included in the analyses was not available.
f. Estimates of heterogeneity are not available for this analysis in the meta-analysis, and this seriously affects the certainty of the evidence.
g. Vast majority of the studies had a high risk of bias (high risk > 60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.
h. The number of high-risk studies was between 50%-60% and the number of low-risk studies was above 25%. It should be noted that sensitivity analyses with low risk of bias studies produced similar results.
i. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%). It should be noted that sensitivity analyses with low risk of bias studies produced similar results.
j. This has been rated as serious because the number of high risk studies was above 25%

GRADE Table 4: Psychotherapy compared to pharmacotherapy in adults with depressive disorders (subgroup: moderate depression)

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Psychotherapy [a] compared to pharmacotherapy [b] in adults with moderate depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
32	RCT	very serious [d]	not serious	not serious	serious [e]	none	NR	RR **1.03** [CI 0.94 to 1.14]	⊕◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning -- Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors psychotherapy; below 1 favors pharmacotherapy

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder – moderate baseline depression according to the Hamilton Depression Rating Scale
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. This has been rated as serious because the number of participants included in the analyses was not available.

GRADE Table 5: Combined therapy compared to psychotherapy alone in adults with depressive disorders (subgroup: moderate depression)

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to psychotherapy alone in adults with moderate depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
11	RCT	very serious [d]	not serious	not serious	serious [e]	none	NR	RR **1.19** [CI 1.05 to 1.37]	⨁◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors combined therapy; below 1 favors psychotherapy

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder - moderate baseline depression according to the Hamilton Depression Rating Scale.
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. This has been rated as serious because the number of participants included in the analyses was not available.

GRADE Table 6: Combined therapy compared to pharmacotherapy alone in adults with depressive disorders (subgroup: moderate depression)

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to pharmacotherapy alone in adults with moderate depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
11	RCT	very serious [d]	not serious	not serious	serious [e]	publication bias strongly suspected [f]	NR	RR **1.23** [CI 1.09 to 1.41]	⨁◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors combined therapy; below 1 favors pharmacotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder - moderate baseline depression according to the Hamilton Depression Rating Scale.
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. This has been rated as serious because the number of participants included in the analyses was not available.
f. Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 7: Psychotherapy compared to pharmacotherapy in adults with depressive disorders (subgroup: severe depression)

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Psychotherapy [a] compared to pharmacotherapy [b] in adults with severe depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
4	RCT	very serious [d]	not serious	not serious	serious [e]	none	NR	RR **1.09** [CI 0.72 to 1.64]	⊕◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors psychotherapy; below 1 favors pharmacotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder – severe baseline depression according to the Hamilton Depression Rating Scale
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. This has been rated as serious because the number of participants included in the analyses was not available.

GRADE Table 8: Combined therapy compared to psychotherapy alone in adults with depressive disorders (subgroup: severe depression)
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to psychotherapy alone in adults with severe depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
2	RCT	very serious [d]	serious [e]	not serious	serious [f]	none	NR	RR **1.33** [CI 0.91 to 1.92]	⊕◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors combined therapy; below 1 favors psychotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder - severe baseline depression according to the Hamilton Depression Rating Scale.
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. The 95% CI for the heterogeneity estimates were not available. This has been rated as serious as the heterogeneity was larger than 50% (I^2 = 65%)
f. This has been rated as serious because the number of participants included in the analyses was not available.

GRADE Table 9: Combined therapy compared to pharmacotherapy alone in adults with depressive disorders (subgroup: severe depression)

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Combined therapy (psychotherapy [a] + pharmacotherapy [b]) compared to pharmacotherapy alone in adults with severe depression [c]
Population: Adults diagnosed with depression
Reference List: Cuijpers et al., 2020

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Treatment response – Cuijpers, 2020										
6	RCT	very serious [d]	not serious	not serious	serious [e]	none	NR	RR **1.45** [CI 1.10 to 1.89]	⊕◯◯◯ VERY LOW	CRITICAL
Improved QAL and functioning - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects - Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Remission - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT
Sustained Response - Not available										
-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **RR:** Relative Risk; **QAL:** Quality of life

Interpretation of outcomes:
Treatment response – above 1 favors combined therapy; below 1 favors pharmacotherapy.

Explanations:

a. Psychotherapies include: ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, Narrative therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, Social group, social skills, stress management and self-control.
b. Pharmacotherapies include – SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant and others.
c. Adults with acute depressive disorder - severe baseline depression according to the Hamilton Depression Rating Scale.
d. The risk of bias for the primary studies in this analysis could not be estimated. Therefore, the aggregated risk of bias across all included studies was taken. It has been rated as very serious because a vast majority of the studies have a high risk of bias (>60%)
e. This has been rated as serious because the number of participants included in the analyses was not available.

GRADE Table 10: Sustained response in psychotherapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in psychotherapy -> psychotherapy [a] compared to pharmacotherapy -> pharmacotherapy [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021 [e]										
8	RCT	serious	very serious	not serious	not serious	none	NR	OR **1.53** [CI 1.00 to 2.35]	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **0.71** [CI 0.45 to 1.14]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors psychotherapy -> psychotherapy; below 1 favors pharmacotherapy -> pharmacotherapy
Acceptability - below 1 favors psychotherapy -> psychotherapy; above 1 favors pharmacotherapy -> pharmacotherapy

Explanations:
a. Acute psychotherapy treatment with a maintenance phase of psychotherapy.
b. Acute pharmacotherapy treatment with a maintenance phase of pharmacotherapy.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. Certainty assessment is based on the CINeMA approach conducted by the study.
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated.
h. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 11: Sustained response in combined therapy compared to psychotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in combined -> combined [a] compared to psychotherapy -> psychotherapy [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021 [e]										
5	RCT	very serious	serious	not serious	not serious	none	NR	OR **1.65** [CI 1.04 to 2.61]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **0.95** [CI 0.57 to 1.58]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors combined -> combined; below 1 favors psychotherapy -> psychotherapy
Acceptability - below 1 favors combined -> combined; above 1 favors psychotherapy -> psychotherapy

Explanations:

a. Acute combined treatment with a maintenance phase of combined therapy. The most frequently used types of psychotherapies in combined treatment included cognitive behavior therapy, non-directive supportive therapy, interpersonal psychotherapy, behavioral activation and psychodynamic therapy. The most frequently used antidepressants were duloxetine, agomelatine, paroxetine, venlafaxine and fluoxetine.
b. Acute psychotherapy treatment with a maintenance phase of psychotherapy.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. Certainty assessment is based on the CINeMA approach conducted by the study.
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated.
h. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 12: Sustained response in combined therapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in combined -> combined [a] compared to pharmacotherapy -> pharmacotherapy [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021 [e]										
7	RCT	very serious	not serious	not serious	not serious	none	NR	OR 2. 52 [CI 1.66 to 3.85]	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **0.68** [CI 0.43 to 1.07]	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors combined -> combined; below 1 favors pharmacotherapy -> combined
Acceptability - below 1 favors combined -> combined; above 1 favors pharmacotherapy -> combined

Explanations:

a. Acute combined treatment with a maintenance phase of combined therapy. The most frequently used types of psychotherapies in combined treatment included cognitive behavior therapy, non-directive supportive therapy, interpersonal psychotherapy, behavioral activation and psychodynamic therapy. The most frequently used antidepressants were duloxetine, ago-melatine, paroxetine, venlafaxine and fluoxetine.
b. Acute pharmacotherapy treatment with a maintenance phase of pharmacotherapy.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. Certainty assessment is based on the CINeMA approach conducted by the study.
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated.
h. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 13: Sustained response in combined therapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in combined -> combined [a] compared to pharmacotherapy -> combined [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021										
NR	RCT	very serious [e]	serious [f]	not serious	serious [g]	none	NR	OR 2.97 [CI 0.71 to 12.45]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [e]	serious [f]	not serious	serious [g]	none	NR	OR **0.81** [CI 0.19 to 3.55]	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors combined -> combined; below 1 favors pharmacotherapy -> combined
Acceptability - below 1 favors combined -> combined; above 1 favors pharmacotherapy -> combined

Explanations:
a. Acute combined treatment with a maintenance phase of combined therapy. The most frequently used types of psychotherapies in combined treatment included cognitive behavior therapy, non-directive supportive therapy, interpersonal psychotherapy, behavioral activation and psychodynamic therapy. The most frequently used antidepressants were duloxetine, ago- melatine, paroxetine, venlafaxine and fluoxetine.
b. Acute pharmacotherapy treatment with a maintenance phase of combined therapy.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
f. This has been rated as serious because the I^2 was not reported and could not be calculated.
g. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 14: Sustained response in psychotherapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in psychotherapy->naturalistic follow up [a] compared to pharmacotherapy->naturalistic follow up [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI) [d]		
Sustained Response – Furukawa, 2021 [e]										
10	RCT	very serious	serious	not serious	not serious	none	NR	OR **1.66** [CI 1.13 to 2.44]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **1.09** [CI 0.70 to 1.70]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors psychotherapy -> naturalistic follow up; below 1 favors pharmacotherapy -> naturalistic follow up
Acceptability - below 1 favors psychotherapy -> naturalistic follow up; above 1 favors pharmacotherapy -> naturalistic follow up

Explanations:
a. Acute psychotherapy treatment with a naturalistic follow up.
b. Acute pharmacotherapy treatment with a naturalistic follow up.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. Certainty assessment is based on the CINeMA approach conducted by the study
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated.
h. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 15: Sustained response in combined therapy compared to psychotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in combined->naturalistic follow up [a] compared to psychotherapy->naturalistic follow up [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021 [e]										
8	RCT	very serious	serious	not serious	serious	none	NR	OR **1.08** [CI 0.74 to 1.56]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **0.68** [CI 0.44 to 1.07]	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors combined -> naturalistic follow up; below 1 favors psychotherapy -> naturalistic follow up
Acceptability - below 1 favors combined -> naturalistic follow up; above 1 favors psychotherapy -> naturalistic follow up

Explanations:

a. Acute combined treatment with a naturalistic follow up. The most frequently used types of psychotherapies in combined treatment included cognitive behavior therapy, non-directive supportive therapy, interpersonal psychotherapy, behavioral activation and psychodynamic therapy. The most frequently used antidepressants were duloxetine, ago- melatine, paroxetine, venlafaxine and fluoxetine.
b. Acute psychotherapy treatment with a naturalistic follow up.
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months.
e. Certainty assessment is based on the CINeMA approach conducted by the study.
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated.
h. This has been rated as serious because the number of participants in the analyses was not available.

GRADE Table 16: Sustained response in combined therapy compared to pharmacotherapy in adults with depressive disorders

Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Sustained response in combined->naturalistic follow up [a] compared to pharmacotherapy->naturalistic follow up [b] in adults with depression [c]
Population: Adults diagnosed with depression
Reference List: Furukawa et al., 2021

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute [d] (95% CI)		
Sustained Response – Furukawa, 2021 [e]										
9	RCT	very serious	serious	not serious	serious	none	NR	OR **1.80** [CI 1.21 to 2.67]	⨁⨁◯◯ LOW	CRITICAL
Adverse effects – Acceptability (all cause drop out) - Furukawa, 2021										
NR	RCT	very serious [f]	serious [g]	not serious	serious [h]	none	NR	OR **0.75** [CI 0.48 to 1.16]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RCTs**: Randomized Controlled Trials; **OR:** Odds ratio

Interpretation of outcomes:
Sustained response – above 1 favors combined -> naturalistic follow up; below 1 favors pharmacotherapy -> naturalistic follow up
Acceptability - below 1 favors combined -> naturalistic follow up; above 1 favors pharmacotherapy -> naturalistic follow up

Explanations:

a. Acute combined treatment with a naturalistic follow up. The most frequently used types of psychotherapies in combined treatment included cognitive behavior therapy, non-directive supportive therapy, interpersonal psychotherapy, behavioral activation and psychodynamic therapy. The most frequently used antidepressants were duloxetine, ago- melatine, paroxetine, venlafaxine and fluoxetine.
b. Acute pharmacotherapy treatment with a naturalistic follow up
c. Adults diagnosed with depressive disorder. The participants' weighted mean age (reported for 12,940 people) was 43.4±10.1, and 68% of the participants (8,668 out of 12,749 people for whom gender was reported) were women.
d. The length of effect size calculation was at the follow up that was the closest point to 12 months
e. Certainty assessment is based on the CINeMA approach conducted by the study
f. The risk of bias was aggregated for the entire meta-analyses. It has been rated as very serious because a vast majority of the studies had a high risk of bias (>60%).
g. This has been rated as serious because the I^2 was not reported and could not be calculated
h. This has been rated as serious because the number of participants in the analyses was not available.

3.6. Additional evidence not mentioned in GRADE tables

Cuijpers et al., 2021: PURPOSE Most patients with depression are treated by general practitioners, and most of those patients prefer psychotherapy over pharmacotherapy. No network meta-analyses have examined the effects of psychotherapy compared with pharmacotherapy, combined treatment, care as usual, and other control conditions among patients in primary care. METHODS We conducted systematic searches of bibliographic databases to identify randomized trials comparing psychotherapy with pharmacotherapy, combined treatment, care as usual, waitlist, and pill placebo. The main outcome was treatment response (50% improvement of depressive symptoms from baseline to end point). RESULTS A total of 58 studies with 9,301 patients were included. Both psychotherapy and pharmacotherapy were significantly more effective than care as usual (relative risk [RR] for response = 1.60; 95% CI, 1.40-1.83 and RR = 1.65; 95% CI, 1.35-2.03, respectively) and waitlist (RR = 2.35; 95% CI, 1.57-3.51 and RR = 2.43; 95% CI, 1.57-3.74, respectively) control groups. We found no significant differences between psychotherapy and pharmacotherapy (RR = 1.03; 95% CI, 0.88-1.22). The effects were significantly greater for combined treatment compared with psychotherapy alone (RR = 1.35; 95% CI, 1.00-1.81). The difference between combined treatment and pharmacotherapy became significant when limited to studies with low risk of bias and studies limited to cognitive behavior therapy. CONCLUSIONS Psychotherapy is likely effective for the treatment of depression when compared with care as usual or waitlist, with effects comparable to those of pharmacotherapy. Combined treatment might be better than either psychotherapy or pharmacotherapy alone.
Fournier et al., 2022: Background: Baseline severity has emerged as a key predictor of acute response to treatments for depression. The goals of this individual patient data meta-analysis were to compare the relapse prevention effects of acute phase cognitive behavioral therapy (CBT) vs. acute phase antidepressant medications (ADM) either continued (-c) or discontinued (-d) and determine whether baseline depression severity moderated these effects. Methods: We included all available relevant randomized trials of CBT versus ADM in adult outpatients with depression. Cox proportional hazards models were used to examine whether treatment condition, baseline severity, and additional characteristics were associated with relapse. Results: Using individual participant data from 5 of 10 published trials (N = 341), CBT (HR = 0.38, 95% CI 0.26–0.57) and ADM-c (HR = 0.48, 95% CI 0.29–0.80) were superior to ADM-d in preventing relapse over 12 months but did not differ from each other (HR = 1.26, 95% CI 0.76–2.09). Baseline severity did not moderate these effects. Conclusions: Regardless of a patient's baseline symptom severity, CBT and ADM-c both prevent depressive relapse substantially better than medication discontinuation. Given the shorter duration of treatment and equivalent longer-term outcomes, treatment with CBT might be considered a first choice for adults with depression.

Kappelmann et al., 2020: Background: Antidepressant medication (ADM) and psychotherapy are effective treatments for major depressive disorder (MDD). It is unclear, however, if treatments differ in their effectiveness at the symptom level and whether symptom information can be utilised to inform treatment allocation. The present study synthesises comparative effectiveness information from randomised controlled trials (RCTs) of ADM versus psychotherapy for MDD at the symptom level and develops and tests the Symptom-Oriented Therapy (SOrT) metric for precision treatment allocation. Methods: First, we conducted systematic review and meta-analyses of RCTs comparing ADM and psychotherapy at the individual symptom level. We searched PubMed Medline, PsycINFO, and the Cochrane Central Register of Controlled Trials databases, a database specific for psychotherapy RCTs, and looked for unpublished RCTs. Random-effects meta-analyses were applied on sum-scores and for individual symptoms for the Hamilton Rating Scale for Depression (HAM-D) and Beck Depression Inventory (BDI) measures. Second, we computed the SOrT metric, which combines meta-analytic effect sizes with patients' symptom profiles. The SOrT metric was evaluated using data from the Munich Antidepressant

Response Signature (MARS) study (*n* = 407) and the Emory Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study (*n* = 234). Results: The systematic review identified 38 RCTs for qualitative inclusion, 27 and 19 for quantitative inclusion at the sum-score level, and 9 and 4 for quantitative inclusion on individual symptom level for the HAM-D and BDI, respectively. Neither meta-analytic strategy revealed significant differences in the effectiveness of ADM and psychotherapy across the two depression measures. The SOrT metric did not show meaningful associations with other clinical variables in the MARS sample, and there was no indication of utility of the metric for better treatment allocation from PReDICT data. Conclusions: This registered report showed no differences of ADM and psychotherapy for the treatment of MDD at sum-score and symptom levels. Symptom-based metrics such as the proposed SOrT metric do not inform allocation to these treatments, but predictive value of symptom information requires further testing for other treatment comparisons.

Leichsenring et al., 2022: Mental disorders represent a worldwide public health concern. Psychotherapies and pharmacotherapies are recommended as first line treatments. However, evidence has emerged that their efficacy may be overestimated, due to a variety of shortcomings in clinical trials (e.g., publication bias, weak control conditions such as waiting list). We performed an umbrella review of recent meta-analyses of randomized controlled trials (RCTs) of psychotherapies and pharmacotherapies for the main mental disorders in adults. We selected meta-analyses that formally assessed risk of bias or quality of studies, excluded weak comparators, and used effect sizes for target symptoms as primary outcome. We searched PubMed and PsycINFO and individual records of the Cochrane Library for meta-analyses published between January 2014 and March 2021 comparing psychotherapies or pharmacotherapies with placebo or treatment-as-usual (TAU), or psychotherapies vs. pharmacotherapies head-to-head, or the combination of psychotherapy with pharmacotherapy to either monotherapy. One hundred and two meta-analyses, encompassing 3,782 RCTs and 650,514 patients, were included, covering depressive disorders, anxiety disorders, post-traumatic stress disorder, obsessive-compulsive disorder, somatoform disorders, eating disorders, attention-deficit/hyperactivity disorder, substance use disorders, insomnia, schizophrenia spectrum disorders, and bipolar disorder. Across disorders and treatments, the majority of effect sizes for target symptoms were small. A random effect meta-analytic evaluation of the effect sizes reported by the largest meta-analyses per disorder yielded a standardized mean difference (SMD) of 0.34 (95% CI: 0.26-0.42) for psychotherapies and 0.36 (95% CI: 0.32-0.41) for pharmacotherapies compared with placebo or TAU. The SMD for head-to-head comparisons of psychotherapies vs. pharmacotherapies was 0.11 (95% CI: –0.05 to 0.26). The SMD for the combined treatment compared with either monotherapy was 0.31 (95% CI: 0.19-0.44). Risk of bias was often high. After more than half a century of research, thousands of RCTs and millions of invested funds, the effect sizes of psychotherapies and pharmacotherapies for mental disorders are limited, suggesting a ceiling effect for treatment research as presently conducted. A paradigm shift in research seems to be required to achieve further progress.

Machmutow et al., 2019: Background: Persistent depressive disorder (PDD) is defined as a depressive disorder with a minimum illness duration of two years, including four diagnostic subgroups (dysthymia, chronic major depression, recurrent major depression with incomplete remission between episodes, and double depression). Persistent forms of depression represent a substantial proportion of depressive disorders, with a lifetime prevalence ranging from 3% to 6% in the Western world. Growing evidence indicates that PDD responds well to several acute interventions, such as combined psychological and pharmacological treatments. Yet, given the high rates of relapse and recurrences of depression following response to acute treatment, long-term continuation and maintenance therapy are of great importance. To date, there has been no evidence synthesis available on continuation and maintenance treatments of PDDs. Objectives: To assess the effects of pharmacological and psychological (either alone or combined) continuation

and maintenance treatments for persistent depressive disorder, in comparison with each other, placebo (drug/attention placebo/non-specific treatment control), and treatment as usual (TAU). Continuation treatments are defined as treatments given to currently remitted people (remission is defined as depressive symptoms dropping below case level) or to people who previously responded to an antidepressant treatment. Maintenance therapy is given during recovery (which is defined as remission lasting longer than six months). Search methods: We searched Ovid MEDLINE (1950-), Embase (1974-), PsycINFO (1967-) and the Cochrane Central Register of Controlled Trials (CENTRAL) to 28 September 2018. An earlier search of these databases was also conducted for RCTs via the Cochrane Common Mental Disorders Controlled Trial Register (CCMD-CTR) (all years to 11 Dec 2015). In addition we searched grey literature resources as well as the international trial registers ClinicalTrials.gov and ICTRP to 28 September 2018. We screened reference lists of included studies and contacted the first author of all included studies. Selection criteria: We included randomized (RCTs) and non-randomized controlled trials (NRCTs) in adults with formally diagnosed PDD, receiving pharmacological, psychological, or combined continuation and maintenance interventions. Data collection and analysis: Two review authors independently selected studies and extracted and analyzed data. The primary efficacy outcome was relapse/ recurrence rate of depression. The primary acceptance outcome was dropout due to any reason other than relapse/recurrence. We performed random-effects meta-analyses using risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI). Main results: We included 10 studies (seven RCTs, three NRCTs) involving 840 participants in this review, from which five studies investigated continuation treatments and five studies investigated maintenance treatments. Overall, the included studies were at low-to-moderate risk of bias. For the three NRCTs, the most common source of risk of bias was selection of reported results. For the seven RCTs, the most common sources of risk of bias was non-blinding of outcome assessment and other bias (especially conflict of interest due to pharmaceutical sponsoring).

Ross et al., 2019: Background: Most guidelines for major depressive disorder recommend initial treatment with either a second-generation antidepressant (SGA) or cognitive behavioral therapy (CBT). Although most trials suggest that these treatments have similar efficacy, their health economic implications are uncertain. Objective: To quantify the cost-effectiveness of CBT versus SGA for initial treatment of depression. Design: Decision analytic model. Data Sources: Relative effectiveness data from a meta-analysis of randomized controlled trials; additional clinical and economic data from other publications. Target Population: Adults with newly diagnosed major depressive disorder in the United States. Time Horizon: 1 to 5 years. Perspectives: Health care sector and societal. Intervention: Initial treatment with either an SGA or group and individual CBT. Outcome Measures: Costs in 2014 U.S. dollars, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. Results of Base-Case Analysis: In model projections, CBT produced higher QALYs (3 days more at 1 year and 20 days more at 5 years) with higher costs at 1 year (health care sector, $900; societal, $1500) but lower costs at 5 years (health care sector, −$1800; societal, −$2500). Results of Sensitivity Analysis: In probabilistic sensitivity analyses, SGA had a 64% to 77% likelihood of having an incremental cost-effectiveness ratio of $100 000 or less per QALY at 1 year; CBT had a 73% to 77% likelihood at 5 years. Uncertainty in the relative risk for relapse of depression contributed the most to overall uncertainty in the optimal treatment. Limitation: Long-term trials comparing CBT and SGA are lacking. Conclusion: Neither SGAs nor CBT provides consistently superior cost-effectiveness relative to the other. Given many patients' preference for psychotherapy over pharmacotherapy, increasing patient access to CBT may be warranted.

Zimmerman, 2019: Severity is an important consideration in treatment decision-making for depression. Two controversies in the treatment of depression are related to the issue of severity. First, are antidepressants only effective for severely depressed patients? Second, should the

severity of depression be used as the basis for recommending medication or psychotherapy as first-line treatment? More specifically, should patients with severe depression preferentially be treated with medication? A related question is whether psychotherapy is beneficial for severely depressed patients. Some controversial articles sparked coverage in the popular press related to these questions and stimulated subsequent research on the impact of depression severity on treatment efficacy. The results of three recent large pooled analyses of patient level data indicate that the efficacy of antidepressants is not limited to the narrow band of patients who score highest on symptom severity scales. A meta-analysis of 132 controlled psychotherapy studies of more than 10,000 patients found that greater mean baseline symptom severity did not predict poorer response. A pooled analysis of individual patient data from 16 studies comparing antidepressants and cognitive behavior therapy found that severity was not associated with differential treatment outcome. These results are discussed in the context of recommendations in official treatment guidelines.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 3: Summary of findings table

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
GRADE Table 1 Psychotherapy compared to pharmacotherapy in adults with depressive disorders	Cuijpers et al., 2020	Reduction in mental health symptoms	Reduction in depressive symptoms	50	SMD **0.04** [CI -0.09 to 0.16]	⊕◯◯◯ VERY LOW
			Treatment response	59	RR **0.99** [CI 0.92 to 1.08]	⊕⊕◯◯ LOW
			Remission	47	RR **1.01** [CI 0.93 to 1.10]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	58	RR **1.17** [CI 1.02 to 1.32]	⊕◯◯◯ VERY LOW
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	Long-term effect (6-12 months)	NR	RR **0.85** [CI 0.74 to 0.98]	⊕◯◯◯ VERY LOW
GRADE Table 2 Combined therapy compared to psychotherapy alone in adults with depressive disorders	Cuijpers et al., 2020	Reduction in mental health symptoms	Reduction in depressive symptoms	19	SMD **0.30** [CI 0.14 to 0.45]	⊕⊕◯◯ LOW
			Treatment response	19	RR **1.27** [CI 1.14 to 1.39]	⊕⊕◯◯ LOW
			Remission	15	RR **1.22** [CI 1.08 to 1.39]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	18	RR **1.06** [CI 0.89 to 1.26]	⊕◯◯◯ VERY LOW
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	Long-term effect (6-12 months)	NR	RR **0.84** [CI 0.71 to 0.99]	⊕◯◯◯ VERY LOW

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
GRADE Table 3 Combined therapy compared to pharmacotherapy alone in adults with depressive disorders	Cuijpers et al., 2020	Reduction in mental health symptoms	Reduction in depressive symptoms	41	SMD **0.33** [CI 0.20 to 0.47]	⊕◯◯◯ VERY LOW
			Treatment response	46	RR **1.25** [CI 1.14 to 1.37]	⊕◯◯◯ VERY LOW
			Remission	25	RR **1.23** [CI 1.09 to 1.39]	⊕⊕⊕◯ MODERATE
		Adverse effects	All cause dropout	41	RR **1.23** [CI 1.05 to 1.45]	⊕◯◯◯ VERY LOW
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	Long-term effect (6-12 months)	NR	RR **0.72** [CI 0.62 to 0.83]	⊕◯◯◯ VERY LOW
GRADE Table 4 Psychotherapy compared to pharmacotherapy alone in adults with depressive disorders (subgroup: moderate depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	32	RR **1.03** [CI 0.94 to 1.14]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	-	-	-	N/A
GRADE Table 5 Combined therapy compared to psychotherapy alone in adults with depressive disorders (subgroup: moderate depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	11	RR **1.19** [CI 1.05 to 1.37]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
		Sustained Response	Long-term effect (6-12 months)	-	-	N/A
GRADE Table 6 Combined therapy compared to pharmacotherapy alone in adults with depressive disorders (subgroup: moderate depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	11	RR **1.23** [CI 1.09 to 1.41]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	-	-	-	N/A
GRADE Table 7 Psychotherapy compared to pharmacotherapy in adults with depressive disorders (subgroup: severe depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	4	RR **1.09** [CI 0.72 to 1.64]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	-	-	-	N/A
GRADE Table 8 Combined therapy compared to psychotherapy alone in adults with depressive disorders (subgroup: severe depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	2	RR **1.33** [CI 0.91 to 1.92]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
		Sustained Response	-	-	-	N/A
GRADE Table 9 Combined therapy compared to pharmacotherapy alone in adults with depressive disorders (subgroup: severe depression)	Cuijpers et al., 2020	Reduction in mental health symptoms	Treatment response	6	RR **1.45** [CI 1.10 to 1.89]	⊕◯◯◯ VERY LOW
			Remission	-	-	N/A
		Adverse effects	All cause dropout	-	-	N/A
		Improvement in quality of life and functioning	-	-	-	N/A
		Sustained Response	-	-	-	N/A
GRADE Table 10 Acute psychotherapy followed by maintenance psychotherapy compared to acute pharmacotherapy followed by maintenance pharmacotherapy in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	8	OR **1.53** [CI 1.00 to 2.35]	⊕⊕⊕◯ MODERATE
		Adverse effects	All cause dropout	NR	OR **0.71** [CI 0.45 to 1.14]	⊕◯◯◯ VERY LOW
GRADE Table 11 Acute combined therapy followed by maintenance combined therapy compared to acute psychotherapy followed by maintenance psychotherapy in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	5	OR **1.65** [CI 1.04 to 2.61]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	NR	OR **0.95** [CI 0.57 to 1.58]	⊕◯◯◯ VERY LOW

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
GRADE Table 12 Acute combined therapy followed by maintenance combined therapy compared to acute pharmacotherapy followed by maintenance pharmacotherapy in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	7	OR 2.52 [CI 1.66 to 3.85]	⊕⊕⊕◯ MODERATE
		Adverse effects	All cause dropout	NR	OR **0.68** [CI 0.43 to 1.07]	⊕◯◯◯ VERY LOW
GRADE Table 13 Acute combined therapy followed by maintenance combined therapy compared to acute pharmacotherapy followed by maintenance combined therapy in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	NR	OR 2.97 [CI 0.71 to 12.45]	⊕◯◯◯ VERY LOW
		Adverse effects	All cause dropout	NR	OR **0.81** [CI 0.19 to 3.55]	⊕◯◯◯ VERY LOW
GRADE Table 14 Acute psychotherapy with a naturalistic follow-up compared to acute pharmacotherapy with a naturalistic follow-up in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	10	OR **1.66** [CI 1.13 to 2.44]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	NR	OR **1.09** [CI 0.70 to 1.70]	⊕◯◯◯ VERY LOW
GRADE Table 15 Acute combined therapy with a naturalistic follow-up compared to acute psychotherapy with a	Furukawa, 2021	Sustained Response	Sustained Response	8	OR **1.08** [CI 0.74 to 1.56]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	NR	OR **0.68** [CI 0.44 to 1.07]	⊕◯◯◯ VERY LOW

GRADE Table	Source	Outcome	Specific outcome	Number of Studies	Effects	Certainty of Evidence
naturalistic follow-up in adults with depressive disorders						
GRADE Table 16 Acute combined therapy with a naturalistic follow-up compared to acute pharmacotherapy with a naturalistic follow-up in adults with depressive disorders	Furukawa, 2021	Sustained Response	Sustained Response	9	OR **1.80** [CI 1.21 to 2.67]	⊕⊕◯◯ LOW
		Adverse effects	All cause dropout	NR	OR **0.75** [CI 0.48 to 1.16]	⊕◯◯◯ VERY LOW

4.2 Evidence to decision

Table 4: Evidence to decision table
Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognised priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	• By 2030, depression is predicted to be one of the leading causes of disability and premature mortality worldwide. • Reducing the burden of depression by developing evidence-based interventions is now a major global priority (World Bank Group & WHO, 2016).	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	**ACUTE PHASE TREATMENTS** • **Combined** therapy was better than **pharmacotherapy** alone in the reduction of depressive symptoms (SMD= 0.33), treatment response (RR=1.25) and remission (RR= 1.23). These effects were sustained at 6-12 months follow-up (RR= 0.72), favouring combined treatment.	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		• **Combined** therapy was better than **psychotherapy** alone in the reduction of depressive symptoms (SMD= 0.30), treatment response (RR= 1.27) and remission (RR= 1.22). These effects were sustained at 6-12 months follow-up (RR= 0.84), favouring combined treatment. • No significant differences were found between **pharmacotherapy** alone and **psychotherapy** alone in the reduction of depressive symptoms, treatment response and remission. However, **psychotherapy** was more effective than **pharmacotherapy** at 6-12 months follow-up (sustained response RR= 0.85). **Moderate depression** • For individuals with moderate depression, **combined therapy** had a significantly better treatment response compared to **pharmacotherapy** alone (RR= 1.23) and **psychotherapy** alone (RR= 1.19). No differences were found between psychotherapy alone and pharmacotherapy alone.	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		<u>Severe depression</u> • For individuals with severe depression, **combined therapy** had a better treatment response compared to **pharmacotherapy alone** (RR= 1.09). There were no differences between psychotherapy alone and pharmacotherapy alone, and between combined therapy and psychotherapy alone. **ACUTE AND MAINTENANCE PHASE TREATMENTS** • Acute **psychotherapy** followed by maintenance psychotherapy had better sustained response (at around 12 months post-acute treatment) than acute **pharmacotherapy** followed by pharmacotherapy (OR= 1.53). • Acute **combined** therapy followed by maintenance combined therapy had better sustained response than acute **psychotherapy** followed by maintenance psychotherapy (OR= 1.65) and that acute **pharmacotherapy** followed by maintenance pharmacotherapy (OR= 2.52).Both **psychotherapy** (OR= 1.66) and **combined therapy** (OR= 1.80) followed by naturalistic follow-ups	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			were better than **pharmacotherapy** with a naturalistic follow up around 12 months post-acute treatment.	
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	• Acceptability (all cause study drop-out) was significantly better for **combined therapy** compared to **pharmacotherapy** alone (RR= 1.23) • **Psychotherapy** alone had also higher acceptability rates compared to **pharmacotherapy** alone (RR= 1.17). • No significant differences were found between **combined therapy** and **psychotherapy** regarding treatment acceptability. • In the meta-regression, there were no significant modification effects of age, proportion of women and baseline severity of depression for any of the interventions.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects	☐ Very low ☒ **Low** ☐ Moderate ☐ High ☐ No included studies	None of the results were assessed at a high level of certainty. **MODERATE** The certainty of the evidence was assessed as moderate for three analyses: 1) superiority of combined treatment compared to pharmacotherapy alone in terms of remission (RR= 1.23), 2) superiority of psychotherapy in both acute and maintenance phases compared to pharmacotherapy alone in both phases (OR = 1.53), 3) superiority of combined treatment in both acute and maintenance phases compared to pharmacotherapy alone in both phases (OR= 2.52) **LOW and VERY LOW** The certainty of the evidence was assessed as low for 9 analyses and as very low for 21.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called 'utility values'.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	• There was no direct evidence to evaluate values and preferences of people. • *Overall, the studies highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and wellbeing. • The value could be limited by certain factors and barriers present in the health systems. For instance, low awareness, poor funding and poor political buy-in, or other social barriers (Badu *et al.* 2018; Padmanathan & De Silva 2013; Sarkar *et al.* 2021; Verhey *et al.* 2020). • Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions (Amaral *et al.* 2018; Brooke-Sumner *et al.* 2015; Dickson & Bangpan 2018; Verhey *et al.* 2020).	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgments regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ **Probably favors the intervention** ☐ Favors the intervention ☐ Varies ☐ Don't know	• In terms of treatment efficacy, combined psychotherapy and pharmacotherapy showed the best results across most of the analyses. Psychotherapy showed higher sustained response than pharmacotherapy over the long term. • In terms of treatment acceptability, combined therapy and psychotherapy alone showed lower drop-out rates than pharmacotherapy alone.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which <u>fewer</u> resources are required? • How large is the difference in each item of resource use for which <u>more</u> resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate resource requirements.	Additional comments: • Varies depending on the type of antidepressant, psychological treatment and treatment duration
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	There was no direct evidence to evaluate resource requirements.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Cost effectiveness	Does the cost-effectiveness of the intervention favor the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgments regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☒ **No included studies**	No reviews examining cost effectiveness identified. Individualized CBT is likely to be cost-effective both in combination with medication compared with medication alone and as standalone therapy compared with usual care, community referral, or bibliotherapy (Brettschneider et al, 2015; Wong and Knapp 2020). Group CBT being cost-effective compared with SSRIs, TCAs, usual care, and bibliotherapy.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favor of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate health equity, equality and non-discrimination. *The review noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers • Affordability - medication and treatment costs These factors may be exacerbated for certain groups: • People with low education/literacy - e.g. written instructions, psychoeducation materials • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Low resource settings - affordability/cost considerations exacerbated	
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	There was no direct evidence to evaluate feasibility. *Included reviews considered feasibility, and how this can be enhanced • Acceptability of interventions for stakeholders - requires increased engagement with specialist staff, increased visibility of the task-sharing workforce within health facilities, perception of usefulness by providers and service users (e.g. via positive feedback), context-specific interventions, standardised implementation steps for simpler decision-making and delivery • Health worker workload, competency- requires training, refreshers, supervision; networking with others in same role. • Availability of a task-sharing workforce • Availability of caregivers • Participant education and literacy requires verbal explanations/tasks.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			• Logistical issues such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • Limited resources/mental health budget Sustainability considerations: • Training and supervision • Integrating into routine clinical practice Provider type (e.g. formally employed lay health workers vs. volunteers)	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socio-culturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favor of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socio-culturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socio-culturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☐ Varies ☒ **Don't know**	There was no direct evidence to evaluate alignment with human rights principle and socio-cultural acceptability. *The review noted a number of considerations which would impact the right to health and access to healthcare. E.g. stigma and discrimination and lack of confidentiality could affect the help-seeking among service users. • The importance of socio-cultural acceptability of MNS interventions	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	identity, disability status, education, socio-economic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		was clearly expressed. Pre-intervention considerations that take into account cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility. <u>Mitigating steps</u> to improve sociocultural acceptability include: • To train health workers in non-judgemental care • Integrate preventative mental health awareness messages to reduce the stigma • Train acceptable counsellors for the local settings and target groups Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility and fidelity.	

4.3. Summary of judgements

Table 5: Summary of judgements

This provides a snapshot of the evidence to decision table.

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	✓ **Moderate**	- Large
Undesirable effects	- Don't know	- Varies		- Large	- Moderate	- Small	✓ **Trivial**
Certainty of the evidence	- No included studies			- Very low	✓ **Low**	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	✓ **Probably no important uncertainty or variability**	- No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favors comparison	- Probably favors comparison	- Does not favor either	✓ **Probably favors intervention**	- Favors intervention
Resources required	- Don't know	✓ **Varies**	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favors comparison	- Probably favors comparison	- Does not favor either	- Probably favors intervention	- Favors intervention
Equity, equality and non-discrimination	- Don't know	✓ **Varies**	- Reduced	Probably reduced	- Probably no impact	- Probably increased	- Increased
Feasibility	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes
Human rights and socio-cultural acceptability	✓ **Don't know**	- Varies		- No	- Probably No	- Probably Yes	- Yes

✓ Indicates category selected, - Indicates category not selected

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Appendix I: Search terms used to identify systematic reviews

PubMed

1# Depression

"Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR “depress*”[tiab] OR “dysthymi*”[tiab] OR “mood disorder*”[tiab] OR “affective disorder*”[tiab] OR “dysphoric disorder*”[tiab]

2# Antidepressants

"Antidepressive Agents"[Mesh:NoExp] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Antidepressive Agents, Tricyclic" [Mesh] OR "Fluoxetine"[Mesh] OR "Citalopram"[Mesh] OR "Sertraline"[Mesh] OR "Nortriptyline"[Mesh] OR "Antidepressive Agents" [Pharmacological Action] OR "Serotonin Uptake Inhibitors" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "antidepressiv*"[tiab] OR "anti-depressiv*"[tiab] OR antidepressant*[tiab] OR "anti-depressant*"[tiab] OR thymoleptic*[tiab] OR thymoanaleptic*[tiab] OR "Serotonin Reuptake Inhibitor*"[tiab] OR "Serotonin Re-uptake Inhibitor*"[tiab] OR "Serotonin uptake Inhibitor*"[tiab] OR “serotonin specific reuptake inhibitor*”[tiab] OR “serotonin specific re-uptake inhibitor*”[tiab] OR SSRI*[tiab] OR TCA[tiab] OR TCAs[tiab] OR alaproclate [tiab] OR Citalopram [tiab] OR Celexa [tiab] OR Cipramil [tiab] OR Escitalopram [tiab] OR Lexapro [tiab] OR Cipralex [tiab] OR Fluoxetine [tiab] OR Prozac [tiab] OR Sarafem [tiab] OR Fluvoxamine [tiab] OR Luvox [tiab] OR Faverin [tiab] OR Paroxetine [tiab] OR Paxil [tiab] OR Seroxat [tiab] OR Sertraline [tiab] OR Zoloft [tiab] OR Lustral [tiab] OR Vilazodone [tiab] OR Viibryd [tiab] OR femoxetine [tiab] OR indalpine [tiab] OR Zimeldine [tiab] OR Amitriptyline [tiab] OR Elavil [tiab] OR Endep [tiab] OR Amitriptylinoxide [tiab] OR Amioxid [tiab] OR Ambivalon [tiab] OR Equilibrin [tiab] OR Clomipramine [tiab] OR Anafranil [tiab] OR Desipramine [tiab] OR Norpramin [tiab] OR Pertofrane [tiab] OR Dibenzepin [tiab] OR Noveril [tiab] OR Victoril [tiab] OR Dimetacrine [tiab] OR Istonil [tiab] OR Dosulepin [tiab] OR Prothiaden [tiab] OR Doxepin [tiab] OR Adapin [tiab] OR Sinequan [tiab] OR Imipramine [tiab] OR Tofranil [tiab] OR Lofepramine [tiab] OR Lomont [tiab] OR Gamanil [tiab] OR Melitracen [tiab] OR Dixeran [tiab] OR Melixeran [tiab] OR Trausabun [tiab] OR Nitroxazepine [tiab] OR Sintamil [tiab] OR Nortriptyline [tiab] OR Pamelor [tiab] OR Aventyl [tiab] OR Noxiptiline [tiab] OR Agedal [tiab] OR Elronon [tiab] OR Nogedal [tiab] OR Opipramol [tiab] OR Insidon [tiab] OR Pipofezine [tiab] OR Azafen [tiab] OR Azaphen [tiab] OR Protriptyline [tiab] OR Vivactil [tiab] OR Trimipramine [tiab] OR Surmontil [tiab] OR Amoxapine [tiab] OR Asendin [tiab] OR cericlamine [tiab] OR dapoxetine [tiab] OR ifoxetine [tiab] OR litoxetine [tiab] OR lubazodone [tiab] OR moxifetin [tiab] OR nomelidine [tiab] OR norcitalopram [tiab] OR norfluoxetine [tiab] OR seproxetine [tiab] OR norsertraline [tiab] OR omiloxetine [tiab]

3# Psychotherapies

“Psychotherapy”[Mesh] OR “Counseling”[Mesh] OR psychotherap*[Tiab] OR cbt[Tiab] OR counselling[Tiab] OR counseling[Tiab] OR “Eye Movement Desensitization Reprocessing”[tiab] OR “Eye Movement Desensitization and Reprocessing”[tiab] OR “Eye Movement Desensitisation Reprocessing”[tiab] OR “Eye Movement Desensitisation and Reprocessing”[tiab] OR EMDR[tiab] OR “Bibliotherap*”[tiab] OR

mindfulness[Tiab] OR “Autogenic Training”[tiab] OR Logotherap*[tiab] OR "cognitive restructuring"[Tiab] OR "self-control training*"[Tiab] OR "assertiveness training"[Tiab] OR ((“therapy”[SubHeading] OR therap*[Tiab] OR “Therapeutics”[Mesh] OR treatment*[Tiab] OR intervention*[tiab]) AND (“brief psychodynamic”[Tiab] OR “short psychodynamic”[tiab] OR "problem-solving"[Tiab] OR "compassion-focused"[Tiab] OR "compassion-focussed"[Tiab] OR “compassion-based”[tiab] OR constructivist*[Tiab] OR metacognitive[tiab] OR “meta-cognitive”[Tiab] OR "solution-focused"[Tiab] OR "solution-focussed"[Tiab] OR "self-control”[Tiab] OR psychosocial[tiab] OR “peer support“[tiab] OR “task-shifted”[tiab] OR Relaxation[tiab] OR “dialectical behavior”[tiab] OR “emotion-focused”[tiab] OR narrative[tiab] OR “person-centred”[tiab] OR “person-centered”[tiab] OR “Narrative”[tiab] OR “meaning-centered”[tiab] OR “humanistic”[tiab] OR “client-centered”[tiab] OR “meaning-centred”[tiab] OR “client-centred”[tiab] OR “Rogerian”[tiab] OR “Nondirective”[tiab] OR “Non-directive”[tiab] OR “Supportive”[tiab] OR “Life review”[tiab] OR "acceptance and commitment"[Tiab] OR (“schema”[tiab] AND brief[tiab]) OR (“gestalt”[tiab] AND brief[tiab]))) OR "behavior therap*"[Tiab] OR "behaviors therap*"[Tiab] OR "behavioral therap*"[Tiab] OR "behaviour therap*"[Tiab] OR "behaviours therap*"[Tiab] OR "behavioural therap*"[Tiab] OR "cognition therap*"[Tiab] OR “cognitive therap*”[tiab] OR "behavior treatment*"[Tiab] OR "behaviors treatment*"[Tiab] OR "behavioral treatment*"[Tiab] OR "behaviour treatment*"[Tiab] OR "behaviours treatment*"[Tiab] OR "behavioural treatment*"[Tiab] OR "cognition treatment*"[Tiab] OR “cognitive treatment*”[tiab] OR "behavior intervention*"[Tiab] OR "behaviors intervention*"[Tiab] OR "behavioral intervention*"[Tiab] OR "behaviour intervention*"[Tiab] OR "behaviours intervention*"[Tiab] OR "behavioural intervention*"[Tiab] OR "cognition intervention*"[Tiab] OR “cognitive intervention*”[tiab] OR "behavior activation*"[Tiab] OR "behaviors activation*"[Tiab] OR "behavioral activation*"[Tiab] OR "behaviour activation*"[Tiab] OR "behaviours activation*"[Tiab] OR "behavioural activation*"[Tiab] OR exposure[tiab]

4# SR + MA filter

("Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR metaanaly*[tiab] OR meta-analy*[tiab] or metanaly*[tiab] OR "Systematic Review" [Publication Type] OR systematic[sb] OR meta-analysis[Filter] OR systematicreview[Filter] OR "Cochrane Database Syst Rev"[Journal] or prisma[tiab] OR “preferred reporting items”[tiab] OR prospero[tiab] OR ((systemati*[ti] OR umbrella[ti] OR “structured literature”[ti]) AND (review[ti] OR overview[ti])) OR “systematic review”[tiab] OR “umbrella review”[tiab] OR “structured literature review”[tiab] OR “systematic qualitative review”[tiab] OR “systematic quantitative review”[tiab] OR “systematic search and review”[tiab] OR “systematized review”[tiab] OR “systematised review”[tiab] OR “systemic review”[tiab] OR “systematic literature review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematically review”[tiab] OR “scoping literature review”[tiab] OR “scoping review”[tiab] OR “systematic critical review”[tiab] OR “systematic integrative review”[tiab] OR “systematic evidence review”[tiab] OR “systematic integrative literature review”[tiab] OR “systematic mixed studies review”[tiab] OR “systematized literature review”[tiab] OR “systematic overview”[tiab] OR “Systematic narrative review”[tiab] OR “narrative review”[tiab] OR metasynthes*[tiab] OR meta-synthes*[tiab]) NOT ("Comment" [Publication Type] OR

"Letter" [Publication Type] OR "Editorial" [Publication Type] OR (("Animals"[Mesh] OR "Models, Animal"[Mesh]) NOT "Humans"[Mesh]))

 # Timeframe
2019-2022

Appendix II: Decision Tree used to evaluate ROB GRADE item

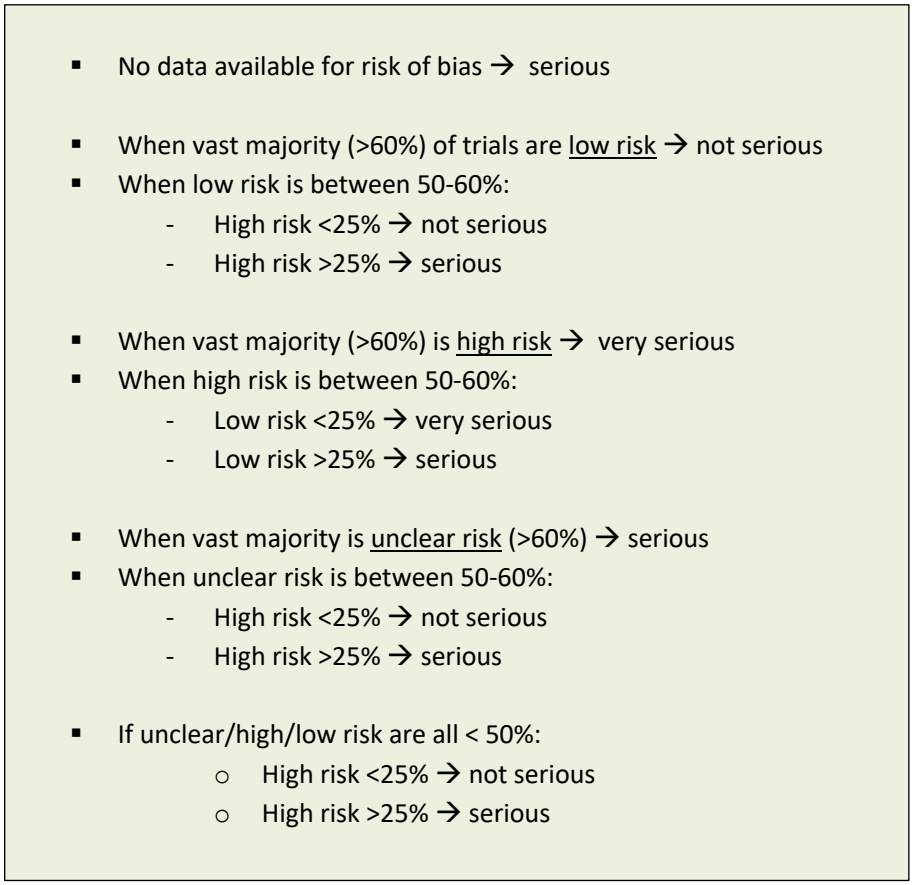

Figure 2: Developed tree for the assessment of the risk of bias item in GRADE