Depression module – evidence profile DEP1: Antidepressants (tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors [SSRIs]) in adults with depressive episode/disorder

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

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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 & 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., 2012; Ferrari et al., 2013). By 2030, depression is predicted to be one of the leading causes of disability and premature mortality worldwide (Mathers & Loncar, 2006). Reducing the depression burden by developing and scaling up evidence-based interventions is now a major global priority (World Bank Group & World Health Organization [WHO], 2016).

Different types of antidepressants effectively reduce depressive symptomatology (Cipriani et al., 2018) and are currently recommended as a first-line treatment for depression (Nathan & Gorman, 2015; Fletcher et al., 2020; WHO, 2016). However, the effects of antidepressants vary, and many patients do not improve or even experience deterioration (Thomas et al., 2013). Additionally, a long-standing concern is non-adherence to medications, which leads to symptom worsening, chronicity and increased suicidal rates (Ho et al., 2016). Therefore, there is a need to further evaluate the short- and long-term balance between benefits and harms of antidepressants (Cipriani et al., 2018; Ioannidis, 2008). An increasing number of trials assessing the effectiveness and safety of antidepressant medications are being published every year. Recent meta-analyses provide evidence about the 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 efficacy and safety of antidepressant medications for depression. Focusing on the most commonly prescribed antidepressants, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), we evaluated whether these pharmacotherapies were more effective and as safe as treatment as usual in adults with depressive disorders or elevated symptoms of depression. We reviewed the effects in a wide range of outcomes, including symptom reduction, suicide-related outcomes, adverse effects, and improvements in functioning.

2. Methodology

Evidence from recent meta-analyses covering the effectiveness and safety of pharmacotherapy for adults with depressive episode or disorders were summarized.

2.1 PICO question

Are antidepressants (tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI)) better (more effective than/as safe as) than treatment as usual in adults with depressive episode/disorder?

Population (P): Adults with depressive episode/disorder and/or elevated depressive symptoms
Intervention (I): Antidepressant medicines: TCAs, SSRIs
Comparator (C): Placebo, treatment as usual
Outcomes (O):

List critical outcomes:

- **Critical outcome 1:** Reduction of symptoms
- **Critical outcome 2:** Adverse effects
- **Critical outcome 3:** Suicide-related outcomes
- **Critical outcome 4:** Improvement in quality of life and in functioning

List important outcomes:

None specified

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 Vrije Universiteit Amsterdam. We designed the search strings by combining blocks with free and index terms indicative for (i) Depression (*Type of participants*), (ii) Antidepressants (TCAs and SSRIs) (*Types of interventions*), and (iii) terms related to systematic reviews and meta-analyses (*Type of studies*). The search strings for PubMed can be accessed in Appendix I. In line with the WHO guideline methodology, indicating that evidence obtained for the development of guidelines should be as recent as possible (WHO, 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) Evaluated the effectiveness or safety of SSRIs or TCAs compared to pill placebo/treatment as usual (iv) Reported outcomes regarding mental health symptoms, adverse effects, quality of life and functioning and suicide-related outcomes. 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

Rayyaan 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 Evaluation). 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 Appendix II.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics: I^2, 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 ($\alpha = 0.05$ and $\beta = 0.20$) 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

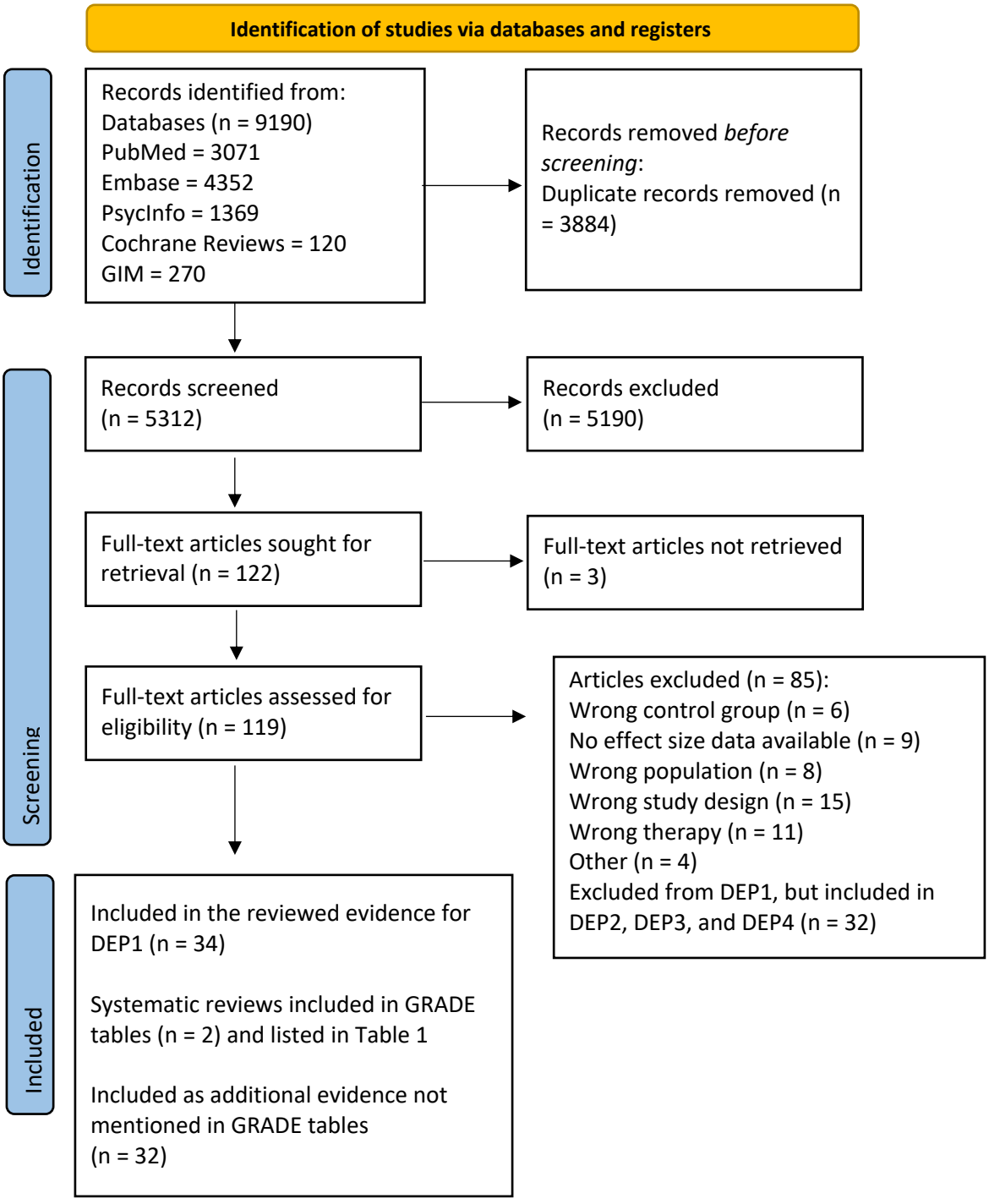
Since we reviewed existing systematic reviews, we considered the subgroups or subsets that were available in the included meta-analyses. The available subgroups were:

- Types of pharmacological interventions: SSRI and TCAs.

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 Lists of studies included and excluded

Studies included in GRADE tables/footnotes (2 studies)

CAO B., XU L., CHEN Y., WANG D., LEE Y., ROSENBLAT J.D., et al. (2021). Comparative efficacy of pharmacological treatments on measures of self-rated functional outcomes using the Sheehan Disability Scale in patients with major depressive disorder: a systematic review and network meta-analysis. CNS Spectr. 1-9.

CIPRIANI* A., FURUKAWA T.A., SALANTI G., CHAIMANI A., ATKINSON L.Z., OGAWA Y., et al. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 391:1357-1366.

*CIPRIANI et al. (2018) has been identified as the most recent high-quality meta-analysis available on the effectiveness of citalopram (SSRI), escitalopram (SSRI), fluoxetine (SSRI), fluvoxamine (SSRI), paroxetine (SSRI), sertraline (SSRI), amitriptyline (TCA), and clomipramine (TCA), for depressive symptom and response, and on all-cause discontinuation and adverse effects. The study was found through reference-screening of studies identified in the search of studies published between years 2019 and 2022.

Studies excluded from GRADE tables/footnotes (33 studies)

ARAUJO, J. S. A., DELGADO, I. F. & PAUMGARTTEN, F. J. R. 2020. Antenatal exposure to antidepressant drugs and the risk of neurodevelopmental and psychiatric disorders: a systematic review. Cad Saude Publica, 36, e00026619.

CHANG, Q., MA, X. Y., XU, X. R., SU, H., WU, Q. J. & ZHAO, Y. H. 2020. Antidepressant Use in Depressed Women During Pregnancy and the Risk of Preterm Birth: A Systematic Review and Meta-Analysis of 23 Cohort Studies. Front Pharmacol, 11, 659.

CHEN, C. & SHAN, W. 2019. Pharmacological and non-pharmacological treatments for major depressive disorder in adults: A systematic review and network meta-analysis. *Psychiatry Res,* 281**,** 112595.

CHEN, L., LI, X., LI, C. & ZOU, C. 2020. Antidepressant use and colorectal cancer morbidity and mortality: A dose-response meta analysis. *Medicine (Baltimore),* 99**,** e20185.

FITTON, C. A., STEINER, M. F. C., AUCOTT, L., PELL, J. P., MACKAY, D. F., FLEMING, M. & MCLAY, J. S. 2020. In utero exposure to antidepressant medication and neonatal and child outcomes: a systematic review. Acta Psychiatr Scand, 141, 21-33.

GUO, S., CHEN, L., CHENG, S. & XU, H. 2019. Comparative cardiovascular safety of selective serotonin reuptake inhibitors (SSRIs) among Chinese senile depression patients: A network meta-analysis of randomized controlled trials. Medicine (Baltimore), 98, e15786.

GUO, S., YANG, Y., PEI, X. J. & LIU, F. Y. 2020. Comparative risk of Selective Serotonin Reuptake Inhibitors (SSRIs)-induced nausea among Chinese senile depression patients: A network meta-analysis of randomized-controlled trials. *Medicine (Baltimore),* 99**,** e19133.

GUO, X., MCCUTCHEON, R. A., PILLINGER, T., MIZUNO, Y., NATESAN, S., BROWN, K. & HOWES, O. 2020. The magnitude and heterogeneity of antidepressant response in depression: A meta-analysis of over 45,000 patients. J Affect Disord, 276, 991-1000.

GUTSMIEDL, K., KRAUSE, M., BIGHELLI, I., SCHNEIDER-THOMA, J. & LEUCHT, S. 2020. How well do elderly patients with major depressive disorder respond to antidepressants: a systematic review and single-group meta-analysis. *BMC Psychiatry,* 20**,** 102.

HALVORSEN, A., HESEL, B., ØSTERGAARD, S. D. & DANIELSEN, A. A. 2019. In utero exposure to selective serotonin reuptake inhibitors and development of mental disorders: a systematic review and meta-analysis. *Acta Psychiatr Scand,* 139**,** 493-507.

HE, W., ZHOU, Y., MA, J., WEI, B. & FU, Y. 2020. Effect of antidepressants on death in patients with heart failure: a systematic review and meta-analysis. *Heart Fail Rev,* 25**,** 919-926.

HIERONYMUS, F., LISINSKI, A., NILSSON, S. & ERIKSSON, E. 2019. Influence of baseline severity on the effects of SSRIs in depression: an item-based, patient-level post-hoc analysis. Lancet Psychiatry, 6, 745-752.

HOLPER, L. & HENGARTNER, M. P. 2020. Comparative efficacy of placebos in short-term antidepressant trials for major depression: a secondary meta-analysis of placebo-controlled trials. *BMC Psychiatry,* 20**,** 437.

KATO, M., HORI, H., INOUE, T., IGA, J., IWATA, M., INAGAKI, T., SHINOHARA, K., IMAI, H., MURATA, A., MISHIMA, K. & TAJIKA, A. 2021. Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis. Mol Psychiatry, 26, 118-133.

KAUTZKY, A., SLAMANIG, R., UNGER, A. & HÖFLICH, A. 2022. Neonatal outcome and adaption after in utero exposure to antidepressants: A systematic review and meta-analysis. Acta Psychiatr Scand, 145, 6-28.

KIM, Y., LEE, Y. S., KIM, M. G., SONG, Y. K., KIM, Y., JANG, H., KIM, J. H., HAN, N., JI, E., KIM, I. W. & OH, J. M. 2019. The effect of selective serotonin reuptake inhibitors on major adverse cardiovascular events: a meta-analysis of randomized-controlled studies in depression. *Int Clin Psychopharmacol,* 34**,** 9-17.

MASLEJ, M. M., FURUKAWA, T. A., CIPRIANI, A., ANDREWS, P. W., SANCHES, M., TOMLINSON, A., VOLKMANN, C., MCCUTCHEON, R. A., HOWES, O., GUO, X. & MULSANT, B. H. 2021. Individual Differences in Response to Antidepressants: A Meta-analysis of Placebo-Controlled Randomized Clinical Trials. *JAMA Psychiatry,* 78**,** 490-497.

MUNKHOLM, K., PALUDAN-MÜLLER, A. S. & BOESEN, K. 2019. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open,* 9**,** e024886.

OLIVA, V., LIPPI, M., PACI, R., DEL FABRO, L., DELVECCHIO, G., BRAMBILLA, P., DE RONCHI, D., FANELLI, G. & SERRETTI, A. 2021. Gastrointestinal side effects associated with antidepressant treatments in patients with major depressive disorder: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry,* 109**,** 110266.

ROTHMORE, J. 2020. Antidepressant-induced sexual dysfunction. *Medical Journal of Australia,* 212**,** 329-334.

SALISBURY-AFSHAR, E. 2020. Adverse Events of Pharmacologic Treatments of Major Depression in Older Adults. *Am Fam Physician,* 101**,** 179-181.

SINYOR, M., CHEUNG, C. P., ABRAHA, H. Y., LANCTÔT, K. L., SALEEM, M., LIU, C. S., LI, A., JUDA, A., LEVITT, A. J., CHEUNG, A. H. & SCHAFFER, A. 2020. Antidepressant-placebo differences for specific adverse events in major depressive disorder: A systematic review. *J Affect Disord,* 267**,** 185-190.

SOBIERAJ, D. M., BAKER, W. L., MARTINEZ, B. K., HERN, EZ, A. V., COLEMAN, C. I., ROSS, J. S., BERG, K. M. & STEFFENS, D. C. 2019. AHRQ Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US).

SOBIERAJ, D. M., MARTINEZ, B. K., HERN, EZ, A. V., COLEMAN, C. I., ROSS, J. S., BERG, K. M., STEFFENS, D. C. & BAKER, W. L. 2019. Adverse Effects of Pharmacologic Treatments of Major Depression in Older Adults. *J Am Geriatr Soc,* 67**,** 1571-1581.

THARMARAJA, T., STAHL, D., HOPKINS, C. W. P., PERSAUD, S. J., JONES, P. M., ISMAIL, K. & MOULTON, C. D. 2019. The Association Between Selective Serotonin Reuptake Inhibitors and Glycemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Psychosom Med, 81, 570-583.

TRAJKOVA, S., D'ERRICO, A., SOFFIETTI, R., SACERDOTE, C. & RICCERI, F. 2019. Use of Antidepressants and Risk of Incident Stroke: A Systematic Review and Meta-Analysis. *Neuroepidemiology,* 53**,** 142-151.

UGUZ, F. 2020. Selective serotonin reuptake inhibitors and the risk of congenital anomalies: a systematic review of current meta-analyses. *Expert Opin Drug Saf,* 19**,** 1595-1604.

VISWANATHAN, M., MIDDLETON, J. C., STUEBE, A. M., BERKMAN, N. D., GOULDING, A. N., MCLAURIN-JIANG, S., DOTSON, A. B., COKER-SCHWIMMER, M., BAKER, C., VOISIN, C. E., BANN, C. & GAYNES, B. N. 2021. Maternal, Fetal, and Child Outcomes of Mental Health Treatments in Women: A Meta-Analysis of Pharmacotherapy. *Psychiatric Research and Clinical Practice,* 3**,** 123-140.

WANG, Y., LIU, D., LI, X., LIU, Y. & WU, Y. 2021. Antidepressants use and the risk of type 2 diabetes mellitus: A systematic review and meta-analysis. *Journal of Affective Disorders,* 287**,** 41-53.

WANG, Y., YE, Z., LIU, L. & CUI, X. 2019. Antidepressant use and risk of venous thromboembolism: A systematic review and meta-analysis. *Journal of Pharmacy and Pharmaceutical Sciences,* 22**,** 57-71.

WEN, F. K., CROSBY, K., MILLER, B. H., ROMMEN, M., KIRZNER, S. J., HOBERECHT, T. & MIGDALSKI, A. 2020. Association of first-line antidepressants and incident adverse metabolic effects. *Can Fam Physician,* 66**,** 898-900.

XING, D., WU, R., CHEN, L. & WANG, T. 2020. Maternal use of antidepressants during pregnancy and risks for adverse perinatal outcomes: a meta-analysis. *J Psychosom Res,* 137**,** 110231.

YUAN, Z., CHEN, Z., XUE, M., ZHANG, J. & LENG, L. 2020. Application of antidepressants in depression: A systematic review and meta-analysis. *J Clin Neurosci,* 80**,** 169-181.

Table 1. PICO table

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
1	Pharmacotherapy (Citalopram) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Citalopram (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Citalopram (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	-	No available recent meta-analytic evidence on this outcome (N/A)
		Suicide-related outcomes	-	N/A
2	Pharmacotherapy (Escitalopram) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Escitalopram (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Escitalopram (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning in Escitalopram (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
3	Pharmacotherapy (Fluoxetine) compared to pill placebo in	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Fluoxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
	adults with depressive disorders	Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Fluoxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning in Fluoxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
4	Pharmacotherapy (Fluvoxamine) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Fluvoxamine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Fluvoxamine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	-	N/A
		Suicide-related outcomes	-	N/A
5	Pharmacotherapy (Paroxetine) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Paroxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Paroxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning in Paroxetine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
6	Pharmacotherapy (Sertraline) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Sertraline (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Sertraline (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning in Sertraline (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
7	Pharmacotherapy (Amitriptyline) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Amitriptyline (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Amitriptyline (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning in Amitriptyline (SSRI) vs

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
				pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
8	Pharmacotherapy (Clomipramine) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the effectiveness of Clomipramine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Adverse effects	Cipriani et al., 2018	Most recent high-quality meta-analysis available on the adverse effects of Clomipramine (SSRI) vs pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Improvement in quality of life and functioning	-	N/A
		Suicide-related outcomes	-	N/A
9	Pharmacotherapy (Group SSRI) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	-	N/A
		Adverse effects	-	N/A
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning between group SSRI and pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression
		Suicide-related outcomes	-	N/A
10	Pharmacotherapy (Group TCA) compared to pill placebo in adults with depressive disorders	Reduction in mental health symptoms	-	N/A
		Adverse effects	-	N/A
		Improvement in quality of life and functioning	Cao et al., 2021	Most recent high-quality meta-analysis available on improvement in functioning between group TCA and pill placebo on depressive symptoms in adults with elevated symptoms and/or diagnosis of depression

Serial number	Intervention/ comparison	Outcomes	Systematic reviews (name, year)	Justification/explanation for systematic review
		Suicide-related outcomes	-	N/A

N/A: No available recent meta-analytic evidence on this outcome; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants

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

Cao et al., 2021: OBJECTIVE: More than 50% patients with major depressive disorder (MDD) have severe functional impairment. The restoration of patient functioning is a critical therapeutic goal among patients with MDD. We conducted a systematic review and network meta-analysis to evaluate the efficacy of pharmacological treatments on self-rated functional outcomes using the Sheehan Disability Scale in adults with MDD in randomized clinical trials. METHODS: PubMed, Embase, PsycInfo, Cochrane Library, and ClinicalTrials.gov were searched from inception to 10 December 2019. Summary statistics are reported as weighted mean differences with 95% confidence intervals. Interventions were ranked using the surface under the cumulative ranking probabilities. RESULTS: We included 42 randomized controlled trials (RCTs) (n = 18 998) evaluating the efficacy of 13 different pharmacological treatments on functional outcomes, as measured by the Sheehan Disability Scale (SDS). Duloxetine was the most effective pharmacological agent on functional outcomes, followed by (ranked by efficacy): paroxetine, levomilnacipran, venlafaxine, quetiapine, desvenlafaxine, agomelatine, escitalopram, amitriptyline, bupropion, sertraline, vortioxetine, and fluoxetine. Serotonin and norepinephrine reuptake inhibitors were more effective than other drug classes. Additionally, the comparison-adjusted funnel plot suggested the publication bias between small and large studies was relatively low. CONCLUSIONS: Our results indicate that there may be differences across antidepressant agents and classes with respect to self-reported functional outcomes. Validation and replication of these findings in large-scale RCTs are warranted. Our research results will be clinically useful for guiding psychiatrists in treating patients with MDD and functional impairment. PROSPERO registration number CRD42018116663.

Cipriani et al., 2018: Background: Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder. Methods: We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycInfo, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomized controlled trials from their inception to 8 January 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalized criteria. We excluded quasi-randomized trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the *Cochrane handbook for systematic reviews of interventions* and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary odds ratios (ORs) using pairwise and network meta-analysis with random effects. This study is registered with PROSPERO, number CRD42012002291. Findings: We identified 28 552 citations and of these included 522 trials comprising 116 477 participants. In terms of efficacy, all antidepressants were more effective than placebo, with ORs ranging

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

between 2.13 (95% credible interval [CrI] 1.89–2.41) for amitriptyline and 1.37 (1.16–1.63) for reboxetine. For acceptability, only agomelatine (OR 0.84, 95% CrI 0.72–0.97) and fluoxetine (0.88, 0.80–0.96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1.30, 1.01–1.68). When all trials were considered, differences in ORs between antidepressants ranged from 1.15 to 1.55 for efficacy and from 0.64 to 0.83 for acceptability, with wide CrIs on most of the comparative analyses. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1.19–1.96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0.51–0.84). For acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0.43–0.77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1.30–2.32). 46 (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low; and the certainty of evidence was moderate to very low. Interpretation: All antidepressants were more efficacious than placebo in adults with major depressive disorder. Smaller differences between active drugs were found when placebo-controlled trials were included in the analysis, whereas there was more variability in efficacy and acceptability in head-to-head trials. These results should serve evidence-based practice and inform patients, physicians, guideline developers, and policy-makers on the relative merits of the different antidepressants.

3.4 Grading the evidence

GRADE Table 1. Pharmacotherapy (Citalopram– SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018

Certainty assessment								Effect	Certainty	Import-ance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other con-siderations	№ of patients	Absolute (95% CI)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
14[b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [d]	3802[b]	SMD **-0.24** [CI -0.31 to -0.17]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
14[b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [d]	3802[b]	OR **1.52** [CI 1.33 to 1.74]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
14[b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [d]	3802[b]	OR **0.94** [CI 0.80 to 1.09]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										

Certainty assessment								Effect	Certainty	Import-ance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other con-siderations	№ of patients	Absolute (95% CI)		
14 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [d]	3802 [b]	OR **1.87** [CI 1.39 to 2.51]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										
-	-	-	-	-		-	-	-	-	CRITICAL
Improvement in QAL and functioning – Not available										
-	-	-	-	-			-	-	-	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo

Response (efficacy) – Above 1 favours treatment; below 1 favours placebo

All-cause dropout – Below 1 favours treatment; above 1 favours placebo

Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo

a Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons.

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 2. Pharmacotherapy (Escitalopram – SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018; Cao 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)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
21 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [f]	6432 [b]	SMD **-0.29** [CI -0.35 to -0.24]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
21 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [f]	6432 [b]	OR **1.68** [CI 1.50 to 1.87]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
21 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [f]	6432 [b]	OR **0.90** [CI 0.80 to 1.02]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
21 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [f]	6432 [b]	OR **1.72** [CI 1.38 to 2.14]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Improvement in functioning – Cao et al., 2021										
NR	RCT	serious [d]	serious [e]	not serious	serious [f]	none	NR	~~S~~MD **-1.59** (SDS) [CI -2.89 to -0.28]	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale
Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo
Response (efficacy) – Above 1 favours treatment; below 1 favours placebo
All-cause dropout – Below 1 favours treatment; above 1 favours placebo
Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo

a **Cipriani et al., 2018:** Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale. **Cao et al., 2021:** Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.
b The number of studies and the number of participants is extracted from the direct pairwise comparisons
c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.
d The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.
e Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.
f The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.
g Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 3. Pharmacotherapy (Fluoxetine – SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018; Cao 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)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
43 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	8619 [b]	SMD **-0.23** [CI -0.28 to -0.19]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
43 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	8619 [b]	OR **1.52** [CI 1.40 to 1.66]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
43 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	8619 [b]	OR **0.88** [CI 0.80 to 0.96]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
43 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	8619 [b]	OR **1.82** [CI 1.56 to 2.13]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Improvement in functioning – Cao et al., 2021										
NR	RCT	serious [d]	serious [e]	not serious	serious [f]	none	NR	~~S~~MD **0.30** (SDS) [CI -1.90 to 2.50]	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale; NR: not reported

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo
Response (efficacy) – Above 1 favours treatment; below 1 favours placebo
All-cause dropout – Below 1 favours treatment; above 1 favours placebo
Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo

a **Cipriani et al, 2018:** Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale. **Cao et al., 2021:** Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.

e Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.

f The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.

g Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 4. Pharmacotherapy (Fluvoxamine – SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018

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 – Change in depressive symptoms – Cipriani et al., 2018										
14 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[d]	1688 [b]	SMD **-0.32** [CI -0.43 to -0.22]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
14 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[d]	1688 [b]	OR **1.69** [CI 1.41 to 2.02]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
14 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[d]	1688 [b]	OR **1.10** [CI 0.91 to 1.33]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
14 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[d]	1688 [b]	OR **2.83** [CI 2.12 to 3.80]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo

Response (efficacy) – Above 1 favours treatment; below 1 favours placebo

All-cause dropout – Below 1 favours treatment; above 1 favours placebo

Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo

a Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons.

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 5. Pharmacotherapy (Paroxetine – SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018; Cao 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)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
49 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	10 243 [b]	SMD **-0.32** [CI -0.37 to -0.28]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
49 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	10 243 [b]	OR **1.75** [CI 1.61 to 1.90]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
49 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	10 243 [b]	OR **0.95** [CI 0.87 to 1.03]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
49 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	10 243 [b]	OR **2.19** [CI 1.90 to 2.53]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Improvement in functioning – Cao et al., 2021										
NR	RCT	serious [d]	serious [e]	not serious	serious [f]	none	NR	~~S~~MD **-2.51** (SDS) [CI -4.08 to -0.94]	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale; NR: not reported

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo
Response (efficacy) – Above 1 favours treatment; below 1 favours placebo
All-cause dropout – Below 1 favours treatment; above 1 favours placebo
Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo

a Cipriani et al., 2018: Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale. **Cao et al., 2021:** Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.

e Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.

f The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.

g Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 6. Pharmacotherapy (Sertraline – SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018; Cao 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)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
24 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	4872 [b]	SMD **-0.27** [CI -0.34 to -0.21]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
24 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	4872 [b]	OR **1.67** [CI 1.49 to 1.87]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
24 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	4872 [b]	OR **0.96** [CI 0.85 to 1.08]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
24 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	4872 [b]	OR **2.01** [CI 1.61 to 2.52]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Improvement in functioning – Cao et al., 2021										
NR	RCT	serious [d]	serious [e]	not serious	serious [f]	none	NR	~~S~~MD **-1.30** (SDS) [CI -3.36 to 0.76]	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale; NR: not reported

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo
Response (efficacy) – Above 1 favours treatment; below 1 favours placebo
All-cause dropout – Below 1 favours treatment; above 1 favours placebo
Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo

a **Cipriani et al., 2018:** Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale. **Cao et al., 2021:** Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons.

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.

e Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.

f The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.

g Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 7. Pharmacotherapy (Amitriptyline – TCA) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cipriani et al., 2018; Cao 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)		
Reduction in mental health symptoms – Change in depressive symptoms – Cipriani et al., 2018										
36 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	3563 [b]	SMD **-0.48** [CI -0.55 to -0.41]	⊕⊕◯◯ LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
36 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	3563 [b]	OR **2.13** [CI 1.89 to 2.14]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
36 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	3563 [b]	OR **0.95** [CI 0.83 to 1.08]	⊕⊕◯◯ LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
36 [b]	RCT	serious [c]	not serious	not serious	not serious	publication bias strongly suspected[g]	3563 [b]	OR **3.11** [CI 2.54 to 3.82]	⊕⊕◯◯ LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Improvement in functioning – Cao et al., 2021										
NR	RCT	serious [d]	serious [e]	not serious	serious [f]	none	NR	~~S~~MD **-1.30** (SDS) [CI -5.34 to 2.47]	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale
Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo
Response (efficacy) – Above 1 favours treatment; below 1 favours placebo
All-cause dropout – Below 1 favours treatment; above 1 favours placebo
Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo

a **Cipriani et al., 2018:** Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale. **Cao et al., 2021:** Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.
b The number of studies and the number of participants is extracted from the direct pairwise comparisons.
c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.
d The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.
e Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.
f The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.
g Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 8. Pharmacotherapy (Clomipramine – TCA) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General Adult [a]
Reference List: Cipriani et al., 2018

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 – Change in depressive symptoms – Cipriani et al., 2018										
1 [b]	RCT	serious [c]	not serious	not serious	very serious [d]	publication bias strongly suspected[e]	38 [b]	SMD **-0.33** [CI -0.45 to -0.21]	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in mental health symptoms – Response (efficacy) – Cipriani et al., 2018										
1 [b]	RCT	serious [c]	not serious	not serious	very serious [d]	publication bias strongly suspected[e]	38 [b]	OR **1.49** [CI 1.21 to 1.85]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – All-cause dropout – Cipriani et al., 2018										
1 [b]	RCT	serious [c]	not serious	not serious	very serious [d]	publication bias strongly suspected[e]	38 [b]	OR **1.30** [CI 1.01 to 1.68]	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects – Dropout due to adverse events – Cipriani et al., 2018										
1 [b]	RCT	serious [c]	not serious	not serious	very serious [d]	publication bias strongly suspected[e]	38 [b]	OR **4.44** [CI 3.07 to 6.50]	⊕◯◯◯ VERY LOW	CRITICAL
Suicide-related outcomes – Not available										

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life

Interpretation of outcomes:

Change in depressive symptoms – Below 0 favours treatment; above 0 favours placebo

Response (efficacy) – Above 1 favours treatment; below 1 favours placebo

All-cause dropout – Below 1 favours treatment; above 1 favours placebo

Dropout due to adverse events – Below 1 favours treatment; above 1 favours placebo

a Adults (>18 years) with elevated symptoms and/or diagnosis of depression. The mean age of the sample was 44 years and 62.3% were women. Most of the participants had moderate to severe depression with a mean baseline severity score of 25.7 (SD 3.97) on the Hamilton Depression Rating Scale.

b The number of studies and the number of participants is extracted from the direct pairwise comparisons.

c Vast majority of the included studies (>60%) have an unclear risk of bias and this seriously affects the certainty of evidence.

d This has been rated as very serious because the number of participants was below 100.

e Statistical tests (Egger's test, funnel plots) suggest the presence of publication bias.

GRADE Table 9. Pharmacotherapy (Pooled SSRI) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General Adult [a]
Reference List: Cao 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)		
Reduction in mental health symptoms – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Suicide-related outcomes – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Cao et al., 2021										
NR	RCT	serious [b]	serious [c]	not serious	serious [d]	none	NR	~~S~~MD **-1.42** (SDS) [CI -2.32 to -0.52]	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale
Interpretation of outcomes:
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo
a Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.
b The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.
c Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.
d The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.

GRADE Table 10. Pharmacotherapy (Pooled TCA) compared to pill placebo in adults with depressive disorders
Author(s): Arpana Amarnath, Marketa Ciharova, Clara Miguel
Question: Pharmacotherapy compared to pill placebo in adults with depression
Population: General adult [a]
Reference List: Cao 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)		
Reduction in mental health symptoms – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse effects – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Suicide-related outcomes – Not available										
-	-	-	-	-	-	-	-	-	-	CRITICAL
Improvement in QAL and functioning – Cao et al., 2021										
NR	RCT	serious [b]	serious [c]	not serious	serious [d]	none	NR	~~S~~MD **-1.42** (SDS) [CI -5.01 to 2.17]	⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; RCTs: randomized controlled trials; SMD: standard mean difference; QAL: quality of life; SDS: Sheehan Disability Scale
Interpretation of outcomes:
Improvement in functioning – Below 0 favours treatment; above 0 favours placebo
a Adults (>18 years) with a diagnosis of major depressive disorder. The mean age was 44.1 years and 63.5% were women.
b The risk of bias assessment was aggregated for the entire meta-analysis. It has been rated as serious as a vast majority of the included studies (>60%) have an unclear risk of bias.
c Estimates of heterogeneity were not available and this seriously affects the certainty of evidence.
d The number of participants included in the analyses was not reported. This seriously affects the certainty of evidence.

3.5 Additional evidence not mentioned in GRADE tables

Araujo et al, 2020: This study investigated whether antenatal exposure to antidepressants (Ads) increases the risks of autism spectrum disorders (ASD), attention deficit/hyperactivity disorders (ADHD), schizophrenia and other mental illnesses, and cognitive and developmental deficits in infants or preschool children. PubMed, EMBASE, BIREME/BVS databases were searched to identify studies examining associations of Ads in pregnancy with neurodevelopmental and psychiatric disorders. Twenty studies addressed ASD and/or ADHD risks while 30 focused on developmental and cognitive deficits in infants or preschool children. Most studies detected no association of antenatal AD with ASD after adjustment of risk ratios for maternal depression or psychiatric disorders. Some studies showed that maternal depression, regardless of whether it is treated or untreated, increased ASD risks. Seven out of 8 studies found no increase in ADHD risk associated with antenatal exposure to selective serotonin reuptake inhibitors, the most commonly used AD. No consistent evidence was found linking AD in pregnancy to neurocognitive developmental deficits in infants or preschool children. A residual confounding by indication (depression severity) remained in almost all studies. This systematic review found no consistent evidence suggesting that Ads in pregnancy increase risks of ASD, ADHD, and neurocognitive development deficits. Some studies, however, found evidence that maternal depression increases ASD risks.

Chang et al., 2020: OBJECTIVE: The associations between maternal use of antidepressant during pregnancy and preterm birth (PTB) has been the subject of much discussion and controversy. The aim of the present study was to systematically review the association between antidepressant use during pregnancy and the risk of PTB, especially in depressed women. METHODS: A computerized search was conducted in PubMed, PsycInfo, and Embase before June 30, 2019, supplemented with a manual search of the reference lists, to identify original research regarding PTB rates in women taking antidepressants during pregnancy. A random-effects model was used to calculate the summarized relative risks (RRs) and 95% confidence intervals (CIs). The potential for publication bias was examined through Begg's and Egger's tests. RESULTS: A total of 2279 articles were reviewed, 23 of which were selected. The risk of PTB was increased in women with depression [1.58 (1.23-2.04)] and in the general pregnant female population [1.35 (1.11-1.63)] who used antidepressants during pregnancy. Similar results were observed in depressed women treated with selective serotonin reuptake inhibitors (SSRIs) during pregnancy [1.46 (1.32-1.61)]. There was no significantly increased risk of PTB observed with SSRI use in the general pregnant female population [1.25 (1.00-1.57)], and the heterogeneity of these studies was high. CONCLUSIONS: The results of this meta-analysis indicate maternal antidepressant use is associated with a significantly increased risk of PTB in infants. Health care providers and pregnant women must weigh the risk-benefit potential of these drugs when making decisions about whether to treat with antidepressant during pregnancy.

Chen and Shen, 2020: Depression has brought huge disease burden to the world. This systematic review aimed to compare the efficacy and safety of pharmacological and non-pharmacological treatments for major depressive disorder (MDD). We searched electronic databases with time range from 1 January 1990 to 5 September 2018. Randomized controlled trials (RCTs) including adult patients with MDD were eligible for inclusion. We conducted network meta-analyses using multivariate meta-analyses models under the frequency framework. Primary outcomes were efficacy (response rate) and safety (overall risk of adverse events). We estimated summary odds ratios (ORs) based on group-level data. 20 937 citations were identified, 91 trials comprising 10 991 participants were included in efficacy study, and 32 trials comprising 5245 participants were included in safety study. In terms of efficacy, all treatments studied (acupuncture, mirtazapine, herbal medicine, venlafaxine, physical exercise, cognitive-behavioural therapy (CBT), bupropion, fluoxetine, and vortioxetine) except for probiotics were significantly more effective

than placebo. In terms of safety, bupropion, fluoxetine, venlafaxine, and vortioxetine were significantly less safe than placebo. Herbal medicine and mirtazapine had no significant difference in overall risk of adverse events compared with placebo. Acupuncture, CBT, physical exercise and probiotics were lack of eligible safety data.

Chen et al., 2020: The risk of colorectal cancer associated to antidepressant use remains unclear. The purpose of this meta-analysis was to investigate the risk of colorectal cancer associated to antidepressant use. MEDLINE, Embase, Web of Science, and Cochrane Database were accessed from the dates of their establishment to October 2018, to collect study of antidepressant use and colorectal cancer morbidity and mortality. Then a meta-analysis was conducted using Stata 12.0 software. A total of 11 publications involving 109 506 participants were included. The meta-analysis showed that antidepressant use was not associated with colorectal cancer morbidity (relative risk (RR): 0.97; 95% confidence interval (CI): 0.94-1.01) and mortality (RR: 1.08; 95% CI: 0.99-1.17). Subgroup analysis showed selective serotonin reuptake inhibitor (RR: 0.99; 95% CI: 0.96-1.03) or serotonin norepinephrine reuptake inhibitor (RR: 1.04; 95% CI: 0.86-1.26) were not associated with colorectal cancer risk; however, TCA was associated with colorectal cancer risk decrement (RR: 0.92; 95% CI: 0.87-0.98). Furthermore, the results also showed that antidepressant use was not associated with colorectal cancer risk in Europe and North America (RR: 0.97; 95% CI: 0.92-1.02) and Asia (RR: 1.00; 95% CI: 0.95-1.26). Additionally, a dose-response showed per one year of duration of antidepressant use incremental increase was not associated with colorectal cancer risk (RR: 0.96; 95% CI: 0.87-1.09). Evidence suggests that antidepressant use was not associated with colorectal cancer morbidity and mortality. The cumulative duration of antidepressant use did not utilized played critical roles.

Fitton et al., 2020: OBJECTIVE: The aim of this study is to systematically review published studies, reporting outcomes to offspring following in utero exposure to antidepressant medications, which used an untreated depressed comparison group. METHODS: OVID, Scopus, EBSCO Collections, the Cochrane Library and Web of Science databases were searched for relevant publications published between January 1950 and May 2018 and a total of 188 potentially eligible studies were identified. RESULTS: Following review, 16 primary studies were eligible for inclusion. Antidepressant exposure was associated with an increased risk of lower gestational age, preterm birth, but not low birthweight or being small for gestational age compared to untreated depression. There is some evidence that congenital defects are associated with antidepressant use, particularly between cardiac defects and paroxetine use. There is conflicting evidence regarding neurodevelopment in offspring, with some reports of increased incidence of autistic spectrum disorders and depression, but also reports of no problems when measuring emotional symptoms, peer problems, conduct problems and hyperactivity-inattention scores. CONCLUSION: When compared with an untreated depressed group, antidepressant exposure was associated with adverse outcomes at birth, while there is insufficient data to determine whether the association between antidepressants and congenital defects or developmental disorders is a true association. However, although we compared treated vs. untreated depression there still may be residual confounding as an untreated depressed group is likely to have less severe depression.

Guo et al., 2019: BACKGROUND: Senile depression patients in China usually present with a higher risk of coronary heart disease that may trigger cardiac death. Selective serotonin reuptake inhibitors (SSRIs) were the most prescribed antidepressants in China; the cardiovascular safety of SSRIs when used in Chinese senile depression patients has not been evaluated. METHODS: A network of meta-analysis was conducted to fill the objectives. PubMed, Embase databases, and 2 Chinese language electronic databases WANFANG and CNKI were searched for the related articles. The primary outcome of the present study was the number of cardiovascular reactions when each SSRI drug was used among senile depression patients in China. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated within pairwise and network

meta-analysis. RESULTS: Fifteen trials were identified, including 1432 patients; the network meta-analysis showed that Chinese senile depression patients treated by Escitalopram were associated with a lower risk of cardiovascular reaction (CDR) than Paroxetine (ORs 0.37, 95% CI 0.14-0.37). Escitalopram also exhibited distinct advantages compared with other SSRIs. The rank of SSRIs with respect to cardiovascular safety was Escitalopram > Sertraline > Citalopram > Paroxetine > Fluoxetine, respectively. CONCLUSION: Escitalopram exhibited distinct advantages compared with other SSRIs, while Fluoxetine had the biggest cardiovascular reaction probability.

Guo, Yang et al., 2020: OBJECTIVES: To compare the therapeutic effect of six SSRIs among the Chinese senile depression patients. And drug-induced nausea leads to low compliance in elderly depression patients in China, it is urgent to assess the safety of six SSRIs with respect to induced-nausea among the Chinese senile depression patients. METHOD: In the present study, a network of meta-analysis was conducted to assess the efficacy of 6 SSRIs among the Chinese senile depression patients, in addition, the safety of 6 SSRIs with respect to induced nausea among the Chinese senile depression patients was also evaluated. PubMed, Embase databases, WanFang, CNKI, ChongqingWeiPu were searched for the related articles. The primary outcome of this study were the number of effective cases of SSRIs and the number of cases of nausea caused by SSRIs in Chinese elderly depressed patients. Odds ratios (ORs) and corresponding 95% confidence intervals(95% CIs) were calculated within pairwise and network meta-analysis. RESULTS: Twenty-eight trials were identified, including 2246 patients, the network meta-analysis indicated that Escitalopram was associated with a lower risk of nausea compared Paroxetine (OR 0.49, 95% CI 0.34-0.69) when they were used in Chinese elderly depressed patients. Escitalopram also exhibited distinct advantages compared other SSRIs.In terms of drug efficacy, Escitalopram was significantly superior to Paroxetine (OR = 2.26, 95% CI 1.55-3.37). CONCLUSION: The rank of SSRIs with respect to induced nausea was: Combination of EP > Fluoxetine > Paroxetine > Citalopram > Sertraline > Fluvoxamine > Escitalopram, respectively.

Guo, McCutcheon et al., 2020: OBJECTIVE: To determine the relative variability and magnitude of symptomatic improvement in antidepressant-treated individuals compared to placebo-treated individuals, and to investigate moderating factors. METHODS: Multiple databases and previous publications were searched through February 2019 to identify all randomized controlled trials comparing placebo and antidepressants in acute treatment of depression. Primary outcome was relative variability of change in symptom severity in antidepressant-treated individuals compared to placebo-treated patients quantified using the coefficient of variation ratio (CVR). RESULTS: Of 9389 identified records, 134 were found to be eligible (total n = 46 646). Antidepressant-treated patients showed a significantly greater magnitude (g = 0.28, 95% CI 0.25-0.30, p < 0.0001) and lower variability (CVR = 0.94, 95% CI 0.93-0.95, p < 0.0001) of change in symptom severity relative to placebo-treated patients. Compared to placebo antidepressant-related improvement was more uniform in older studies (z = 3.01, p = 0.003) and in studies where antidepressants showed greater efficacy (z = -7.21, p < 0.0001). | Imipramine, moclobemide, amitriptyline and mirtazapine showed significantly lower CVR than several other antidepressants. However, no difference in CVR exists between multiple and single-neurotransmitter profile antidepressants (z = -0.01, p = .99). CONCLUSION: There is lower variability and greater magnitude of change in symptom severity with antidepressant treatment relative to placebo. This is not consistent with our hypothesis that there are distinct sub-groups of treatment-responsive and treatment-resistant patients with major depression. Our results in-stead suggest that antidepressants show a relatively uniform effect.

Gutsmield et al., 2020: BACKGROUND: Depression is one of the leading causes of the global burden of disease, and it has particularly negative consequences for elderly patients. Antidepressants are the most frequently used treatment. We present the first single-group meta-analysis examining: (i) the response rates of elderly patients to antidepressants, and (ii) the

determinants of antidepressants response in this population. METHODS: We searched multiple databases for randomized controlled trials on antidepressants in the elderly with major depressive disorder above 65 years (last search: December 2017). Response was defined as 50% improvement on validated rating scales. We extracted response rates from studies and imputed the missing ones with a validated method. Data were pooled in a single-group meta-analysis. Additionally, several potential moderators of response to antidepressants were examined by subgroup and meta-regression analyses. RESULTS: We included 44 studies with a total of 6373 participants receiving antidepressants. On average, 50.7% of the patients reached a reduction of at least 50% on the Hamilton Depression Scale (HAMD). Subgroup and meta-regression analyses revealed a better response to treatment for patients in antidepressant-controlled trials compared to placebo-controlled trials. Mean age, study duration, percentage of woman, severity of illness at baseline, dose of antidepressants in fluoxetine equivalents, year of publication, setting (in- or out-patients), antidepressant groups (SSRI, TCA, SSNRI, α2-antagonist, SNRI, MAO-inhibitor), ITT (intention-to-treat) analysis vs completer analysis, sponsorship and overall risk of bias were not significant moderators of response. CONCLUSIONS: Our findings suggest an improvement in symptoms can be found in about 50% of the elderly with major depressive disorder treated with antidepressants.

Halvorsen et al., 2019: OBJECTIVE: Several studies have investigated whether in utero exposure to selective serotonin reuptake inhibitors (SSRIs) is associated with increased risk of developing mental or behavioural disorders. The aim of this study was to perform a systematic review and meta-analysis based on this literature. METHODS: A systematic search of eligible literature in PubMed, Embase, and PsycInfo and subsequent meta-analysis was conducted in adherence with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline. RESULTS: A total of 20 studies were included in the review, and results from 18 of these were meta-analyzed. We found a statistically significant positive association between in utero exposure to SSRIs and mental or behavioural disorders such as autism spectrum disorder (hazard ratio [HR] = 1.27; 95% confidence interval [CI] = 1.10-1.47), attention-deficit/hyperactivity disorder (HR = 1.33; 95% CI = 1.06-1.66) and mental retardation (HR = 1.41; 95% CI = 1.03-1.91). Confounding by indication was identified in five of seven studies investigating this aspect. CONCLUSION: Exposure to SSRIs in utero is associated with increased risk of developing mental or behavioural disorders. However, these associations do not necessarily reflect a causal relationship since the results included in this meta-analysis are likely affected by residual confounding by indication, which is likely to account for some (or all) of the positive association.

He et al, 2020: Depression is associated with an increased risk of death in patients with heart failure (HF); however, the association between the use of antidepressants and HF prognoses remains controversial. Therefore, this meta-analysis aimed to evaluate the effect of antidepressants on the risk of death in HF patients. We retrieved data from the PubMed and EMBASE databases until August 2019 for studies reporting the use of antidepressants in HF patients. Data were extracted from the eligible articles, and a random effects model was used to pool the effect estimates (risk ratios (RRs) and 95% confidence intervals (CIs)). A total of 8 studies were included in this meta-analysis. Overall, the use of antidepressants was associated with increased risks of all-cause death (RR = 1.27; 95% CI, 1.21–1.34) and cardiovascular death (RR = 1.14; 95% CI, 1.08–1.20) in HF patients with or without depression. Specifically, HF patients with depression taking antidepressants had increased risks of all-cause death (RR = 1.21; 95% CI, 1.16–1.27) and cardiovascular death (RR = 1.21; 95% CI, 1.13–1.30). Compared with nonusers, the use of selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), and selective serotonin reuptake inhibitors (SNRIs) significantly increased the rate of all-cause death (SSRIs (RR = 1.26; 95% CI, 1.19–1.32), TCAs (RR = 1.30; 95% CI, 1.16–1.46), and SNRIs (RR = 1.17; 95% CI, 1.08–1.26)) but not cardiovascular death (SSRIs (RR = 1.03; 95% CI, 0.84–1.26), TCAs (RR = 1.02; 95% CI, 0.86–1.21), and SNRIs (RR = 0.92; 95% CI, 0.48–1.78)). Based on current publications, the use of

antidepressants could increase the risk of all-cause death in HF patients, regardless of whether they have depression or the type of antidepressants they use. Further study is needed to determine the relationship between antidepressant use and cardiovascular death.

Hieronymus et al., 2019: Background: Reports claiming that antidepressants are effective only in patients with severe depression have affected treatment guidelines but these reports usually use a disputed measure of improvement, a decrease in the sum-score of the 17-item Hamilton Depression Rating Scale (HDRS-17), and are based on group-level rather than patient-level data. Method: In this item-based, patient-level, post-hoc analysis, we pooled data from all completed, acute-phase, placebo-controlled, industry-sponsored, HDRS-based trials of the SSRIs citalopram, paroxetine, or sertraline in adult major depression. Patient-level data were pooled and subjected to item-based post-hoc analyses to assess the effect of baseline severity of depression on the response to treatment as assessed with HDRS-17 sum score, the depressed mood item of the HDRS, a six-item HDRS subscale (HDRS-6), and the remaining 11 HDRS items not included in this subscale (non-HDRS-6). Patients were defined as having non-severe depression if they had a baseline HDRS-17 sum score of 18 points or less and as having severe depression if they had a score of 27 points or more. Findings: Our study population consisted of 8262 patients from 28 placebo-controlled SSRI trials. Participants were treated with either citalopram (n=744), paroxetine (n=2981), sertraline (n=1202), fluoxetine (active-control group; n=754), or placebo (n=2581). 654 patients were defined as having non-severe depression and 1377 as having severe depression. Patients with non-severe and severe depression did not differ with respect to SSRI-induced decrease in depressed mood and other HDRS symptoms belonging to the HDRS-6 subscale. However, after exclusion of patients with rare extreme baseline values, a positive association was seen between severity and efficacy when using HDRS-17 sum score as the effect parameter. This result was largely due to a more pronounced response to treatment with respect to non-HDRS-6 items in patients with severe depression than in those with non-severe depression. This outcome could be explained by non-HDRS-6 items, more so than HDRS-6 items, being more severe and prevalent at baseline in severe than in non-severe cases; hence, less room was left for improvement in these areas in patients with non-severe depression. Interpretation: The use of an outcome measure that includes symptoms that rate low at baseline in patients with non-severe depression might result in the interpretation that SSRIs are ineffective in these patients. With respect to alleviation of HDRS-6 items, SSRIs appear to be as effective in patients with non-severe depression as in those with severe depression.

Holper and Hengartner 2020: BACKGROUND: The issue of unblinded outcome-assessors and patients has repeatedly been stressed as a flaw in allegedly double-blind antidepressant trials. Unblinding bias can for example result from a drug's marked side-effects. If such unblinding bias is present for a given drug, then it might be expected that the placebos of that drug are rated significantly less effective than that of other antidepressants. METHODS: To test this hypothesis, the present exploratory analysis conducted a Bayesian network meta-analysis (NMA) comparing the efficacy of 19 different placebos in placebo-controlled trials provided in the dataset by Cipriani et al. (2018). Primary outcome was efficacy (continuous) estimated on the standardized mean difference (SMD) scale and defined as the pre-post change on the Hamilton Depression scale (HAMD-17), on which information was available in N = 258 trials. RESULTS: Comparative placebo ranking suggested mirtazapine-placebo (SMD -2.0 [- 5.0-1.0 95% CrI]) to be the most, and amitriptyline- (SMD 1.2 [- 1.6-3.9 95% CrI]) and trazodone- (SMD 2.1 [- 0.9-5.2 95% CrI]) placebos to be the least effective placebos. Other placebos suggested to be more effective than amitriptyline- and trazodone-placebos (based on 95% CrIs excluding zero) were citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, and venlafaxine placebos. These NMA results were corroborated by the observation that the relative efficacy between drug and placebo was considerably larger for amitriptyline and trazodone than for instance mirtazapine, duloxetine, and venlafaxine, supported by a small and insignificant correlation between drug-

efficacy and placebo-efficacy (r = - 0.202, p = 0.408). DISCUSSION: The present exploratory NMA indicates that distinguishable side-effects of older drugs may unblind outcome-assessors thus resulting in overestimation of the average drug-placebo difference and underrating bias in placebo-arms, particularly for the older antidepressant drugs amitriptyline and trazodone. If confirmed in prospective studies, these findings suggest that efficacy rankings for antidepressants are susceptible to bias and should be considered unreliable or misleading. The analysis is limited by the focus on the single-comparison placebos (76%, i.e. placebos assessed in two-arm trials), since double-comparison placebos (25%, i.e. placebos assessed in three-arm trials) are hard to interpret and therefore not included in the present interpretation. Another limitation is the problem of multiplicity, which was only approximately accounted for in the Bayesian NMA by modelling treatment effects as exchangeable.

Kato et al., 2021: A significant clinical issue encountered after a successful acute major depressive disorder (MDD) treatment is the relapse of depressive symptoms. Although continuing maintenance therapy with antidepressants is generally recommended, there is no established protocol on whether or not it is necessary to prescribe the antidepressant used to achieve remission. In this meta-analysis, the risk of relapse and treatment failure when either continuing with the same drug used to achieved remission or switching to a placebo was assessed in several clinically significant subgroups. The pooled odds ratio (OR) (±95% confidence intervals [CI]) was calculated using a random effects model. Across 40 studies (n = 8890), the relapse rate was significantly lower in the antidepressant group than the placebo group by about 20% (OR = 0.38, CI: 0.33-0.43, p < 0.00001; 20.9% vs 39.7%). The difference in the relapse rate between the antidepressant and placebo groups was greater for tricyclics (25.3%; OR = 0.30, CI: 0.17-0.50, p < 0.00001), SSRIs (21.8%; OR = 0.33, CI: 0.28-0.38, p < 0.00001), and other newer agents (16.0%; OR = 0.44, CI: 0.36-0.54, p < 0.00001) in that order, while the effect size of acceptability was greater for SSRIs than for other antidepressants. A flexible dose schedule (OR = 0.30, CI: 0.23-0.48, p < 0.00001) had a greater effect size than a fixed dose (OR = 0.41, CI: 0.36-0.48, p < 0.00001) in comparison to placebo. Even in studies assigned after continuous treatment for more than 6 months after remission, the continued use of antidepressants had a lower relapse rate than the use of a placebo (OR = 0.40, CI: 0.29-0.55, p < 0.00001; 20.2% vs 37.2%). The difference in relapse rate was similar from a maintenance period of 6 months (OR = 0.41, CI: 0.35-0.48, p < 0.00001; 19.6% vs 37.6%) to over 1 year (OR = 0.35, CI: 0.29-0.41, p < 0.00001; 19.9% vs 39.8%). The all-cause dropout of antidepressant and placebo groups was 43% and 58%, respectively, (OR = 0.47, CI: 0.40-0.55, p < 0.00001). The tolerability rate was ~4% for both groups. The rate of relapse (OR = 0.32, CI: 0.18-0.64, p = 0.0010, 41.0% vs 66.7%) and all-cause dropout among adolescents was higher than in adults. To prevent relapse and treatment failure, maintenance therapy, and careful attention for at least 6 months after remission is recommended. SSRIs are well-balanced agents, and flexible dose adjustments are more effective for relapse prevention.

Kautzky et al., 2021: OBJECTIVE: Major depressive disorder (MDD) and anxiety disorders are both common and especially challenging during pregnancy. Considering possible risks of intrauterine drug exposure of the child, the role of psychopharmacological treatment is ambiguous and various negative obstetric outcomes were inconsistently associated with medication. Consequently, a critical examination of peri- and postnatal phenomena associated with intrauterine exposure to antidepressants based on serotonin reuptake inhibition (SRI) and subsumed under the term “poor neonatal adaptation syndrome” (PNAS) is urgently called for. METHODS: A comprehensive literature search was conducted, revealing a total number of 33 relevant studies and 69 individual outcomes among 3025 screened studies. Seventeen outcomes allowed meta-analytic evaluation (random effects model). Measures for heterogeneity (I(2)) and contour-enhanced funnel plots were generated. RESULTS: Single studies showed increased risks for deficits in neurological functioning and autonomous adaptation in SRI exposed infants. Meta-analytical evaluation showed increased symptom occurrence or severity in exposed neonates for

low APGAR scores, birth weight, size for gestational age, preterm delivery, neuromuscular and autonomous regulation, and higher rates of admission to specialized care. Mostly, increased risk after SRI exposure was supported by comparison to unexposed infants born to mothers diagnosed with depression. CONCLUSION: Whereas statistically significant evidence for various effects of intrauterine exposure to SRI was found, the clinical relevance remains unresolved because of inherently low data quality in this research domain and insufficiently defined samples and outcomes. More systematic research under ethical considerations is required to improve multiprofessional counseling in the many women dealing with MDD during pregnancy and the peripartum.

Kim et al., 2019: It has been reported that selective serotonin reuptake inhibitors (SSRIs) might induce major adverse cardiovascular events (MACE), but the association between the use of SSRIs and MACE has not been elucidated as yet. Therefore, the aim of this study was to evaluate the association between the use of SSRIs and MACE in depressed patients with previous cardiovascular events. Two researchers independently selected randomized-controlled studies (RCTs) according to the predefined inclusion criteria and evaluated the quality of articles. A quantitative analysis was carried out to estimate pooled risk ratios (RRs) for the association between the use of SSRIs and MACE. Ten RCTs were selected in the final analysis. The use of SSRIs in depressed patients with previous cardiovascular events significantly decreased the risk of MACE [RR: 0.74; 95% confidence interval (CI): 0.55-0.99]. The risk of myocardial infarction was also reduced significantly (RR: 0.59, 95% CI: 0.37-0.93), associations with stroke and all-cause-death (cardiac or other causes): risk of stroke (RR: 0.88, 95% CI: 0.35-2.25) or all-cause death (RR: 0.83; 95% CI: 0.66-1.05). This meta-analysis suggests that the use of SSRIs decreased the risk of MACE by significantly reducing the risk of myocardial infraction in patients with depression and previous cardiovascular events.

Maslej et al., 2021: IMPORTANCE: Antidepressants are commonly used to treat major depressive disorder (MDD). Antidepressant outcomes can vary based on individual differences; however, it is unclear whether specific factors determine this variability or whether it is at random. OBJECTIVE: To investigate the assumption of systematic variability in symptomatic response to antidepressants and to assess whether variability is associated with MDD severity, antidepressant class, or study publication year. DATA SOURCES: Data used were updated from a network meta-analysis of treatment with licensed antidepressants in adults with MDD. The Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, and PsycInfo were searched from inception to March 21, 2019. Additional sources were international trial registries and sponsors, drug companies and regulatory agencies' websites, and reference lists of published articles. Data were analyzed between June 8, 2020, and June 13, 2020. STUDY SELECTION: Analysis was restricted to double-blind, randomized placebo-controlled trials with depression scores available at the study's end point. DATA EXTRACTION AND SYNTHESIS: Baseline means, number of participants, end point means and SDs of total depression scores, antidepressant type, and publication year were extracted. MAIN OUTCOMES AND MEASURES: Log SDs (bln $\hat{\sigma}$) were derived for treatment groups (i.e. antidepressant and placebo). A random-slope mixed-effects model was conducted to estimate the difference in bln $\hat{\sigma}$ between treatment groups while controlling for end point mean. Secondary models determined whether differences in variability between groups were associated with baseline MDD severity; antidepressant class (selective serotonin reuptake inhibitors and other related drugs; serotonin and norepinephrine reuptake inhibitors; norepinephrine-dopamine reuptake inhibitors; noradrenergic agents; or other antidepressants); and publication year. RESULTS: In the 91 eligible trials (18 965 participants), variability in response did not differ significantly between antidepressants and placebo (bln $\hat{\sigma}$, 1.02; 95% CI 0.99-1.05; P = .19). This finding is consistent with a range of treatment effect SDs (up to 16.10), depending on the association between the antidepressant and placebo effects. Variability was not associated with baseline MDD severity or publication year. Responses

to noradrenergic agents were 11% more variable than responses to selective serotonin reuptake inhibitors (bln $\hat{\sigma}$, 1.11; 95% CI 1.01-1.21; *P* = .02). CONCLUSIONS AND RELEVANCE: Although this study cannot rule out the possibility of treatment effect heterogeneity, it does not provide empirical support for personalizing antidepressant treatment based solely on total depression scores. Future studies should explore whether individual symptom scores or biomarkers are associated with variability in response to antidepressants.

Munkholm et al., 2019: OBJECTIVES: To investigate whether the conclusion of a recent systematic review and network meta-analysis (Cipriani et al., 2018) that antidepressants are more efficacious than placebo for adult depression was supported by the evidence. DESIGN: Reanalysis of a systematic review, with meta-analyses. DATA SOURCES: 522 trials (116 477 participants) as reported in the systematic review by Cipriani et al. and clinical study reports for 19 of these trials. ANALYSIS: We used the *Cochrane Handbook*'s risk of bias tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the risk of bias and the certainty of evidence, respectively. The impact of several study characteristics and publication status was estimated using pairwise subgroup meta-analyses. RESULTS: Several methodological limitations in the evidence base of antidepressants were either unrecognized or underestimated in the systematic review by Cipriani et al. The effect size for antidepressants versus placebo on investigator-rated depression symptom scales was higher in trials with a 'placebo run-in' study design compared with trials without a placebo run-in design (p = 0.05). The effect size of antidepressants was higher in published trials compared with unpublished trials (p < 0.0001). The outcome data reported by Cipriani et al. differed from the clinical study reports in 12 (63%) of 19 trials. The certainty of the evidence for the placebo-controlled comparisons should be very low according to GRADE due to a high risk of bias, indirectness of the evidence and publication bias. The mean difference between antidepressants and placebo on the 17-item Hamilton depression rating scale (range 0–52 points) was 1.97 points (95% CI 1.74 to 2.21). CONCLUSIONS: The evidence does not support definitive conclusions regarding the benefits of antidepressants for depression in adults. It is unclear whether antidepressants are more efficacious than placebo.

Olivia et al., 2021: Gastrointestinal side effects (SEs) are frequently observed in patients with major depressive disorder (MDD) while taking antidepressants and may lead to treatment discontinuation. The aim of this meta-analysis is to provide quantitative measures on short-term rates of gastrointestinal SEs in MDD patients treated with second-generation antidepressants. An electronic search of the literature was conducted by using MEDLINE, ISI Web of Science - Web of Science Core Collection, and Cochrane Library databases. Eligible studies had to focus on the use of at least one of 15 antidepressants commonly used in MDD (i.e. agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, and vortioxetine) and report data on treatment-emergent gastrointestinal SEs (i.e. nausea/vomiting, diarrhoea, constipation, abdominal pain, dyspepsia, anorexia, increased appetite and dry mouth) within 12 weeks of treatment. Overall, 304 studies were included in the meta-analyses. All the considered antidepressants showed higher rates of gastrointestinal SEs than placebo. Escitalopram and sertraline were shown to be the least tolerated antidepressants on the gastrointestinal tract, being associated with all the considered SEs with the exception of constipation and increased appetite, while mirtazapine was shown to be the antidepressant with fewer side effects on the gut, being only associated with increased appetite. In conclusion, commonly used antidepressants showed different profiles of gastrointestinal SEs, possibly related to their mechanisms of action. The specific tolerability profile of each compound should be considered by clinicians when prescribing antidepressants in order to improve adherence to treatment and increase positive outcomes in patients with MDD.

Rothmore, 2020: Sexual dysfunction is a frequent, potentially distressing, adverse effect of antidepressants and a leading cause of medication non-adherence. Sexual function should be actively assessed at baseline, at regular intervals during treatment, and after treatment cessation. Trials comparing the risk of sexual dysfunction with individual antidepressants are inadequate, but it is reasonable to conclude that the risk is greatest with selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), less with tricyclic antidepressants (except clomipramine) and mirtazapine, and least with moclobemide, agomelatine, reboxetine and bupropion. Management of antidepressant-induced sexual dysfunction requires an individualized approach (e.g. considering other causes, dose reduction, addition of medication to treat the adverse effect, switching to a different antidepressant). Post-SSRI sexual dysfunction has been recently identified as a potential, although rare, adverse effect of SSRIs and SNRIs. Consider the possibility of post-SSRI sexual dysfunction in patients in whom sexual dysfunction was absent before starting antidepressants but develops during or soon after antidepressant treatment and still persists after remission from depression and discontinuation of the drug.

Salisbury-Afshar, 2020: Key clinical issue: What are the adverse events of antidepressants prescribed to treat major depressive disorder in adults 65 years and older? Evidence-based answer: Selective serotonin reuptake inhibitors (SSRIs) cause adverse events at a similar frequency to placebo and have lower dis-continuation rates than tricyclic antidepressants during up to 12 weeks of treatment. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Serotonin-norepinephrine reuptake inhibitors (SNRIs) cause more adverse events and greater discontinuation of therapy during up to 12 weeks of treatment compared with placebo. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) Duloxetine increases the risk of falls over 12 to 24 weeks of treatment compared with placebo.1 (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.)

Sinyor et al., 2020: BACKGROUND: Adverse events (AEs) are known to occur while patients are treated with placebos, part of the so-called nocebo effect. Yet evidence is limited regarding the likelihood that specific AEs occurring with antidepressant treatment are or are not due to nocebo effects. METHODS: This study identified 56 placebo-controlled, randomized controlled trials (RCTs) of antidepressant monotherapy for adults with major depressive disorder that reported AE rates in sufficient detail for comparison. Poisson regression analyses compared rates of AEs according to antidepressant class weighted by study population to determine which separated from placebo. A “nocebo index” was also calculated (with 0 defined as the lowest rate and 1 or higher indicating the same or greater rate of an AE in the placebo group). RESULTS: Numerous AEs did not differ statistically between antidepressant classes and placebo including worsening psychiatric symptoms, all forms of pain, weight gain and respiratory symptoms. Nevertheless, a number of AEs were significantly more common in antidepressants than placebos across multiple antidepressant classes. These were predominantly neurological, sexual and anticholinergic effects. Several AEs that separated statistically between antidepressants and placebos nevertheless had moderate nocebo indices (≥0.5). For example, dizziness in SSRIs separated significantly from placebo (OR 1.50, 95% CI 1.13–1.99) but had a nocebo index of 0.67. LIMITATIONS: This study relied on multiple RCTs with subtle design differences. CONCLUSIONS: This study identified several AEs that are likely the physiological result of antidepressants and many that likely represent nocebo effects. These results should inform clinical decision making and discussions with patients.

Sobieraj, Baker et al., 2019a: OBJECTIVE: To assess selected adverse events of antidepressants in the treatment of major depressive disorder (MDD) in adults 65 years old or older. Antidepressants included in this review, as determined by expert opinion, are selective serotonin reuptake

inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, trazodone, vilazodone, and vortioxetine. DATA SOURCES: MEDLINE, Embase, Cochrane Central, and PsycInfo bibliographic databases from earliest date through May 15, 2018; hand searches of references of relevant studies; www.clinicaltrials.gov; and the International Controlled Trials Registry Platform. REVIEW METHODS: Two investigators screened abstracts and subsequently reviewed full-text files. We abstracted data, performed meta-analyses when appropriate, assessed the risk of bias of each individual study, and graded the strength of evidence (SOE) for each comparison and selected outcomes. Number needed to harm (NNH) is reported for graded outcomes with statistically significant findings. RESULTS: Nineteen randomized controlled trials (RCTs) and two observational studies reported in 41 articles were included. Studies mostly evaluated treatment of the acute phase (<12 weeks) of MDD that was of moderate severity in patients 65 years and older, required subjects to be free from uncontrolled medical comorbidities or psychological conditions, and relied on spontaneous reporting of adverse events. Evidence was scarce and conclusions (based on statistical significance) for a given comparison and outcome are based often on a single study, particularly for specific adverse events. None of the RCTs were powered or designed to capture adverse events and most RCTs studied low doses of antidepressants. Observational data were limited by residual confounding. SSRIs (escitalopram and fluoxetine, moderate SOE), vortioxetine (high SOE), and bupropion extended release (moderate SOE) had a statistically similar frequency of adverse events compared with placebo, whereas SNRIs (duloxetine and venlafaxine) were found to cause a greater number of adverse events (high SOE, NNH 10) compared with placebo during treatment of the acute phase of MDD. Both SSRIs (citalopram, escitalopram, and fluoxetine) and SNRIs caused a greater number of withdrawals due to adverse events than placebo (SSRIs, low SOE, NNH 11; SNRIs, moderate SOE, NNH 17). Duloxetine led to a greater number of falls compared with placebo (moderate SOE, NNH 10) over 24 weeks of treatment. A single observational study provided evidence on long-term use of antidepressants (low SOE) and suggested increased risk of adverse events (SSRIs), falls (SSRIs, SNRI venlafaxine, mirtazapine, trazadone), fractures (SSRIs, SNRI venlafaxine, mirtazapine), and mortality (SSRIs, SNRI venlafaxine, mirtazapine, trazadone) compared to no antidepressant. Evidence for the comparative harms of different antidepressants was limited to single RCTs, mostly studying treatment of the acute phase of MDD (<12 weeks). Comparing SSRIs to each other or SSRIs to SNRIs showed statistically similar rates of adverse events (moderate SOE). SSRIs (paroxetine, citalopram, sertraline) had fewer withdrawals due to adverse events than tricyclic antidepressants (amitriptyline or nortriptyline) (low SOE, number needed to treat [NNT] 13), as did mirtazapine compared with paroxetine (low SOE, NNT 9). Vortioxetine had fewer adverse events than with duloxetine (high SOE, NNT 6). Increasing age was associated with greater incidence of serious adverse events with escitalopram (low SOE). The increased risk of falls on duloxetine may be associated with the presence of cardiopulmonary conditions (low SOE). CONCLUSIONS: In patients 65 years of age or older, treatment of the acute phase of MDD with SNRIs (duloxetine and venlafaxine) led to a greater number of adverse events compared with placebo, while adverse events were statistically similar to placebo with SSRIs (escitalopram, fluoxetine), vortioxetine, and bupropion. SSRIs (citalopram, escitalopram, and fluoxetine) and SNRIs duloxetine and venlafaxine) led to a greater number of study withdrawals due to adverse events than placebo, and duloxetine increased the risk of falls. Further characterization of the comparative safety of antidepressants is difficult because few studies were identified, comparisons were based on statistical significance, trials were not powered to identify small differences in adverse events, and observational studies may be confounded. Comparative, long-term, well-designed studies that report specific adverse events are needed to better inform decision making in this population.

Sobieraj, Martinez et al., 2019: OBJECTIVES: To assess adverse effects of pharmacologic antidepressants for treatment of major depressive disorder (MDD) in adults 65 years of age or older. DESIGN: Systematic review and meta-analysis. SETTING: Specialist or generalist outpatient

setting, rehabilitation facility, and nursing facilities. PARTICIPANTS: Persons 65 years and older with MDD. INTERVENTION: Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, trazodone, vilazodone, or vortioxetine compared with another antidepressant, placebo, or nonpharmacologic therapy. MEASUREMENTS: Adverse events, arrhythmias, cognitive impairment, falls, fractures, hospitalization, mortality, QTc prolongation, serious adverse events, and withdrawals due to adverse events. RESULTS: Nineteen randomized controlled trials and two observational studies were included. Most studies evaluated treatment of the acute phase (<12 wk) of MDD of moderate severity. SSRIs led to a statistically similar frequency of overall adverse events vs placebo (moderate strength of evidence [SOE]), but SNRIs caused more overall adverse events vs placebo (high SOE) during the acute treatment phase. Both SSRIs and SNRIs led to more study withdrawals due to adverse events vs placebo (SSRIs low SOE; SNRIs moderate SOE). Duloxetine led to a more falls vs placebo (moderate SOE) during 24 weeks of acute and continuation treatment of MDD. CONCLUSION: In patients 65 years of age or older with MDD, treatment of the acute phase of MDD with SNRIs, but not SSRIs, was associated with a statistically greater number of overall adverse events vs placebo. SSRIs and SNRIs led to a greater number of study withdrawals due to adverse events vs placebo. Duloxetine increased the risk of falls that as an outcome was underreported in the literature. Few studies examined head-to-head comparisons, most trials were not powered to evaluate adverse events, and results of observational studies may be confounded. Comparative long-term studies reporting specific adverse events are needed to inform clinical decision making regarding choice of antidepressants in this population.

Tharmaraja et al., 2019: Objective: Individual studies have reported conflicting effects of selective serotonin reuptake inhibitors (SSRIs) on glycemia. We systematically reviewed the effects of SSRIs on glycemia and whether metabolic and psychological factors moderated these effects. Methods: We systematically searched for placebo-controlled randomized controlled trials investigating the effect of SSRIs on glycemia (fasting blood glucose or HbA1c) as a primary or secondary outcome. Random effects meta-analysis was conducted to compute an overall treatment effect. Meta-regression tested whether depression, type 2 diabetes, insulin resistance, treatment duration, and weight loss moderated treatment effects. Results: Sixteen randomized controlled trials (n = 835) were included and glycemia was usually a secondary outcome. Overall, SSRIs improved glycemia versus placebo (pooled effect size (ES) = −0.34, 95% confidence interval (CI) = −0.48 to −0.21; $p < .001$, $I^2 = 0\%$). Individually, fluoxetine (ES = −0.29, 95% CI = −0.54 to −0.05; p = .018) and escitalopram/citalopram (ES = −0.33, 95% CI = −0.59 to −0.07; p = .012) outperformed placebo, but paroxetine (ES = −0.19, 95% CI = −0.58 to 0.19; p = .33) did not. Results were similar in populations selected for depression as those not. Across studies, baseline insulin resistance (p = .46), treatment duration (p = .47), diabetes status (p = .41), and weight loss (p = .93) did not moderate changes. Heterogeneity for all analyses was nonsignificant. Conclusions: SSRIs seem to have an association with improvement in glycemia, which is not moderated by depression status, diabetes status, or change in weight across studies. Future powered trials with longer treatment duration are needed to confirm these findings.

Trajkova et al., 2019: BACKGROUND: Both depression and use of antidepressants have been reported to be risk factors for stroke, but results from the literature are still not conclusive regarding the risk attributable to antidepressants rather than to the underlying disease. OBJECTIVE: To estimate the risk of incident stroke associated with use of antidepressants, a meta-analysis was performed. METHODS: PubMed, MEDLINE, Cochrane, ProQuest, Scopus, and bibliographies of articles were searched up to September 2018. The final meta-analysis included 31 observational studies. STROBE statement-checklist and GRADE guidelines were used for quality assessment. RESULTS: The random-effects meta-analysis on the association between use of any antidepressant and risk of any stroke resulted in meta-risk ratio (RR) of 1.41 (95% CI 1.13-1.69, I^2 = 93.7%). The pooled estimate for selective serotonin reuptake inhibitors (SSRIs) resulted in a meta-

RR of 1.41 (95% CI 1.13-1.69, I^2 = 94.5%) and for tricyclic antidepressants (TCAs) of 1.08 (95% CI 0.93-1.22, I^2 = 0%). SSRI users displayed a higher risk of ischemic (1.57, 95% CI 1.06-2.09, I^2 = 96.4%) than hemorrhagic stroke (1.34, 95% CI 1.15-1.53, I^2 = 72.9%). Meta-RRs were lower for TCA, although with smaller heterogeneity (ischemic 1.22, 95% CI 0.97-1.46; I^2 = 0%; hemorrhagic: 1.00, 95% CI 0.83-1.18, I^2 = 0%). Restricting to studies on depressed individuals, both SSRI and TCA remained associated with an increased risk of any stroke type (meta-RR for SSRI: 1.27, 95% CI 1.11-1.43, I^2 = 76.6%; meta-RR for TCA: 1.21 (95% CI 1.02-1.40, I^2 = 47.3%). CONCLUSIONS: Despite the high heterogeneity, these results demonstrate that even after adjusting for depression, use of antidepressants retains an independent increased risk of stroke.

Uguz, 2020: Objective: A review of current meta-analyses examining the relationship between maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and congenital anomalies. Methods: PubMed was searched for meta-analyses published in English language between January 2010 and April 2020 by using the following combinations of key words: meta-analysis, pregnancy, antidepressant, SSRI, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, neonatal outcome, birth outcome, congenital malformation, congenital anomaly, birth defect, cardiac malformation and heart defect. Results: A total of 15 meta-analyses met the search criteria. These meta-analyses consistently suggested a significant positive association between the use of SSRIs in general and paroxetine and fluoxetine in particular and the risk of major congenital anomalies. The data also showed a consistency in increased cardiovascular defects in infants due to maternal use of paroxetine. The risk of cardiovascular defects in infants of women using SSRIs in general and fluoxetine and sertraline in particular was controversial. Conclusion: Further large-scale prospective observational studies and meta-analyses on the effects of individual SSRIs other than paroxetine, especially escitalopram and fluvoxamine, are required to reach definitive conclusions.

Vishwanathan et al., 2021: Objective: The authors systematically reviewed evidence on pharmacotherapy for perinatal mental health disorders. Methods: The authors searched for studies of pregnant, postpartum, or reproductive-age women with mental health disorders treated with pharmacotherapy in MEDLINE, Embase, PsycInfo, the Cochrane Library, and trial registries from database inception through 5 June 2020 and surveilled literature through 2 March 2021. Outcomes included symptoms; functional capacity; quality of life; suicidal events; death; and maternal, fetal, infant or child adverse events. Results: 164 studies were included. Regarding benefits, brexanolone for third-trimester or postpartum depression onset may be associated with improved depressive symptoms at 30 days when compared with placebo. Sertraline for postpartum depression may be associated with improved response, remission, and depressive symptoms when compared with placebo. Discontinuing mood stabilizers during pregnancy may be associated with increased recurrence of mood episodes for bipolar disorder. Regarding adverse events, most studies were observational and unable to fully account for confounding. Evidence on congenital and cardiac anomalies for treatment compared with no treatment was inconclusive. Brexanolone for depression onset in the third trimester or the postpartum period may be associated with risk of sedation or somnolence, leading to dose interruption or reduction when compared with placebo. Conclusions: Evidence from few studies supports the use of pharmacotherapy for perinatal mental health disorders. Although many studies report on adverse events, they could not rule out underlying disease severity as the cause of the association between exposures and adverse events. Patients and clinicians need to make informed, collaborative decisions on treatment choices.

Wang et al., 2021: Background: This study aimed at examining the effects of different antidepressants on the new onset of T2DM. Methods: Systematic literature retrieval for cohort and case-control studies was conducted in PubMed, Embase, Web of Science, Cochrane library, Clinical Trials Register of the Cochrane Collaboration and CENTRAL published from January 2000

to October 2020. Pooled estimates were calculated and subgroup analyses were conducted by a fixed or random effects model according to the heterogeneity. Funnel plots and Egger's test were performed to evaluate publication bias. Stata Version 15.1 was used for data analysis. Results: Thirty studies (24 cohort, 4 nested case-control and 2 case-control studies) were included covering 2 875 567 participants with the follow-up periods from 1 year to 18 years (Median=8.4 years). The pooled estimates of antidepressants use and new-onset T2DM were HR=1.24 (95% CI: 1.18–1.31), RR=1.42 (95% CI: 0.99–2.05) and OR=1.17 (95% CI: 1.03–1.32), respectively. However, subgroup analyses showed that only tricyclic antidepressants (TCAs) use was positively associated with the new onset of T2DM in both cohort studies (combined RR=1.39, 95% CI: 1.17–1.65) and case-control studies (combined OR=1.25, 95% CI: 1.05–1.50). Moreover, the risk of T2DM was increased with the duration of antidepressants use in a linear trend (R^2 = 88.51%, *P* = 0.009). Limitations: Heterogeneity might impact the results and inference. Conclusions: Antidepressants use might be a risk factor for the new onset of T2DM. Patients with long-term antidepressants use should be evaluated cautiously for T2DM risk. Routine T2DM screening is necessary in antidepressants users.

Wang et al., 2019: Purpose. Studies provided conflicting results on whether antidepressant use increased the risk of venous thromboembolism (VTE). Our aim was to examine the association between antidepressant use and the risk of VTE. Methods. Pubmed, Embase, and the Cochrane Library were searched up to 13 March 2018. Case-control studies and cohort studies that examined the association between antidepressant use and the risk of VTE, deep vein thrombosis or pulmonary embolism were included. Several subgroup analyses and sensitivity analyses were conducted. GRADE approach was used to assess the quality of evidence. Results. Nine studies (six case-control studies and three cohort studies) were included. Overall, antidepressant use may be associated with an increased risk of VTE (OR 1.27, 95% CI 1.09 to 1.49); however, no association was observed in studies with low risk of bias (OR 1.27, 95% CI 0.84 to 1.92). No association between selective serotonin reuptake inhibitor use and VTE risk was detected in the overall analysis (OR 1.10, 95% CI 0.90 to 1.34) and in subgroup analysis of studies with low risk of bias. Tricyclic antidepressant may be associated with an increased VTE risk (OR 1.26, 95% CI 1.02 to 1.57), and the quality of evidence was rated as very low by GRADE approach; however, no association was observed when we only included studies with low risk of bias. Conclusions. There was no association between selective serotonin reuptake inhibitor use and VTE risk. Tricyclic antidepressant may be associated with an increased VTE risk, but the quality of evidence was very low.

Wen et al., 2020: Selective serotonin reuptake inhibitors (SSRIs) and bupropion statistically significantly increase the risk of incident type 2 diabetes mellitus (T2DM) (strength of recommendation [SOR] B: based on a systematic review and meta-analysis, and a prospective cohort study). Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with weight gain, although there is mixed evidence on both its clinical significance and to what degree depression might be a confounding variable (SOR B: based on three prospective cohort studies). Evidence suggests there is an association between the development of metabolic syndrome and SSRIs, but it might be dependent upon the choice of diagnostic criteria and SSRI serum concentration or dose (SOR B: based on two retrospective cohort studies). No association between SNRIs, bupropion, and incident hyper- tension persists after adjustment for demographic characteristics, socioeconomic factors, and comorbidities. No association was observed between SSRIs and incident hypertension (SOR B: based on a retrospective cohort study).

Xing et al., 2020: OBJECTIVE: To perform an updated and comprehensive meta-analysis on the risks of adverse perinatal outcomes in children whose mothers received antidepressants during pregnancy. METHODS: A systematic literature search of several databases was conducted through

December 2018 to identify relevant studies. Risk estimates and their corresponding 95% confidence intervals (CIs) were pooled using random-effects meta-analysis. Subgroup and sensitivity analyses were performed to explore the source of heterogeneity and test the robustness. RESULTS: Forty-eight cohort and 6 case-control studies were included. In cohort studies, children whose mothers received antidepressants during pregnancy had higher risks of preterm birth (RR = 1.62, 95% CI: 1.37–1.90), low birth weight (RR = 1.37, 95% CI: 1.04–1.80), and admissions to neonatal intensive care unit (RR = 1.60, 95% CI: 1.38–1.85) when compared with children born by depressed but untreated pregnant women. The risks of spontaneous abortions (RR = 1.49, 95% CI: 1.29–1.73), large for gestational age (RR = 1.11, 95% CI: 1.03–1.20), stillbirths (RR = 1.16, 95% CI: 1.02–1.32), low Apgar score at 5 min (RR = 1.91, 95% CI: 1.42–2.56), and neonatal convulsions (RR = 1.97, 95% CI: 1.56–2.48) increased in children whose mothers received antidepressants during pregnancy when compared with children born by healthy pregnant women. CONCLUSION: Compared with children whose mothers did not receive antidepressants during pregnancy, children whose mothers received antidepressants during pregnancy had increased risks of adverse perinatal outcomes. Further research on the dose of antidepressants is needed.

Yuan et al., 2020: BACKGROUND: The type and quantities of antidepressants are increasing, but the efficacy and safety of first-line and emerging drugs vary between studies. In this article, we estimated the efficacy and safety of first-line and emerging antidepressants (anti-inflammatory drugs and ketamine). METHOD: systematic search of Embase, ERIC, MEDLINE, psycARTICLES, and PsycInfo without language restriction for studies on the depression, depressive symptoms, antidepressants, fluoxetine (Prozac), paroxetine, escitalopram, sertraline, fluvoxamine, venlafaxine, duloxetine, NSAIDs, anti-cytokine drugs or pioglitazone published before 1 May 2019. Information on study characteristics, depression or depressive symptoms, antidepressants and the descriptive statistics (including efficacy and safety of antidepressants) was extracted independently by two investigators. Estimates were pooled using random-effects meta-analysis. Differences by study-level characteristics were estimated using stratified meta-analysis and meta-regression. The response and remission of antidepressants were used as clinical evaluation indicators, and the evaluation criteria were clinical depression scales. OR value of antidepressants as assessed by meta-analysis. RESULTS: The literature search retrieved 5529 potentially relevant articles of which 49 studies were finally included. We compared the efficacy of antidepressants (seven first-line antidepressants (fluoxetine, paroxetine, escitalopram, sertraline, fluvoxamine, venlafaxine, duloxetine), there kinds of anti-inflammatory drugs (NASIDs, cytokine-inhibitor, pioglitazone) and ketamine) by comparing the OR values. CONCLUSION: The three drugs with the highest OR value in response were NASID (OR = 3.62(1.58–8.32)), venlafaxine (OR = 3.50(1.83–6.70)) and ketamine (OR = 3.28(1.89–5.68)), while the highest OR value in remission were NASID (OR = 3.17(1.60–6.29)), ketamine (OR = 2.99(1.58–5.67)) and venlafaxine (OR = 2.55(1.72–3.78)). Through reading the literature, we found 69 SNPs associated with depression.

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: Pharmacotherapy **(Citalopram - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018	Reduction in mental health symptoms	Change in depressive symptoms	14	SMD **-0.24** [CI -0.31 to -0.17]	⊕⊕◯◯ LOW
			Response	14	OR **1.52** [CI 1.33 to 1.74]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	14	OR **0.94** [CI 0.80 to 1.09]	⊕⊕◯◯ LOW
			Dropout due to adverse events	14	OR **1.87** [CI 1.39 to 2.51]	⊕⊕◯◯ LOW
		Suicide-related outcomes	_	_	_	N/A
		Improvement in quality of life and functioning	_	_	_	N/A
GRADE Table 2: Pharmacotherapy **(Escitalopram - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018; Cao et al., 2021	Reduction in mental health symptoms	Change in depressive symptoms	21	SMD **-0.29** [CI -0.35 to -0.24]	⊕⊕◯◯ LOW
			Response	21	OR **1.68** [CI 1.50 to 1.87]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	21	OR **0.90** [CI 0.80 to 1.02]	⊕⊕◯◯ LOW
			Dropout due to adverse events	21	OR **1.72** [CI 1.38 to 2.14]	⊕⊕◯◯ LOW
		Suicide-related outcomes	_	_	-	N/A

GRADE Table	Source	Outcome	Specific outcome	Number of studies	Effects	Certainty of evidence
		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-1.59** (SDS) [CI -2.89 to -0.28]	⊕◯◯◯ VERY LOW
GRADE Table 3: Pharmacotherapy **(Fluoxetine - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018; Cao et al., 2021	Reduction in mental health symptoms	Change in depressive symptoms	43	SMD **-0.23** [CI -0.28 to -0.19]	⊕⊕◯◯ LOW
			Response	43	OR **1.52** [CI 1.40 to 1.66]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	43	OR **0.88** [CI 0.80 to 0.96]	⊕⊕◯◯ LOW
			Dropout due to adverse events	43	OR **1.82** [CI 1.56 to 2.13]	⊕⊕◯◯ LOW
		Suicide-related outcomes	_	_	_	N/A
		Improvement in quality of life and functioning	Improvement in functioning	NR	SMD **0.30** [CI -1.90 to 2.50]	⊕◯◯◯ VERY LOW
GRADE Table 4: Pharmacotherapy **(Fluvoxamine - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018	Reduction in mental health symptoms	Change in depressive symptoms	14	SMD **-0.32** [CI -0.43 to -0.22]	⊕⊕◯◯ LOW
			Response	14	OR **1.69** [CI 1.41 to 2.02]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	14	OR **1.10** [CI 0.91 to 1.33]	⊕⊕◯◯ LOW
			Dropout due to adverse events	14	OR **2.83** [CI 2.12 to 3.80]	⊕⊕◯◯ LOW
		Suicide-related outcomes	_	_	_	N/A
		Improvement in quality of life and functioning	_	_	_	N/A

GRADE Table	Source	Outcome	Specific outcome	Number of studies	Effects	Certainty of evidence
GRADE Table 5: Pharmacotherapy **(Paroxetine - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018; Cao et al., 2021	Reduction in mental health symptoms	Change in depressive symptoms	49	SMD **-0.32** [CI -0.37 to -0.28]	⊕⊕◯◯ LOW
			Response	49	OR **1.75** [CI 1.61 to 1.90]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	49	OR **0.95** [CI 0.87 to 1.03]	⊕⊕◯◯ LOW
			Dropout due to adverse events	49	OR **2.19** [CI 1.90 to 2.53]	⊕⊕◯◯ LOW
		Suicide-related outcomes	–	–	–	N/A
		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-2.51** (SDS) [CI -4.08 to -0.94]	⊕◯◯◯ VERY LOW
GRADE Table 6: Pharmacotherapy **(Sertraline - SSRI)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018; Cao et al., 2021	Reduction in mental health symptoms	Change in depressive symptoms	24	SMD **-0.27** [CI -0.34 to -0.21]	⊕⊕◯◯ LOW
			Response	24	OR **1.67** [CI 1.49 to 1.87]	⊕⊕◯◯ LOW
		Adverse effects	All-cause dropout	24	OR **0.96** [CI 0.85 to 1.08]	⊕⊕◯◯ LOW
			Dropout due to adverse events	24	OR **2.01** [CI 1.61 to 2.52]	⊕⊕◯◯ LOW
		Suicide-related outcomes	–	–	–	–
		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-1.30** (SDS) [CI -3.36 to 0.76]	⊕◯◯◯ VERY LOW
GRADE Table 7:	Cipriani et al., 2018;	Reduction in mental health symptoms	Change in depressive symptoms	36	SMD **-0.48** [CI -0.55 to -0.41]	⊕⊕◯◯ LOW
			Response	36	OR **2.13** [CI 1.89 to 2.14]	⊕⊕◯◯ LOW

GRADE Table	Source	Outcome	Specific outcome	Number of studies	Effects	Certainty of evidence
Pharmacotherapy **(Amitriptyline - TCA)** compared to pill placebo in adults with depressive disorders	Cao et al., 2021	Adverse effects	All-cause dropout	36	OR **0.95** [CI 0.83 to 1.08]	⊕⊕◯◯ LOW
			Dropout due to adverse events	36	OR **3.11** [CI 2.54 to 3.82]	⊕⊕◯◯ LOW
		Suicide-related outcomes	–	–	–	N/A
		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-1.30** (SDS) [CI -5.34 to 2.47]	⊕◯◯◯ VERY LOW
GRADE Table 8: Pharmacotherapy **(Clomipramine - TCA)** compared to pill placebo in adults with depressive disorders	Cipriani et al., 2018	Reduction in mental health symptoms	Change in depressive symptoms	1	SMD **-0.33** [CI -0.45 to -0.21]	⊕◯◯◯ VERY LOW
			Response	1	OR **1.49** [CI 1.21 to 1.85]	⊕◯◯◯ VERY LOW
		Adverse effects	All-cause dropout	1	OR **1.30** [CI 1.01 to 1.68]	⊕◯◯◯ VERY LOW
			Dropout due to adverse events	1	OR **4.44** [CI 3.07 to 6.50]	⊕◯◯◯ VERY LOW
		Suicide-related outcomes	–	–	–	N/A
		Improvement in quality of life and functioning	–	–	–	N/A
GRADE Table 9: Pharmacotherapy **(Pooled SSRI)** compared to pill placebo in adults	Cao et al., 2021	Reduction in mental health symptoms	–	–	–	N/A
		Adverse effects	–	–	–	N/A
		Suicide-related outcomes	–	–	–	N/A

GRADE Table	Source	Outcome	Specific outcome	Number of studies	Effects	Certainty of evidence
with depressive disorders		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-1.42** (SDS) [CI -2.32 to -0.52]	⊕◯◯◯ VERY LOW
GRADE Table 10: Pharmacotherapy **(Pooled TCA)** compared to pill placebo in adults with depressive disorders	Cao et al., 2021	Reduction in mental health symptoms	–	–	–	N/A
		Adverse effects	–	–	–	N/A
		Suicide-related outcomes	–	–	–	N/A
		Improvement in quality of life and functioning	Improvement in functioning	NR	~~S~~MD **-1.42** (SDS) [CI -5.01 to 2.17]	⊕◯◯◯ VERY LOW

CI: confidence interval; OR: odds ratio; SMD: standard mean difference; SDS: Sheehan Disability Scale

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 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 recognized 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 depression burden by developing and scaling up evidence-based interventions is therefore a major global priority. • Different types of antidepressants are currently recommended as a first-line treatment for depression. However, the effects of antidepressants vary, and many patients do not improve or even experience deterioration.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgements 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	• SSRIs such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline were significantly better that pill placebo in reducing depressive symptoms. Additionally, TCAs such as amitriptyline and clomipramine were also better than pill placebo in reducing depressive symptoms. • While there was no available data on the improvement in global functioning for citalopram, fluvoxamine and clomipramine, escitalopram and paroxetine were significantly better that pill placebo in improving global functioning. • There were no significant differences between fluoxetine, sertraline and amitriptyline in improving global functioning compared to pill placebo. • Most of the comparisons had similar mean age and baseline	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			severity, apart from a few who had a low or high mean age/baseline severity. Meta-regression of age and baseline severity did not impact the network estimates (Cipriani et al., 2018).	
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgements 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	• Adverse effects varied with type of antidepressant agent. It is smaller for escitalopram, but much larger for amitriptyline • Only Fluoxetine had significantly less discontinuations (due to any reasons) compared to pill placebo, all other included antidepressants did not have significantly less or more discontinuations than pill placebo. • All the antidepressants had more dropouts due to adverse events compared to pill placebo. • There was no direct evidence to evaluate the risk of suicide-related adverse effects of antidepressants.	Additional evidence • Chan et al., 2020 and Fitton et al., 2020: ADM use during pregnancy was associated with an increased risk for preterm birth and congenital defects. • Rothmore, 2020: a risk of sexual dysfunction after ADM use.

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 judgements about the quality of evidence or certainty in estimates of effects	☒ **Very low** ☐ Low ☐ Moderate ☐ High ☐ No included studies	• The certainties of evidence for change in depressive symptoms, response, all-cause dropout, and dropout due to adverse events are **low** for citalopram (SSRI), escitalopram (SSRI), fluoxetine (SSRI), fluvoxamine (SSRI), paroxetine (SSRI), sertraline (SSRI) and amitriptyline (TCA), and **very low for clomipramine** (TCA). • The certainty of evidence for improvement in **quality of life and functioning** for fluoxetine (SSRI), paroxetine (SSRI), sertraline (SSRI), amitriptyline (TCA), pooled SSRIs and pooled TCAs is very low.	

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	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			the interventions (Amaral et al., 2018; Brooke-Sumner et al., 2015; Dickson & Bangpan 2018; Verhey et al., 2020).	
Balance of effects	Does the balance between desirable and undesirable effects favour 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.			
	• Judgements 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)?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☒ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ Don't know	• All included antidepressants were significantly better in reducing **depressive symptoms** than pill placebo. In addition, escitalopram (SSRI) and paroxetine (SSRI) were significantly better than placebo in improving global functioning. • Fluoxetine (SSRI), sertraline (SSRI) and amitriptyline (TCA) were not significantly better in improving **global functioning** than pill placebo. • There were no available data on the improvement in global functioning for citalopram (SSRI), fluvoxamine (SSRI) and clomipramine (SSRI). • Only Fluoxetine had significantly less discontinuations (due to any	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			reasons) compared to pill placebo, all other included antidepressants did not have significantly less or more discontinuations than pill placebo. • All the antidepressants had **more dropouts to due adverse events** compared to pill placebo.	
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. Both generic TCAs and many generic SSRIs are associated with low acquisition costs. Amitriptyline (as a representative of the TCAs) and fluoxetine (not as a representative of SSRIs) are included in the WHO list of essential medicines for the treatment of depressive disorders.	Additional information: • Both generic TCAs and many generic SSRIs are associated with low acquisition costs. • Included in the WHO list of essential medicines for the treatment of depressive disorders

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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 judgements 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.	Additional information: • Both generic TCAs and many generic SSRIs are associated with low acquisition costs. • Included in the WHO list of essential medicines for the treatment of depressive disorders

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Cost effectiveness	Does the cost-effectiveness of the intervention favour 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.			
	• Judgements 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?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☒ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ No included studies	No reviews examining cost-effectiveness identified.	Additional consideration • Several studies show that treatment of depression with antidepressants and psychological interventions can be cost effective and can have a considerable return on investment. (Chisholm et al., 2016).

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 favour 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 and 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	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			instructions, psychoeducation materials • Women – travel restrictions, stronger stigma/shame, caregiving responsibilities 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, standardized	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		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. • Logistical issues, 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)	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally 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 favour of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socioculturally 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 socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic 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	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There was no direct evidence to evaluate alignment with human rights principle and sociocultural acceptability. *The review noted a number of considerations which would impact the right to health and access to health care, e.g. stigma and discrimination and lack of confidentiality could affect the help-seeking among service users. • The importance of sociocultural acceptability of MNS interventions 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	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	and/or impacts on the privacy and dignity of concerned stakeholders justified?		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. **Mitigating steps** to improve sociocultural acceptability include: • 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 sociocultural 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# 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 the risk of bias (ROB) in GRADE

- No data available for risk of bias → serious

- When vast majority (>60%) of trials are **low risk** → not serious
- When low risk is between 50–60%:
  - High risk <25% → not serious
  - High risk >25% → serious

- When vast majority (>60%) is **high risk** → very serious
- When high risk is between 50–60%:
  - Low risk <25% → very serious
  - Low risk >25% → serious

- When vast majority is **unclear risk** (>60%) → serious
- When unclear risk is between 50-60%:
  - High risk <25% → not serious
  - High risk >25% → serious

- If unclear/high/low risk are all < 50%:
  - High risk <25% → not serious
  - High risk >25% → serious