Evidence profiles for the anxiety module (ANX) of the WHO mhGAP

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

2023

World Health Organization

Contents

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

1. Background

Mental, neurological and substance use (MNS) disorders are highly prevalent and constitute a significant burden of disease. However, in many countries, there is a gap between the need for MNS services and available health system capacity and resources. The Mental Health Gap Action Programme (mhGAP) was launched to address this gap and several derivative tools, such as the mhGAP Intervention Guide (mhGAP-IG), have been developed to support its implementation. The mhGAP approach consists of interventions for management of priority MNS conditions, identified on the basis of evidence about the effectiveness and feasibility of scaling up these interventions in low- and middle-income countries.
Priority conditions are identified based on multiple criteria, including: i) representing a high burden (in terms of mortality, morbidity, and disability; ii) resulting in large economic cost; and iii) being associated with human rights violations. In the 2015 updated release, mhGAP-IG 2.0 focused on seven priority conditions. These are depression, psychoses, self-harm/suicide, epilepsy, dementia, disorders due to substance use in adults and mental and behavioural disorders in children and adolescents.

Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1),* ranked among the top 25 leading causes of burden worldwide *(2),* exert a significant social and economic burden *(3)*, and are highly comorbid with other priority conditions *(4)*. What is more, these conditions have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that an estimated 75% of persons with anxiety disorders globally do not receive any care for their condition *(6)*. Thus, the current review was initiated to support the development of World Health Organization (WHO) mhGAP Guidelines on the management of anxiety disorders in non-specialized care settings.

Interventions for anxiety disorders often include pharmacological interventions (e.g. selective serotonin reuptake inhibitors (SSRIs)), psychosocial interventions (e.g. cognitive behavioural and other structured psychotherapies, stress management) *(7)* and in non-specialized care settings may include other forms of brief intervention (e.g. advice on physical activity). Management of anxiety disorders more commonly presenting in non-specialized care settings, including generalized anxiety disorder (GAD), panic disorder (PD) and mixed presentations of these conditions, and excluding social anxiety disorder (SAD) and specific phobia, which may be more common in specialized care, was reviewed. The following report describes the evidence identified and assessed through this review and the development of recommendations for management of these conditions.

2. Methodology

2.1. PICO Questions

The following seven PICO questions concerning management of anxiety disorders in non-specialist care settings were identified by the WHO mhGAP guidelines development group (GDG) for inclusion in this review. The PICO questions are summarized below and further detailed in **Appendix I**.

Table 1. Anxiety Module PICO Questions
Question #1. Are antidepressants (Tricyclic antidepressants [TCA]) and SSRI]) better than (more effective/as safe as) placebo or alternative interventions for adults with anxiety disorders? Population (P): adults with anxiety disorders (excluding SAD, specific phobia) Intervention (I): antidepressant drugs including TCAs and SSRIs Comparator (C): placebo, alternative psychological or pharmacological interventions Outcomes (O): Critical – reduction of symptoms, adverse effects Important – improvement in functioning, sustained response, acceptability profile
Question #2. Are brief, structured psychological interventions (e.g. Cognitive Behavioural Therapy [CBT], Problem Solving Therapy [PST]) in non-specialist care settings better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders? Population (P): adults with anxiety disorders (excluding SAD, specific phobia) Intervention (I): brief, structured psychological interventions Comparator (C): treatment as usual, waitlist, no treatment Outcomes (O): Critical – reduction of symptoms, adverse effects Important – improvement in functioning, sustained response, acceptability profile
Question #3. For adults with anxiety disorders, what is the comparative effectiveness of different formats of psychological interventions? Population (P): adults with anxiety disorders (excluding SAD, specific phobia) Intervention (I): individual psychological treatment, face-to-face psychological interventions, guided self-help psychological interventions, specialist provided psychological interventions Comparator (C): group psychological treatment, digital psychological treatment, unguided self-help psychological interventions, non-specialist provided psychological interventions Outcomes (O): *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile

Question #4. Are stress management techniques better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders?

Population (P): adults with anxiety disorders (excluding SAD, specific phobia)
Intervention (I):
Comparator (C): , waitlist, no treatment
Outcomes (O):
Critical – reduction of symptoms, adverse effects
Important – improvement in functioning, sustained response, acceptability profile

Question #5. Is advice on physical activity better (more effective/as safe as) than treatment as usual, waitlist no treatment in adults with anxiety disorders?

Population (P): adults with anxiety disorders (excluding SAD, specific phobia)
Intervention (I): advice on physical activity
Comparator (C): treatment as usual, waitlist, no treatment
Outcomes (O):
Critical – reduction of symptoms, adverse effects
Important – improvement in functioning, sustained response, acceptability profile

Question #6. Are benzodiazepines better (more effective/as safe as) than placebo for adults with anxiety disorders (excluding social phobia, SAD)?

Population (P): adults with anxiety disorders (excluding social anxiety disorder, specific phobia)
Intervention (I): benzodiazepines prescribed in non-specialized settings
Comparator (C): placebo
Outcomes (O):
Critical – reduction of symptoms, adverse effects
Important – improvement in functioning, sustained response, acceptability profile

Question #7. Is collaborative care better (more effect/as safe as) than treatment as usual, waitlist, no treatment for adults with depression or anxiety (living with physical health conditions)?

Population (P): adults living with physical health conditions and experiencing anxiety disorders (excluding SAD, specific phobia) or depression
Intervention (I): collaborative care
Comparator (C): treatment as usual, wait list, no treatment
Outcomes (O):
Critical – reduction of symptoms, adverse effects
Important – improvement in functioning, sustained response, acceptability profile

2.2. Search strategy

The detailed search strategy is available in the **Appendix I**. PubMed, Scopus, Embase, and the Cochrane Library were searched to identify systematic reviews and meta-analyses to answer each PICO question. Additionally, manual search was conducted in the International prospective register of systematic reviews (PROSPERO) database. Key and MESH terms were used to search databases. For example, a key word "anxiety disorders" included generalized anxiety disorder and panic disorder. Moreover, for a key word "psychological intervention", other alternative synonyms such as psychological treatment, psychotherapy, psychosocial intervention, counselling were used in the search.

Systematic reviews that have been published within the past two years from the time of the initial search in December 2021 (e.g. since 2019) were included in the review. However, it was acknowledged that COVID has led to a delay of many mental health research activities and that this may also impact the availability of systematic reviews within the two-year period preferred in WHO Guideline development.[1] Thus, older reviews were also identified by technical experts, particularly those covering the period since the last update of the mhGAP guideline in 2015, and these were included as additional evidence, where relevant.

2.3. Data collection and analysis

The research team assessed the identified systematic reviews for inclusion following guidance in the WHO handbook for guideline development. Specifically, the WHO handbook for guideline development suggests:

''As the first stage in selecting relevant studies, records retrieved from the bibliographic databases and from other sources are recorded and assessed for eligibility by examining their titles and abstracts only. This assessment is performed in accordance with the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant based on their titles and abstracts is retrieved and examined considering the same inclusion criteria in the second stage of study selection.
Data from eligible studies are then extracted into pre-defined templates that generally include the characteristics of the study design and of the population, intervention, comparator, and outcomes. To ensure accuracy, at least two people should independently assess the eligibility of the studies identified and extract data from study reports.
The search strategy and results should be carefully documented. This involves reporting the databases searched, the strategy used to search each database, the total number of citations retrieved from each database, and the reasons for having excluded some publications after reviewing the full text. The flow of articles throughout the search and up to the final cohort of included studies should be depicted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage. The PRISMA diagram is included in an Appendix to the report of the systematic review or within the text of the report''.

2.4. Selection and coding of identified records

To organise the records, selected systematic reviews were exported to the EndNote X9 software. Duplicate systematic reviews were removed from the EndNote X9 software manually and the abstracts of the remaining systematic reviews were reviewed again. After duplicates removed, articles were further screened by abstract and irrelevant articles were excluded. Finally, full texts of each systematic review were reviewed to select the records that fulfil all the inclusion criteria. Thereafter, articles that were stronger in quality methodologically, addressed multiple outcomes within the question, reviewed participants in non-specific

[1] WHO handbook for guideline development: 2nd edition. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/145714)

population, were published since 2019, and which reviewed widely available interventions were prioritized in the selection process.

2.5. Quality assessment

Existing systematic reviews identified in the selection process were assessed for quality using the Measurement Tool to Assess Systematic Reviews or Assessing the Methodological quality of SysTemAtic Reviews (AMSTAR-2) checklist.[2] Every step of selection of articles and quality assessment was discussed between the review team, the WHO focal point for the module, the WHO Steering Committee and the WHO guideline development methodologist.

Assessment of the certainty of the body of evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to assess the certainty of the evidence base [3]. The GRADE rating provides an indication of confidence in the estimates of the effect of an intervention[4]. Evidence from randomized controlled trials (RCTs) starts at high certainty and may be downgraded for serious or very serious concerns relating to each of the following domains:

- *Risk of bias:* based on the overall risk of bias (methodological limitations) of the trials contributing to each result. For the purpose of grading the evidence, an overall judgement of risk of bias was first made across studies for each risk bias domain, and then across domains. This judgement considered the extent to which studies at high or unclear risk of bias influenced the meta-analysis (i.e. weight).
- *Indirectness:* the extent to which the PICO characteristics of the body of evidence adequately address the clinical questions (PICO) for the guideline.
- *Imprecision:* whether the confidence interval includes both appreciable benefit and harm (or vice versa) and whether the optimal information size was met (based on a guideline of >400 participants for continuous outcomes; > 300 events for binary). Judgements of appreciable benefit (or harm) were based on the thresholds below.
- *Inconsistency*: the extent to which there is unexplained inconsistency in results across studies. Judgements were based on visual inspection of data (overlap in confidence intervals, the direction and magnitude of effect) and statistical measures and tests of heterogeneity.
- *Publication bias:* The likelihood of small study effect or other evidence of publication bias.

A body of evidence is rated as being of **high quality** (i.e. further research is very unlikely to change our confidence in the estimate of effect), **moderate quality** (i.e. further research is likely to have an important impact on our confidence in the estimate effect and may change the estimate), **low quality** (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or **very low quality** (i.e. we are very uncertain about the estimate).

For Network Meta-Analyses, the Confidence in Network Meta-Analysis (CINeMA) approach was used *(8)*. CINeMA is broadly based on the GRADE framework but retains certain differences necessary for evaluating confidence in results from network- meta-analyses. CINeMA covers six domains: (i) within-study bias (referring to the impact of risk of bias in the included studies), (ii) reporting bias (referring to publication and other reporting bias), (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence. CINeMA assigns judgements at three levels (no concerns, some concerns, or major concerns) to each domain. Then,

[2] https://amstar.ca/Amstar_Checklist.php.
[3] Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj*, *336*(7650), 924-926.
[4] Hultcrantz, M., Rind, D., Akl, E. A., Treweek, S., Mustafa, R. A., Iorio, A., ... & Guyatt, G. (2017). The GRADE Working Group clarifies the construct of certainty of evidence. *Journal of Clinical Epidemiology*, *87*, 4-13.

judgements can be summarized to obtain four levels of confidence for each relative treatment effect, corresponding to the usual GRADE assessments of very low, low, moderate, or high.

2.6. Analysis of subgroups or subsets

Subgroup analysis was not a component in any of the PICO questions of concern for this module.

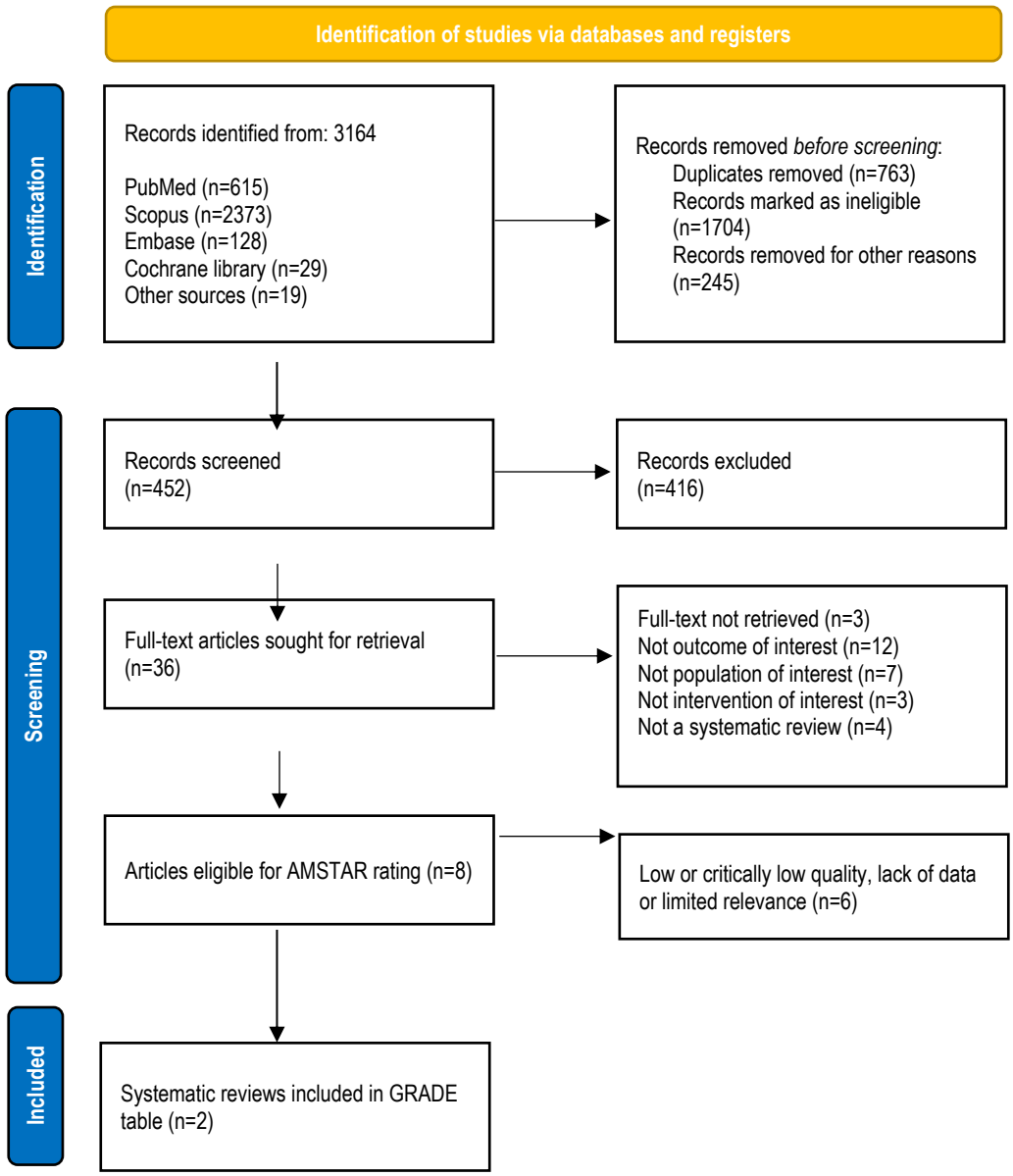
3. Results

QUESTION 1

Are antidepressants (TCA and SSRI) better (more effective/as safe as) than placebo or alternative interventions for adults with anxiety disorders (excluding SAD, specific phobias)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 1: PRISMA 2020 flow diagram[5] for systematic review of reviews which includes searches of databases and registers only for PICO Question #1



[5] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

3.1.1. Included in GRADE tables/footnotes

1. Chawla N, Anothaisintawee T, Charoenrungrueangchai K, Thaipisuttikul P, McKay GJ, Attia J, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2022;376:e066084: 1-15.
2. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768-77. doi:10.1136/bmj-2021-066084

3.1.2. Excluded from GRADE tables/footnotes

1. Gosmann NP, Costa MA, Jaeger MB, Motta LS, Frozi J, Spanemberg L, et al. Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive, and stress disorders: A 3-level network meta-analysis. PLoS Med. 2021;18(6):e1003664: 1-20. doi:10.1371/journal.pmed.100366
2. Du Y, Du B, Diao Y, Yin Z, Li J, Shu Y, et al. Comparative efficacy and acceptability of antidepressants and benzodiazepines for the treatment of panic disorder: A systematic review and network meta-analysis. Asian J Psychiatr. 2021;60:102664. doi:10.1016/j.ajp.2021.102664
3. Quagliato A L, Cosci F, Shader I R, Silberman K E, and, et a. Selective serotonin reuptake inhibitors and benzodiazepines in panic disorder: A meta- analysis of common side effects in acute treatment. J Psychopharmacol. 2019;1-20. doi:10.1177/0269881119859372
4. Kong W, Deng H, Wan J, Zhou Y, Zhou Y, Song B, et al. Comparative Remission Rates and Tolerability of Drugs for Generalised Anxiety Disorder: A Systematic Review and Network Meta-analysis of Double-Blind Randomized Controlled Trials. Front Pharmacol. 2020;11:580858: 1-16. doi:10.3389/fphar.2020.580858
5. Chen TR, Huang HC, Hsu JH, Ouyang WC, Lin KC. Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis. J Psychiatr Res. 2019;118:73-83. doi:10.1016/j.jpsychires.2019.08.014

Table 2: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 1	Antidepressants (TCAs and SSRIs)/Placebo or alternative interventions	Symptom reduction	Slee et al. (2019); Chawla et al. (2019)	Slee et al. (2019) and Chawla et al. (2019) were chosen for symptom reduction in adults with GAD and PD, respectively, over Gosmann et al. (2021) because evidence quality appraisal could not be completed due to limited reporting in Gosmann et al. (2021) and Chen et al. (2019) because the CINeMA approach could not be applied for network meta-analyses due to limited reporting of data.
		Adverse events	Chawla et al. (2022)	Chawla et al. (2022) was chosen for adverse events over Gosmann et al. (2021) because Gosmann did not report adverse events by diagnosis or drug class and instead only reported ORs by specific drug. Slee et al (2019) did not report adverse events.
		Acceptability profile	Chawla et al. (2022); Slee et al (2019)	Chawla et al. (2022) and Slee et al. (2019) were chosen for acceptability profile (measured with number of dropouts) over Gosmann et al. (2021) because Gosmann et al. (2021) only reported comparative acceptability using pairwise comparisons of the dropout by specific medications and did not report differences by diagnosis or drug class.
		Sustained response	No evidence	No reviews available on this outcome.
		Functioning	No evidence	No reviews available on this outcome.

Notes. OR: Odds ratio

3.2. Narrative description of studies that contributed to GRADE analysis

Chawla et al. (2022) conducted a systematic review and network meta-analysis of the effects of individual antidepressants in adults with panic disorder. In total, 87 RCTs (12 800 participants) met the inclusion criteria. Eighty-three studies (95%) included participants with agoraphobia, and duration of panic disorder was 6.9 years before study commencement. The most common duration of treatment was eight weeks (35%), followed by 12 weeks (19%). A total of 21 comparisons were considered for analysis; most compared benzodiazepines with placebo (n=16 studies) and SSRIs with placebo (n=16), followed by TCA versus benzodiazepines (n=8), TCA versus SSRIs (n=8), and SSRIs versus SSRIs (n=6), and TCA versus placebo (n=5), with the remaining comparisons represented in only a few studies. Fifty-two studies reported outcomes for remission, 75 for dropouts, 41 for anxiety symptoms, 22 for depression symptoms, and 54 for adverse events. Quality of life outcomes were not considered as data were only available from seven studies.

Slee et al. (2019) conducted a systematic review and network meta-analysis of the evidence on the effectiveness of pharmacological treatments, including benzodiazepines, for adults with generalized anxiety disorder. In total, 89 studies were included and were published between 1 January 1998, and 31 August 2016. None of the trials deliberately restricted to incident generalized anxiety disorder, and 73 (82%) of 89 studies used the diagnostic and statistical manual (DSM) criteria, which requires a six-month duration of symptoms to complete the diagnosis. These studies ranged in duration of follow up from 4 to 26 weeks (median duration 8 weeks), and all studies included change in Hamilton Anxiety Scale (HAM-A) as a primary or secondary endpoint. In total, 25 441 patients were enrolled in these trials. Sixty-three trials (71%) were placebo-controlled, and 45 (51%) included more than one active drug. Most of the trials were double-blind and were conducted by pharmaceutical companies as part of a clinical development programme.

3.3. Grading the Evidence

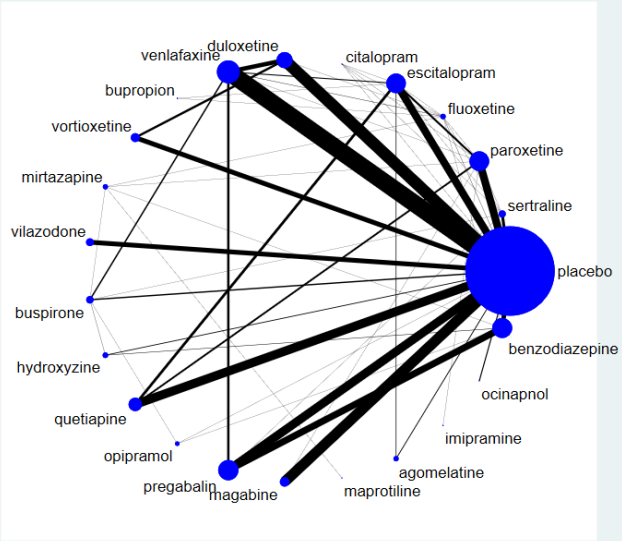
Table 3: Antidepressants vs treatment as usual, waitlist, no treatment, or alternative interventions

Author(s): Brandon Gray, Biksegn Asrat and Davide Papola
Question: Are antidepressants (TCA and SSRI better (more effective/as safe as) placebo or alternative interventions for adults with anxiety disorders (excluding social anxiety disorder, specific phobias)?
Setting: non-specialist care settings
Reference List:
Chawla N, Anothaisintawee T, Charoenrungrueangchai K, Thaipisuttikul P, McKay GJ, Attia J, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2022;376:e066084: 1-15.
Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768-77. doi:10.1136/bmj-2021-066084

Table 3.1 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): placebo
Outcome: reduction of anxiety symptoms
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



	Relative effect** (95% CI)[a]	Confidence in Network Meta-Analysis (CINeMa) ratings						Confidence rating	SUCRA	Number of participants (studies)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
Sertraline	-2.88 (-4.17 to -1.59)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	63.5%	485 (6 RCTs)
Escitalopram	-2.45 (-1.63 to -3.27)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	49.8%	1581 (13 RCTs)
Fluoxetine	2.43 (-1.16 to -3.74)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	49.6%	264 (8 RCTs)
Citalopram	-2.22 (-0.19 to -4.28)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	44.4%	37 (2 RCTs)
Paroxetine	-2.29 (-1.47 to -3.11)	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	⊕◯◯◯ Very Low	44.4%	1862 (17 RCTs)
Imipramine	-0.59 (-3.85 to 2.70)	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕◯◯◯ Very Low	19.5%	26 (1 RCT)

NMA table definitions

* Solid lines represent direct comparisons

** Network Metanalysis estimates are reported as mean differences

Notes. CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking

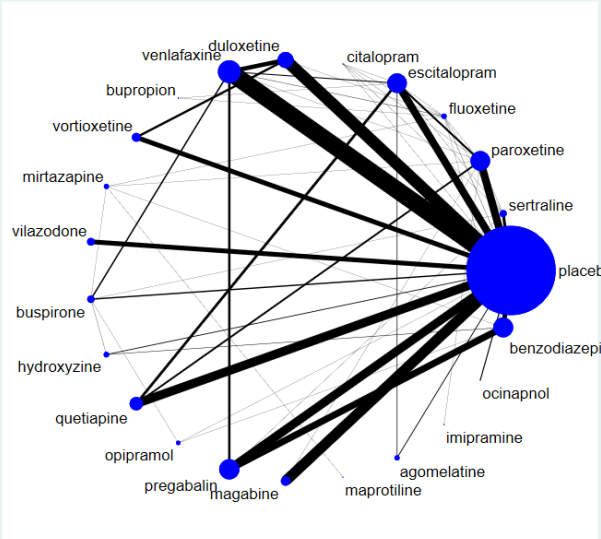
Explanations

a. For all comparisons, negative effects favour the drug. Positive effects favour placebo.

Table 3.2 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): alternative pharmacological interventions
Outcome: reduction of anxiety symptoms
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



Comparison[a]	Relative effect* (95% CI) [a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Bupropion: Escitalopram	-2.85 (-6.12 to 0.43)	No concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	⨁⨁◯◯ Low	1
Bupropion: Fluoxetine	-2.86 (-6.15 to 0.41)	No concerns	Low risk	No concerns	Some concerns	No concerns	Some concerns	⨁⨁◯◯ Low	1
Imipramine: Paroxetine	1.70 (-1.46 to 4.89)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⨁◯◯◯ Very Low	1
Paroxetine: Tiagabine	-1.52 (-3.11 to 0.08)	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⨁⨁◯◯ Low	1
Paroxetine: Quetiapine	1.32 (-0.06 to 2.70)	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⨁⨁◯◯ Low	1

Comparison[a]	Relative effect* (95% CI) [a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Escitalopram: Quetiapine	1.15 (-0.23 to 2.53)	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	1
Agomelatine: Escitalopram	-1.09 (-3.42 to 1.22)	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕⊕⊕◯ Moderate	1
Mirtazapine: Paroxetine	-0.83 (-2.12 to 0.45)	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⊕⊕◯◯ Low	3
Duloxetine: Fluoxetine	-0.70 (-2.19 to 0.84)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕◯◯◯ Very Low	1
Fluoxetine: Mirtazapine	0.69 (-0.92 to 2.26)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕◯◯◯ Very Low	1
Buspirone: Sertraline	0.51 (-1.33 to 2.37)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕◯◯◯ Very Low	1
Paroxetine: Venlafaxine	0.41 (-0.69 to 1.51)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕◯◯◯ Very Low	13
Fluoxetine: Venlafaxine	0.27 (-1.22 to 1.72)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕◯◯◯ Very Low	1
Escitalopram: Venlafaxine	0.24 (-0.86 to 1.34)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕◯◯◯ Very Low	1
Benzodiazepine: Fluoxetine	0.14 (-1.25 to 1.57)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕◯◯◯ Very Low	2

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as mean differences
Notes. CI: Confidence intervals

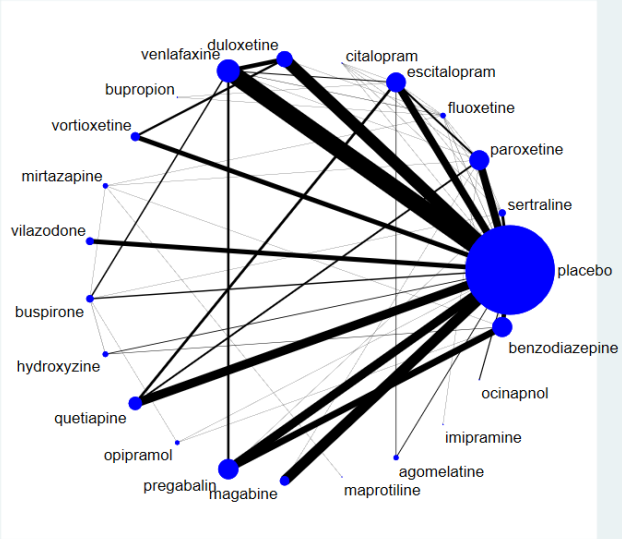
Explanations

a. For all comparisons, negative effects indicate the drug on the left of the comparison is more effective. Positive effects indicate the drug on the right is more effective.

Table 3.3 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): placebo
Outcome: acceptability (dropout rate)
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



	Odds ratio (OR)** (95% CI)[a]	CINeMa ratings						Confidence rating	SUCRA	Number of participants (studies)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
Escitalopram	0.96 (0.79 to 1.16)	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕⊕ High	63.8%	1581 (13 RCTs)
Sertraline	0.94 (0.65 to 1.35)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	63.0%	485 (6 RCTs)
Fluoxetine	1.36 (0.57 to 3.15)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	49.6%	264 (8 RCTs)
Paroxetine	1.24 (1.03 to 1.50)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	37.2%	1862 (17 RCTs)
Citalopram	3.62 (0.74-20.27)	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⊕⊕◯◯ Low	17.0%	37 (2 RCTs)
Impramine	2.83 (0.74 to 12.10)	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕◯◯◯ Very Low	14.2%	26 (1 RCT)

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis estimates are reported as risk ratio

Notes. CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking

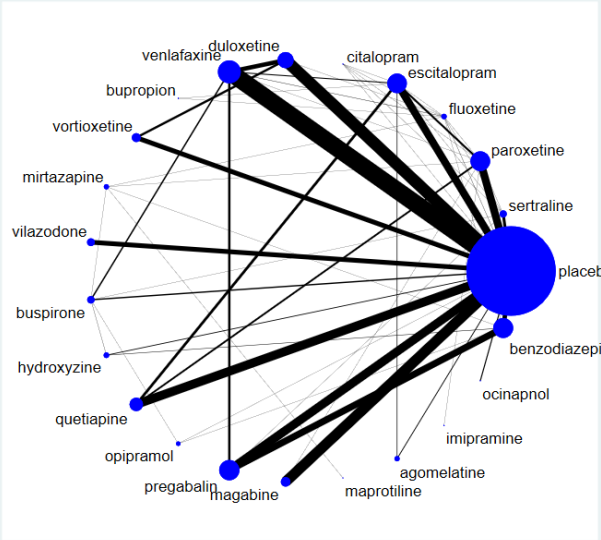
Explanations

a. For all comparisons, OR below 1.00 favour the drug. OR above 1.00 favour placebo.

Table 3.4 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): alternative pharmacological interventions
Outcome: acceptability (dropout rate)
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



Comparison[a]	OR* (95% CI)[a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Mixed Estimates									
Paroxetine: Mirtazapine	2.72 (0.53 to 15.66)	Some concerns	Low risk	No concerns	Major Concerns	No concerns	No concerns	⊕◯◯◯ Very Low	3
Paroxetine: Imipramine	2.29 (0.60 to 9.70)	Some concerns	Low risk	No concerns	Major Concerns	Some concerns	No concerns	⊕◯◯◯ Very Low	1
Fluoxetine: Benzodiazepine	1.06 (0.44 to 2.60)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	2
Escitalopram: Bupropion	1.00 (0.10 to 11.00)	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ Low	1
Quetiapine: Paroxetine	0.86 (0.65 to 1.14)	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⊕⊕⊕⊕ Moderate	1

Comparison[a]	OR* (95% CI)[a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Venlafaxine: Paroxetine	0.82 (0.64 to 1.05)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⨁⨁⨁◯ Moderate	1
Fluoxetine: Duloxetine	0.80 (0.34 to 1.96)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⨁⨁⨁◯ Moderate	1
Escitalopram: Agomelatine	0.70 (0.38 to 1.24)	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	⨁⨁⨁◯ Moderate	1
Fluoxetine: Bupropion	0.70 (0.07 to 9.40)	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⨁⨁◯◯ Low	1

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio
Notes. CI: Confidence intervals

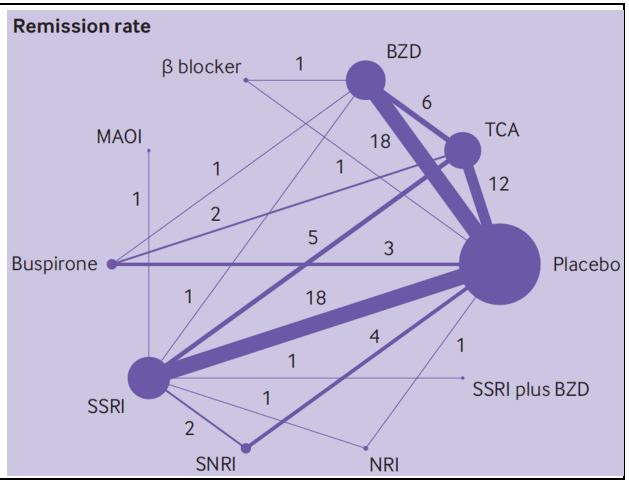
Explanations

a. For all comparisons, OR below 1.00 indicate the drug on the left of the comparison is more tolerable. OR above 1.00 indicate the drug on the right of the comparison is more tolerable.

Table 3.5 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): placebo
Outcome: reduction of anxiety symptoms (remission)
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



	Risk Ratio (RR)** (95% CI)[a]	CINeMa ratings						Confidence rating	SUCRA	No of studies with direct evidence
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
TCA	1.39 (1.26 to 1.54)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	68.7%	12
SSRI	1.38 (1.26 to 1.54)	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	66.4%	18

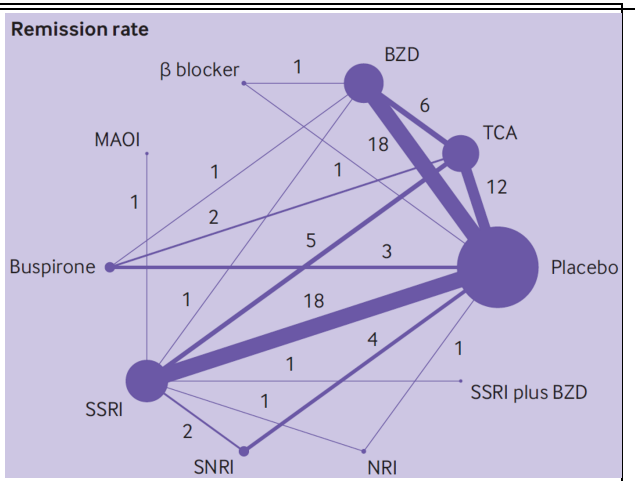
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CI: Confidence intervals. SUCRA: Surface under the cumulative ranking
Notes. SSRI: selective serotonin reuptake inhibitor; SUCRA: Surface under the cumulative ranking; TCAs: tricyclic anti-depressants

Explanations
a. For all comparisons, RR above 1.00 favour the drug. RR below 1.00 favour placebo.

Table 3.6 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): alternative pharmacological interventions
Outcome: reduction of symptoms (remission)
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



Comparison[1]	RR * (95% CI) [a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
TCA: Buspirone	RR 1.26 (0.83 to 1.14)	Major concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕⊕◯◯ Low	2
SSRI: SNRI	RR 1.08 (0.95 to 1.24)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕⊕◯ Moderate	2
BZD: SSRI	RR 1.07 (0.96 to 1.19)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕⊕◯ Moderate	1
SSRI: NRI	RR 1.06 (0.67 to 1.69)	Major concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	⊕◯◯◯ Very Low	1
TCA: SSRI	RR 1.01 (0.89 to 1.14)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕⊕◯◯ Low	5
TCA: BZD	RR 0.94 (0.85 to 1.05)	Some concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	⊕⊕◯◯ Low	6
MAOI: SSRI	RR 0.94 (0.73 to 1.21)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕⊕◯◯ Low	1

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis estimates are reported as risk ratio. CI: Confidence intervals

Notes. BZDs: benzodiazepines; MAOIs: monoamine oxidase inhibitors; NRI: norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCAs: tricyclic anti-depressants

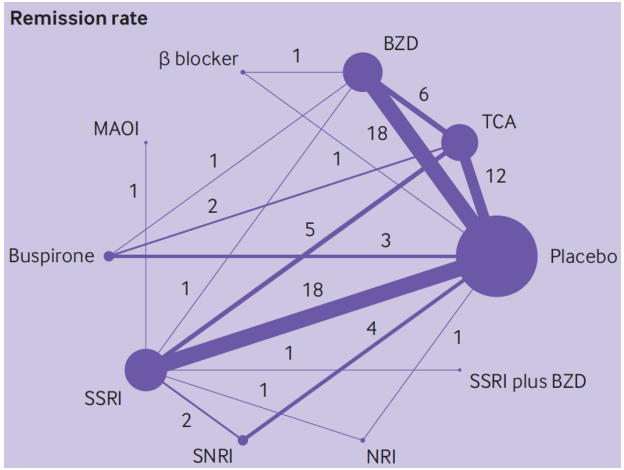
Explanations

a. For all comparisons, RR below 1.00 indicate the drug on the left of the comparison is more effective. RR above 1.00 indicate the drug on the right of the comparison is more effective.

Table 3.7 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): placebo
Outcome: adverse events
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



	RR ** (95% CI)[a]	CINeMa ratings						Confidence rating	SUCRA	No of studies with direct evidence)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
SSRI	RR 1.19 (1.01 to 1.41)	Some concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	⊕⊕◯◯ Low	55.5%	13
TCA	RR 1.79 (1.47 to 2.19)	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	23.8%	6

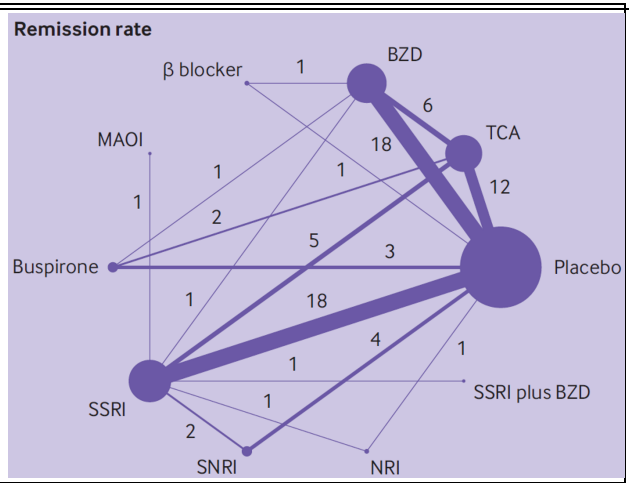
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio
Notes. CI: Confidence interval; SSRI, selective serotonin reuptake inhibitor; SUCRA: Surface under the cumulative ranking; TCAs, tricyclic anti-depressants

Explanations
a. For all comparisons, RR above 1.00 favour the placebo. RR below 1.00 favour the drug.

Table 3.8 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): alternative pharmacological interventions
Outcome: adverse events
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



Comparison[1]	RR * (95% CI)[a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Mixed Estimates									
TCA: Buspirone	RR 2.45 (1.30 to 4.62)	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	1
BZD: SSRI	RR 1.47 (1.18 to 1.84)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕⊕◯ Moderate	1
TCA: SSRI	RR 1.50 (1.20 to 1.88)	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	3
SSRI: NRI	RR 1.12 (0.75 to 1.69)	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ Low	2
MAOI: SSRI	RR 1.05 (0.71 to 1.54)	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ Low	1
TCA: BZD	RR 1.02 (0.83 to 1.25)	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	⊕◯◯◯ Very Low	5

SSRI: SNRI	RR 0.96 (0.69 to 1.35)	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ Low	1

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis estimates are reported as risk ratio. CI: Confidence intervals

Notes. BZDs: benzodiazepines: MAOIs, monoamine oxidase inhibitors; NRI: norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCAs: tricyclic anti-depressants

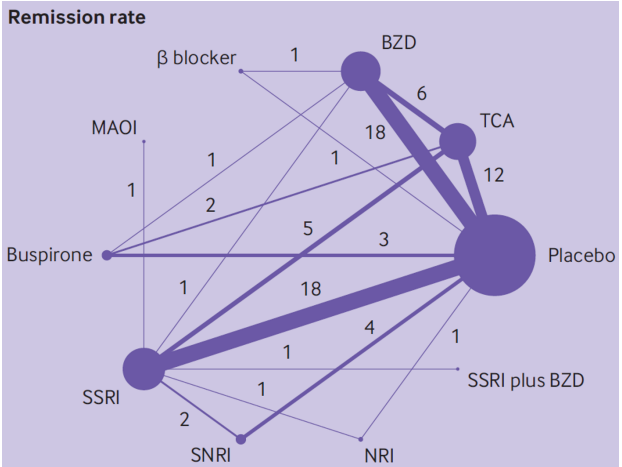
Explanations

a. For all comparisons, RR above 1.00 indicate the drug on the right of the comparison is safer. RR below 1.00 indicate the drug on the left of the comparison is safer.

Table 3.9 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): placebo
Outcome: acceptability (dropout rate)
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



	RR ** (95% CI)[a]	CINeMa ratings						Confidence rating	SUCRA	No of studies with direct evidence)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
TCA	RR 0.71 (0.58 to 0.88)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕⊕◯◯ Low	62.5%	20
SSRI	RR 0.92 (0.77 to 1.10)	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	⊕⊕◯◯ Low	37.6%	21

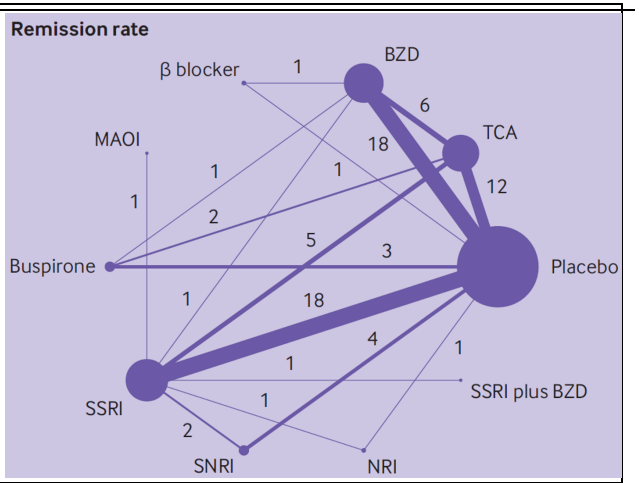
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio
Notes. CI: Confidence intervals; SSRI: selective serotonin reuptake inhibitor; SUCRA: Surface under the cumulative ranking TCAs: tricyclic anti-depressants

Explanations
a. For all comparisons, RR below 1.00 favour the drug. RR above 1.00 favour placebo.

Table 3.10 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: antidepressant drugs including TCAs and SSRIs
Comparator (reference): alternative pharmacological interventions
Outcome: acceptability (dropout rate)
Setting(s): non-specialist care settings
Reference: Chawla et al. (2021)

Geometry of the Network*



Comparison[1]	RR * (95% CI) [a]	Within- study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Number of studies
Mixed Estimates									
TCA: BZD	1.54 (1.19 to 1.99)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕⊕◯◯ **Low**	9
SSRI: NRI	1.32 (0.62 to 2.81)	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ **Low**	1
SSRI: SNRI	1.13 (0.76 to 1.67)	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ **Low**	2
MAOI: SSRI	1.08 (0.53 to 2.22)	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	⊕⊕◯◯ **Low**	1
TCA: SSRI	0.78 (0.61 to 0.99)	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	⊕⊕◯◯ **Low**	7
BZD: SSRI	0.51 (0.38 to 0.67)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕⊕◯ **Moderate**	1

TCA: Buspirone	0.40 (0.21 to 0.74)	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	⨁◯◯◯ **Very Low**	3

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis estimates are reported as risk ratio.

Notes. BZDs: benzodiazepines; CI: Confidence intervals; MAOIs: monoamine oxidase inhibitors; NRI: norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCAs: tricyclic anti-depressants

Explanations

a. For all comparisons, RR above 1.00 favour the drug on the right of the comparison. RR below 1.00 favour the drug on the left of the comparison.

3.4. Additional evidence not mentioned in GRADE tables

Antidepressants vs Placebo and Alternative Pharmacological Interventions for Panic Disorder
Chawla et al. (2019)'s NMA also reported effects for anxiety symptom reduction in adults with panic disorder. However, sufficient data was not reported to perform CINeMA appraisal for network meta-analyses.

For the comparisons of interest, effects were consistent with remission rates reported in the GRADE tables. Overall, Anxiety scores were reported in 39 studies (4112 participants). Evidence from 9 RCTs (1884 participants) indicated SSRIs demonstrated significantly reduced anxiety symptoms relative to placebo (SMD = -0.88; 95% CI -1.32 to -0.44) as did evidence from three RCTs of TCAs vs placebo (SMD = -0.65; 95% CI -1.18 to -0.12). The smaller number of comparisons of antidepressants to alternative treatments also confirmed results reported in GRADE tables for remission rates. Evidence indicated no difference between TCAs and SSRIs (2 RCTs; SMD = -0.23; 95% CI -0.37 to 0.83) and between MAOIs and SSRIs (2 RCTs; SMD = -0.47; 95% CI -0.43 to 1.37).

Antidepressants vs Alternative Psychological Interventions
Only one systematic review was identified that compared antidepressants to psychological interventions in this reports review period (Chen et al. 2019). However, the review was not included in the GRADE tables because sufficient data was not reported to perform CINeMA appraisal for network meta-analyses. Thus, the study and its results are summarized here and are included as additional considerations in the Evidence to Decision table.

Chen et al. (2019) performed a network meta-analysis comprising 57 RCTs to synthesize direct and indirect evidence for alternative psychological and pharmacological interventions for GAD. In total, 91 studies were included comprising 57 pharmacological interventions, 26 psychotherapeutic interventions, six self-help interventions, and two studies comparing pharmacological versus psychotherapeutic interventions and pharmacological versus self-help interventions.

In all 91 RCTs, GAD diagnosis was confirmed through a diagnostic interview. In total, 15 596 participants were randomly assigned in the trials, and 14 812 were included in the analysis; 63.5% of the participants specified in the articles were female (9527/14997). The median of mean age was 40.13 years. The median and mean duration of treatment were 8 and 9.6 weeks respectively. In reporting results, Chen et al. (2019) did not report effect sizes for the two studies that directly compared pharmacological and psychotherapeutic interventions, and instead reported "Overall, compared with placebo, most pharmacological interventions had larger effect sizes than psychological interventions; most psychological interventions showed larger effect sizes than self-help interventions". However, authors also later described the limited number of direct comparison studies as insufficient evidence to report differences in efficacy between pharmacotherapy and psychological and self-help interventions. Thus, results appeared to be inconclusive.

As a result, an exceptional rapid scoping for reviews published before the cut-off date of 2019 used for this reports review was conducted to identify potential additional evidence. In this non-systematic literature search, four potentially relevant systematic reviews (Bandelow et al., 2015; Cuijpers et al., 2013; Mitte, 2005; Roshanaei-Moghaddam et al., 2011) examining relative effects of psychotherapy and pharmacotherapy were identified and assessed for quality, where possible.

Mitte (2005) conducted a systematic review and meta-analysis of CBT for GAD, including studies comparing CBT with pharmacotherapy. CBT and pharmacotherapy (primarily benzodiazepines)

were directly compared in six studies. Results indicated that CBT and pharmacotherapy were not significantly different (SMD = 0.33; 95% CI -0.02 to 0.67) and comparison also demonstrated a significantly lower dropout rate for CBT.

Bandelow et al. (2015) conducted a meta-analysis comparing the absolute (pre–post) and relative (treated vs. control) effect sizes of psychotherapies and pharmacotherapies compared to placebo or waitlist for GAD, PD, and SAD. Head-to-head comparison of psychotherapy and pharmacotherapy was not reported.

Overall, low to very-low quality evidence indicated medications were associated with a significantly higher average pre–post effect sizes (Cohen's d = 2.02; 95% CI: 1.90 to 2.15); 28 051 patients) than psychotherapies (*d* = 1.22; ; 95% CI: 1.14 to 1.30); 6992 patients; P<0.0001) for adults with any anxiety disorder (GAD, PD, or SAD).

In adults with any anxiety disorder, effect sizes were large for SSRI (n=62 RCTs; *d* = 2.09; 95% CI: 1.89 to 2.35) and for TCA (n=15; *d* = 1.83; 95% CI: 1.43 to 2.21) as well as individual CBT (n=93 RCTs; *d* = 1.30; 95% CI: 1.19 to 1.41), group CBT (n=18 RCTs; *d* = 1.22; 95% CI: 0.95 to 1.49) interpersonal therapy (IPT) (n=4 RCTs; *d* = 0.78; 95% CI: 0.54 to 1.01), and EMDR (n=3 RCTs; *d* = 1.03; 95% CI: 0.53 to 1.53).

For PD, effect sizes were also large for SSRIs (n = 25 RCTs; *d* = 1.59; 95% CI: 1.32 to 1.86), TCAs (n=13 RCTs; *d* = 1.68; 95% CI: 1.31 to 2.05), individual CBT (n= 47 RCTs; *d* = 1.24; 95% CI: 1.10 to 1.39), group CBT (n=4 RCTs; *d* = 1.81; 95% CI: 1.50 to 2.12), and EMDR (n=3 RCTs; *d* = 1.03; 95% CI: 0.53 to 1.53) and medium for IPT (n=1 RCT; *d* = 0.56; 95% CI: 0.13 to 1.00). For GAD, effect sizes were large for SSRIs (n=15 RCTs; *d* = 3.48; 95% CI: 3.18 to 3.78), TCAs (n=2 RCTs; *d* = 3.02; 95% CI: 0.89 to 5.15), individual CBT (n=20 RCTs; *d* = 1.81; 95% CI: 1.47 to 2.15), and group CBT (n=1 RCT; *d* = 1.63; 95% CI: 0.97 to 2.28).

Cuijpers et al. (2013) conducted a systematic review and metanalysis comparing psychotherapies (e.g. CBT, IPT, PST) to antidepressants for depressive and anxiety disorders. Low quality evidence from 30 RCTs indicated minimal to non-existent differences between medications and psychotherapy for adults with any anxiety disorder (SMD = 0.10; 95% CI -0.05 to 0.25) and moderate quality evidence from 11 RCTs indicated minimal to non-existent differences between medications and psychotherapy for adults with panic disorder (SMD = 0.00; 95% CI -0.28 to 0.28). Additionally, 1 RCT compared psychotherapy and antidepressants for GAD but results were not reported.

Roshanaei-Moghaddam et al. (2011) conducted a systematic review and meta-analysis of studies comparing CBT to pharmacotherapy (antidepressants and anxiolytics) in adults with anxiety disorders. Very low quality evidence from 21 RCTS indicated minimal to non-existent differences between medications and psychotherapy for adults with any anxiety disorder (SMD = 0.25; 95% CI -0.02 to 0.51), low quality evidence from 11 RCTs indicated effects for panic disorder significantly favoured CBT over medications (SMD = .50, 95% CI: 0.02 to 0.98), and very low quality evidence from one RCT indicated minimal to non-existent differences between medications and psychotherapy for adults with GAD (SMD = 0.88; 95% CI: -0.04 to 1.80).

4. From Evidence to Recommendations

4.1. Summary of findings

Table 4: Summary of findings table from GRADE tables

Table 4.1: Summary of findings table for all comparisons for adults with GAD

GRADE table	Source	Comparison	Outcomes	Effects[a,b]	№ of participants (studies)	Certainty of the evidence
Table 3.1 & 3.3 (Antidepressants vs placebo in adults with GAD)	Slee et al. (2019)	Citalopram: placebo	Symptom reduction	MD -2.22 (-0.19 to -4.28)	37 (2 RCTs)	⨁⨁◯◯ Low
			Acceptability	OR 3.62 (0.74 to 20.27)	37 (2 RCTs)	⨁⨁◯◯ Low
		Escitalopram: placebo	Symptom reduction	MD -2.45 (-1.63 to -3.27)	1581 (13 RCTs)	⨁⨁◯◯ Low
			Acceptability	OR 0.96 (0.79 to 1.16)	1581 (13 RCTs)	⨁⨁⨁⨁ High
		Fluoxetine: placebo	Symptom reduction	MD -2.43 (-1.16 to -3.74)	264 (8 RCTs)	⨁⨁◯◯ Low
			Acceptability	OR 1.36 (0.57 to 3.15)	264 (8 RCTs)	⨁⨁⨁◯ Moderate
		Paroxetine: placebo	Symptom reduction	MD -2.29 (-1.47 to -3.11)	1862 (17 RCTs)	⨁◯◯◯ Very Low
			Acceptability	OR 1.24 (1.03 to 1.50)	1862 (17 RCTs)	⨁◯◯◯ Very Low
		Sertraline: placebo	Symptom reduction	MD -2.88 (-4.17 to -1.59)	485 (6 RCTs)	⨁⨁⨁◯ Moderate

GRADE table	Source	Comparison	Outcomes	Effects[a,b]	№ of participants (studies)	Certainty of the evidence
			Acceptability	OR 0.94 (0.65 to 1.35)	485 (6 RCTs)	⨁⨁⨁◯ Moderate
		Imipramine: placebo	Symptom reduction	MD -0.59 (-3.85 to 2.70)	26 (1 RCT)	⨁◯◯◯ Very Low
			Acceptability	OR 2.83 (0.74 to 12.10)	26 (1 RCT)	⨁◯◯◯ Very Low

Notes. GAD: generalized anxiety disorder; OR: odd ratio; RCT: randomized controlled trial; SM: mean difference

Explanations

a. For all comparisons, negative Mean Difference (MD) effects indicate the comparator on the left of the comparison is more effective. Positive effects indicate the comparator on the right is more effective.

b. For all comparisons, OR below 1.00 indicate the drug is more tolerable. OR above 1.00 indicate placebo is more tolerable.

GRADE table	Source	Comparison	Outcomes	Effects[a,b]	№ of participants (studies)	Certainty of the evidence
Table 3.2, 3.4 (Antidepressants vs alternative pharm interventions in adults with GAD)	Slee et al. (2019)	Agomelatine: Escitalopram	Reduction of symptoms	MD -1.09 (-3.42 to 1.22)	(1 RCT)	⨁⨁⨁◯ Moderate
			Acceptability	OR 0.70 (0.38 to 1.24)	(1 RCT)	⨁⨁⨁◯ Moderate
		Benzodiazepine: Fluoxetine	Reduction of symptoms	MD 0.14 (-1.25 to 1.57)	(2 RCTs)	⨁◯◯◯ Very Low
			Acceptability	OR 1.06 (0.44 to 2.60)	(2 RCTs)	⨁⨁⨁◯ Moderate
		Bupropion: Escitalopram	Reduction of symptoms	MD -2.85 (-6.12 to 0.43)	(1 RCT)	⨁⨁◯◯ Low

			Acceptability	OR 1.00 (0.10 to 11.00)	(1 RCT)	⊕⊕◯◯ Low
		Bupropion: Fluoxetine	Reduction of symptoms	MD -2.86 (-6.15 to 0.41)	(1 RCT)	⊕⊕◯◯ Low
			Acceptability	OR 0.70 (0.07 to 9.40)	(1 RCT)	⊕⊕◯◯ Low
		Buspirone: Sertraline	Reduction of symptoms	MD 0.51 (-1.33 to 2.37)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	No evidence	-	-
		Duloxetine: Fluoxetine	Reduction of symptoms	MD -0.70 (-2.19 to 0.84)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	OR 0.80 (0.34 to 1.96)	(1 RCT)	⊕⊕⊕◯ Moderate
		Escitalopram: Quetiapine	Reduction of symptoms	MD 1.15 (-0.23 to 2.53)	(1 RCT)	⊕⊕⊕◯ Moderate
			Acceptability	No evidence	-	-
		Escitalopram: Venlafaxine	Reduction of symptoms	MD 0.24 (-0.86 to 1.34)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	No evidence	-	-
		Fluoxetine: Mirtazapine	Reduction of symptoms	MD 0.69 (-0.92 to 2.26)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	No evidence	-	-
		Fluoxetine: Venlafaxine	Reduction of symptoms	MD 0.27 (-1.22 to 1.72)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	No evidence	-	-

		Imipramine: Paroxetine	Reduction of symptoms	MD 1.70 (-1.46 to 4.89)	(1 RCT)	⊕◯◯◯ Very Low
			Acceptability	OR 2.29 (0.60 to 9.70)	(1 RCT)	⊕◯◯◯ Very Low
		Mirtazapine: Paroxetine	Reduction of symptoms	MD -0.83 (-2.12 to 0.45)	(3 RCTs)	⊕⊕◯◯ Low
			Acceptability	OR 2.72 (0.53 to 15.66)	(3 RCTs)	⊕◯◯◯ Very Low
		Paroxetine: Quetiapine	Reduction of symptoms	MD 1.32 (-0.06 to 2.70)	(1 RCT)	⊕⊕◯◯ Low
			Acceptability	OR 0.86 (0.65 to 1.14)	(1 RCT)	⊕⊕⊕◯ Moderate
		Paroxetine: Tiagabine	Reduction of symptoms	MD -1.52 (-3.11 to 0.08)	(1 RCT)	⊕⊕◯◯ Low
			Acceptability	No evidence	-	-
		Paroxetine: Venlafaxine	Reduction of symptoms	MD 0.41 (-0.69 to 1.51)	(13 RCTs)	⊕◯◯◯ Very Low
			Acceptability	OR 1.26 (0.98 to 1.62)	(1 RCT)	⊕⊕⊕◯ Moderate

Notes. GAD: generalized anxiety disorder; OR: odd ratio; RCT: randomized controlled trial; SM: mean difference

Explanations

c. For all comparisons, negative Mean Difference (MD) effects indicate the comparator on the left of the comparison is more effective. Positive effects indicate the comparator on the right is more effective.

d. For all comparisons, OR above 1.00 indicate the comparator on the left of the comparison is more tolerable. OR below 1.00 indicate the comparator on the right of the comparison is more tolerable.

Table 4.2: Summary of findings table for all comparisons for adults with PD

GRADE table	Source	Comparison	Outcomes	Effects	№ of participants (studies)	Certainty of the evidence
Tables 3.5, 3.7, 3.9 (Antidepressants vs placebo in adults with PD)	Chawla et al. (2019)	SSRIs: Placebo[a]	Reduction of symptoms (Remission)[b]	RR 1.38 (1.26 to 1.54)	(18 RCTs)	⊕⊕⊕◯ Moderate
			Adverse effects[c]	RR 1.19 (1.01 to 1.41)	(13 RCTs)	⊕⊕◯◯ Low
			Acceptability[c]	RR 0.92 (0.77 to 1.10)	(21 RCTs)	⊕⊕◯◯ Low
		TCAs: Placebo[d]	Reduction of symptoms (Remission) [b]	RR 1.39 (1.26 to 1.54)	(12 RCTs)	⊕⊕⊕◯ Moderate
			Adverse effects[c]	RR 1.79 (1.47 to 2.19)	(6 RCTs)	⊕⊕⊕◯ Moderate
			Acceptability[c]	RR 0.71 (0.58 to 0.88)	(20 RCTs)	⊕⊕◯◯ Low

Notes. PD: panic disorder; RCT: randomized controlled trial; RR: risk ratio; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants

Explanations

a. SSRIs included in Chawla et al.'s review include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

b. For all comparisons on remission, RR above 1.00 indicate favour the drug. RR below 1.00 favour placebo.

c. For all comparisons on adverse effects and acceptability, RR above 1.00 favour placebo. RR below 1.00 favour the drug.

d. TCAs included in Chawla et al.'s review include imipramine and clomipramine.

GRADE table	Source	Comparison	Outcomes	Effects	№ of participants (studies)	Certainty of the evidence
Table 3.6, 3.8, 3.10 (Antidepressants vs. alternative pharm interventions in adults with PD)	Chawla et al. (2019)[a]	BZD: SSRI	Reduction of symptoms (Remission)	RR 1.07 (0.96 to 1.19)	(1 RCT)	⨁⨁⨁◯ Moderate
			Adverse effects	RR 1.47 (1.18 to 1.84)	(1 RCT)	⨁⨁⨁◯ Moderate
			Acceptability	RR 0.51 (0.38 to 0.67)	(1 RCT)	⨁⨁⨁◯ Moderate
		TCA: BZD	Reduction of symptoms (Remission)	RR 0.94 (0.85 to 1.05)	(6 RCTs)	⨁⨁◯◯ Low
			Adverse effects	RR 1.02 (0.83 to 1.25)	(5 RCTs)	⨁◯◯◯ Very Low
			Acceptability	RR 1.54 (1.19 to 1.99)	(9 RCTs)	⨁⨁◯◯ Low
		TCA: Buspirone	Reduction of symptoms (Remission)	RR 1.26 (0.83 to 1.92)	(2 RCTs)	⨁⨁◯◯ Low
			Adverse effects	RR 2.45 (1.30 to 4.62)	(1 RCT)	⨁⨁⨁◯ Moderate
			Acceptability	RR 0.40 (0.21 to 0.74)	(3 RCTs)	⨁◯◯◯ Very Low
		MAOI: SSRI	Reduction of symptoms (Remission)	RR 0.94 (0.73 to 1.21)	(1 RCT)	⨁⨁◯◯ Low
			Adverse effects	RR 1.05 (0.71 to 1.54)	(1 RCT)	⨁⨁◯◯ Low
			Acceptability	RR 1.08 (0.53 to 2.22)	(1 RCT)	⨁⨁◯◯ Low

		SSRI: NRI	Reduction of symptoms (Remission)	RR 1.06 (0.67 to 1.69)	(1 RCT)	⊕◯◯◯ Very Low
			Adverse effects	RR 1.12 (0.75 to 1.69)	(2 RCTs)	⊕⊕◯◯ Low
			Acceptability	RR 1.32 (0.62 to 2.81)	(1 RCT)	⊕⊕◯◯ Low
		SSRI: SNRI	Reduction of symptoms (Remission)	RR 1.08 (0.95 to 1.24)	(2 RCTs)	⊕⊕⊕◯ Moderate
			Adverse effects	RR 0.96 (0.69 to 1.35)	(1 RCT)	⊕⊕◯◯ Low
			Acceptability	RR 1.13 (0.76 to 1.67)	(2 RCTs)	⊕⊕◯◯ Low
		TCA: SSRI	Reduction of symptoms (Remission)	RR 1.01 (0.89 to 1.14)	(5 RCTs)	⊕⊕◯◯ Low
			Adverse effects	RR 1.50 (1.20 to 1.88)	(3 RCTs)	⊕⊕◯◯ Low
			Acceptability	RR 0.78 (0.61 to 0.99)	(7 RCTs)	⊕⊕◯◯ Low

Notes. BZDs: benzodiazepines; MAOIs: monoamine oxidase inhibitors; NRI: norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCAs: tricyclic anti-depressants

Explanations

a. SSRIs included in Chawla et al.'s review include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. TCAs include imipramine and clomipramine.

b. For all comparisons on remission, RR below 1.00 indicate the drug on the left of the comparison is more effective. RR above 1.00 indicate the drug on the right of the comparison is more effective.

c. For all comparisons on adverse events and acceptability, RR above 1.00 favour the drug on the right of the comparison. RR below 1.00 favour the drug on the left of the comparison.

4.2 Evidence to Decision

Table 5: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☒ **Trivial (antidepressants vs alternative pharmacological interventions)** ☒ **Small (antidepressants vs placebo)** ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	**Antidepressants vs Placebo** Evidence suggested a significant benefit of **SSRIs** (citalopram (2 RCTs), escitalopram (13 RCTs), fluoxetine (8 RCTs), paroxetine (17 RCTs) and sertraline (6 RCTs)) vs placebo on anxiety symptom reduction in **adults with GAD** (range: MD -2.22 to -2.88)**.** Evidence suggested a no difference in comparing **TCAs** (impramine (1 RCT)) vs placebo on anxiety symptom reduction in **adults with GAD.** Evidence suggested a significant benefit of **SSRIs** (18 RCTs) vs placebo on anxiety symptom reduction in **adults with PD.** Evidence suggested a significant benefit of **TCAs** (12 RCTs) vs placebo on anxiety symptom reduction in **adults with PD.** **Antidepressants vs Alternative Pharmacological Interventions** Evidence did not suggest significant differences between **SSRIs** (e.g. citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) and any other drug classes reviewed (e.g. SNRIs, MAOIs, anticonvulsants, atypical antipsychotics, benzodiazepines) on anxiety symptom reduction in **adults with GAD**.	**Antidepressants vs Placebo:** In Chawla et al. (2019), according to SUCRA and clustered ranking plots for individual SSRIs, sertraline and escitalopram represented the most efficacious agents with the lowest risk of adverse events. Fluvoxamine, paroxetine, and fluoxetine indicated favourable efficacy but higher risk of adverse events, whereas citalopram showed minimal efficacy in remission and high risk of adverse events. **Antidepressants vs Alternative Psychological Interventions** Mitte (2005) examined CBT and pharmacotherapy (primarily benzodiazepines) in six direct comparison studies. Very low-quality evidence indicated that CBT and pharmacotherapy were not significantly different (SMD = 0.33; 95% CI -0.02 to 0.67) and comparison also demonstrated a significantly lower dropout rate for CBT. Roshanaei-Moghaddam et al. (2011) reported very low quality evidence from 21 RCTs indicating minimal to

Criteria, questions	Judgement	Research evidence	Additional considerations
		Evidence also did not suggest significant differences between **SSRIs** (e.g. citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) and any other drug classes (e.g. SNRIs, MAOIs, anticonvulsants, atypical antipsychotics, benzodiazepines) on anxiety symptom reduction in **adults with PD**. **<u>Antidepressants vs Alternative Psychological Interventions</u>** Only one review (Chen et al., 2019) was identified in the current review period. This review attempted to address this comparison for adults with GAD. However, it could not be GRADED due to lack of data for CINeMA rating of meta-analytic reviews. Additionally, results of the comparison reported in the review were inconclusive due to limited trials conducting direct comparisons. See 'Additional Considerations' for further information from additional reviews which were not included in the GRADE tables because they were published outside the review period. Taken together, results appear to indicate no consistent difference between antidepressants and psychological interventions.	non-existent differences between medications and psychotherapy for adults with any anxiety disorder (SMD = 0.25; 95% CI -0.02 to 0.51), low quality evidence from 11 RCTs indicating effects significantly favoured CBT over medications for adults with PD (SMD = .50, 95% CI: 0.02 to 0.98), and very low quality evidence from one RCT indicating non-significant effects favouring CBT over medications for adults with GAD (SMD = 0.88; 95% CI: -0.04 to 1.80). Cuijpers et al. (2013) reported low quality evidence from 30 RCTs that indicated minimal to non-existent differences between medications and psychotherapy for adults with any anxiety disorder (SMD = 0.10; 95% CI -0.05 to 0.25), moderate quality evidence from 11 RCTs that indicated minimal to non-existent differences between medications and psychotherapy for adults with PD (SMD = 0.00; 95% CI -0.28 to 0.28), and one RCT comparing psychotherapy and antidepressants for GAD where results were not reported. Bandelow et al. (2015) conducted a meta-analysis comparing the absolute (pre–post) and relative (treated vs. control) effect sizes of

Criteria, questions		Judgement	Research evidence	Additional considerations
				psychotherapies and pharmacotherapies compared to placebo or waitlist for GAD, PD, and SAD. Head-to-head comparison of psychotherapy and pharmacotherapy was not reported. Overall, low to very-low quality evidence indicated medications were associated with a significantly higher average pre–post effect sizes (Cohen's d = 2.02; 95% CI: 1.90 to 2.15); 28 051 patients) than psychotherapies (d = 1.22; 95% CI: 1.14 to 1.30); 6992 patients; P<0.0001) for adults with any anxiety disorder (GAD, PD, or social anxiety disorder).
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☒ **Small** ☐ Trivial ☐ Varies ☐ Don't know	**<u>Antidepressants vs Placebo</u>** Evidence suggested an increased risk of **dropout** using one of five SSRIs examined (paroxetine (17 RCTs)) compared to placebo in **adults with GAD.** Evidence suggested no difference in risk of **dropout** using **TCAs** (1 RCT) compared to placebo in **adults with GAD**. Evidence suggested an increased risk of **adverse events** using **SSRIs** (18 RCTs) compared to placebo in **adults with PD.** Evidence suggested no difference in risk of **dropout** using **SSRIs** (21 RCTs) compared to placebo in **adults**	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			with PD. Evidence suggested an increased risk of **adverse events** using **TCAs** (6 RCTs) compared to placebo in **adults with PD.** Evidence suggested a decreased risk of **dropout** using TCAs (20 RCTs) compared to placebo in **adults with PD.** **<u>Antidepressants vs Alternative Pharmacological Interventions</u>** Evidence suggested no difference in risk of **dropout** using **SSRIs and TCAs** (e.g. impramine, citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) compared to other drug classes reviewed (e.g. SNRIs, MAOIs, anticonvulsants, atypical antipsychotics, benzodiazepines) in **adults with GAD**. Evidence suggested a decreased risk of **adverse events** using **SSRIs** compared to benzodiazepines (1 RCT) and TCAs (3 RCTs) and no difference in risk compared to SNRIs, (1 RCT), NRIs (2 RCTs) and MAOIs (1 RCT) in **adults with PD.** Evidence suggested an increased risk of **adverse events** using **TCAs** compared to buspirone (1 RCT) and SSRIs (3 RCTs) and no difference in risk compared to benzodiazepines (5 RCTs) in **adults with PD.** Evidence suggested an increased risk of **dropout** using **SSRIs** compared to benzodiazepines (1 RCT)	

Criteria, questions		Judgement	Research evidence	Additional considerations
			and TCAs (7 RCTs) and no difference in risk compared to SNRIs, (2 RCT), NRIs (2 RCTs) and MAOIs (1 RCT) in **adults with PD.** Evidence suggested an increased risk of **dropout** using **TCAs** compared to benzodiazepines (9 RCT) and a decreased risk compared to buspirone (3 RCTs) and SSRIs (7 RCTs) **adults with PD.** **Antidepressants vs Alternative Psychological Interventions** No evidence identified.	
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	**Antidepressants vs Placebo** The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with GAD** using **SSRIs** vs placebo was LOW. The overall certainty of the evidence for **acceptability** in **adults with GAD** using **SSRIs** vs placebo was MODERATE. The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with GAD** using **TCAs** vs placebo was VERY LOW. The overall certainty of the evidence for **acceptability** in **adults with GAD** using **TCAs** vs placebo was VERY LOW.	**Antidepressants vs Alternative Psychological Interventions** Overall, evidence examining direct comparisons of antidepressants vs psychological interventions appeared to be of low or very low quality where quality assessments were feasible.

Criteria, questions		Judgement	Research evidence	Additional considerations
			The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with PD** using **SSRIs** vs placebo was MODERATE. The overall certainty of the evidence for **adverse events** in **adults with PD** using **SSRIs** vs placebo was LOW. The overall certainty of the evidence for **acceptability** in **adults with PD** using **SSRIs** vs placebo was LOW. The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with PD** using **TCAs** vs placebo was MODERATE. The overall certainty of the evidence for **adverse events** in **adults with PD** using **TCAs** vs placebo was MODERATE. The overall certainty of the evidence for **acceptability** in **adults with PD** using **TCAs** vs placebo was LOW. **<u>Antidepressants vs Alternative Pharmacological Interventions</u>** The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with GAD** using **SSRIs** compared with other drug classes was LOW. The overall certainty of the evidence for **acceptability** in **adults with GAD** using **SSRIs** compared with other drug classes was MODERATE.	

Criteria, questions		Judgement	Research evidence	Additional considerations
			The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with GAD** using **TCAs** compared with other drug classes was VERY LOW. The overall certainty of the evidence for **acceptability** in **adults with GAD** using **TCAs** compared with other drug classes was VERY LOW. The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with PD** using **SSRIs** compared with other drug classes was LOW. The overall certainty of the evidence for **adverse events** in **adults with PD** using **SSRIs** compared with other drug classes was LOW. The overall certainty of the evidence for **acceptability** in **adults with PD** using **SSRIs** compared with other drug classes was LOW. The overall certainty of the evidence for **reduction of anxiety symptoms** in **adults with PD** using **TCAs** compared with other drug classes was LOW. The overall certainty of the evidence for **adverse events** in **adults with PD** using **TCAs** compared with other drug classes was LOW. The overall certainty of the evidence for **acceptability** in **adults with PD** using **TCAs** compared with other drug classes was LOW. **Antidepressants vs Alternative Psychological Interventions**	

Criteria, questions		Judgement	Research evidence	Additional considerations
			No evidence identified.	
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	A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	
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, considering 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)?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the	**Antidepressants vs Placebo** Low quality evidence indicated a significant benefit of SSRIs compared to placebo in the reduction of anxiety symptoms in adults with GAD and no difference in risk of dropout using four of five SSRIs studied.	**Antidepressants vs Alternative Psychological Interventions** See 'Additional Considerations' in this table for the 'Desirable Effects' criteria. In sum, there appears to be no consistent evidence of a significant difference between antidepressants and alternative

Criteria, questions		Judgement	Research evidence	Additional considerations
	- People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	intervention or the comparison ☒ **Probably favours the intervention (antidepressants vs placebo)** ☐ Favours the intervention ☒ **Varies (antidepressants vs alternative pharmacological interventions)** ☐ Don't know	**Thus, the effects favour the use of SSRIs in adults with GAD.** Very low-quality evidence indicated no benefit of TCAs compared to placebo in the reduction of anxiety symptoms in adults with GAD and no difference in risk of dropout. **Thus, the effects do not favour either the use of TCAs or the comparison in adults with GAD.** Moderate quality evidence indicated a significant benefit of SSRIs compared to placebo in the reduction of anxiety symptoms in adults with PD, an increased risk of adverse events using SSRIs and no difference in dropout using SSRIs compared to placebo. **Thus, the effects probably favour the use of SSRIs in adults with PD.** Moderate quality evidence indicated a significant benefit of TCAs compared to placebo in the reduction of anxiety symptoms in adults with PD, an increased risk of adverse events using TCAs and a decreased risk of dropout using TCAs compared to placebo. **Thus, the effects probably favour the use of TCAs in adults with PD.** **<u>Antidepressants vs Alternative Pharmacological Interventions</u>** Low quality evidence did not indicate significant differences between SSRIs and TCAs and other drug classes in the reduction of anxiety symptoms or risk of dropout in adults with GAD. **Thus, the effects do not favour either antidepressants or alternative pharmacological**	psychological interventions. **Thus, the effects do not appear to favour either SSRIs or TCAs over alternative psychological interventions in adults with anxiety disorders**

Criteria, questions		Judgement	Research evidence	Additional considerations
			interventions in adults with GAD. Low quality evidence did not indicate significant differences between SSRIs and TCAs and other drug classes in the reduction of anxiety symptoms in adults with PD. Low quality evidence did indicate a decreased risk of adverse events and an increased risk of dropout using SSRIs compared to benzodiazepines and an increased risk of adverse events and dropout using TCAs compared to benzodiazepines. There was no difference in risk for adverse events or dropout using SSRIs or TCAs compared to SNRIs, NRIs and MAOIs in adults with PD**. Thus, the effects do not favour either SSRIs or TCAs over alternative pharmacological interventions reviewed in adults with PD.** **Antidepressants vs Alternative Psychological Interventions** No evidence identified in the review period. Additional considerations appear to indicate no significant difference between antidepressants and psychological interventions.	
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 fewer resources are required? • How large is the difference in each item of resource use for which more 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	There was no direct evidence to evaluate resource requirements. However, a recent global study described the investment case for scaling up the response to public health and economic burden of common mental disorders, including depression and anxiety disorders. Results indicated the benefit to cost ratios for anxiety disorders ranged from 3.3 to 4.0, indicating a substantial return on investment	Anecdotal evidence indicates in many low- and middle-income countries, continuous availability of psychotropics in non-specialized health care is a challenge. However, both generic TCAs and many generic SSRIs are associated with low acquisition costs.

Criteria, questions		Judgement	Research evidence	Additional considerations
		☐ Large savings ☐ Varies ☒ **Don't know**	in increased economic productivity and improved health *(21)*.	
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**	No direct evidence identified.	No 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?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison	No reviews that examined cost effectiveness were identified.	Ophuis et al. (2017) indicated that four out of five studies comparing psychological interventions with pharmacological interventions showed that psychological interventions were more cost-effective than pharmacotherapy. In many low- and middle-income countries, continuous availability of

Criteria, questions		Judgement	Research evidence	Additional considerations
	• Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Probably favours the intervention ☐ Favours the intervention ☒ **Varies** ☐ No included studies		psychotropics in non-specialized health care is a challenge. Both generic TCAs and many generic SSRIs are associated with low acquisition costs.
Health equity, equality, and non-discrimination	What would be the impact on health equity, equality and non-discrimination? 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	*The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available, and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers. • Affordability - medication and treatment costs. These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials). • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities. • Low resource settings - affordability/cost considerations exacerbated.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
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	The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 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** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) 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 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: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			• 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.	

Notes. BZDs: benzodiazepines; CBT: cognitive behavioural therapy; CI: confidence interval; CINeMA: ;GAD: generalized anxiety disorder; GDG: guidelines development group; MAOIs: monoamine oxidase inhibitors; MNS: mental, neurological and substance use; NRI: norepinephrine reuptake inhibitor; PD: panic disorder; RCT: randomized controlled trial; SMD: standard mean difference; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin norepinephrine reuptake inhibitor; TCAs: tricyclic anti-depressants

4.3. Summary of judgements

Table 6: Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects – placebo comparison	- Don't know	Varies		Trivial	✓ **Small**	- Moderate	- Large
Desirable effects – active comparison	- Don't know	Varies		✓ **Trivial**	- Small	- Moderate	- Large
Undesirable effects – placebo comparison	- Don't know	- Varies		- Large	- Moderate	✓ **Small**	Trivial
Undesirable effects – active comparison	- 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 – placebo comparison	- Don't know	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	✓ **Probably favours intervention**	- Favours intervention
Balance of effects – active comparison	- Don't know	✓ **Varies**	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours 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**	- Favours no intervention	- Probably favours no intervention	- Does not favour either	- Probably favours intervention	- Favours 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

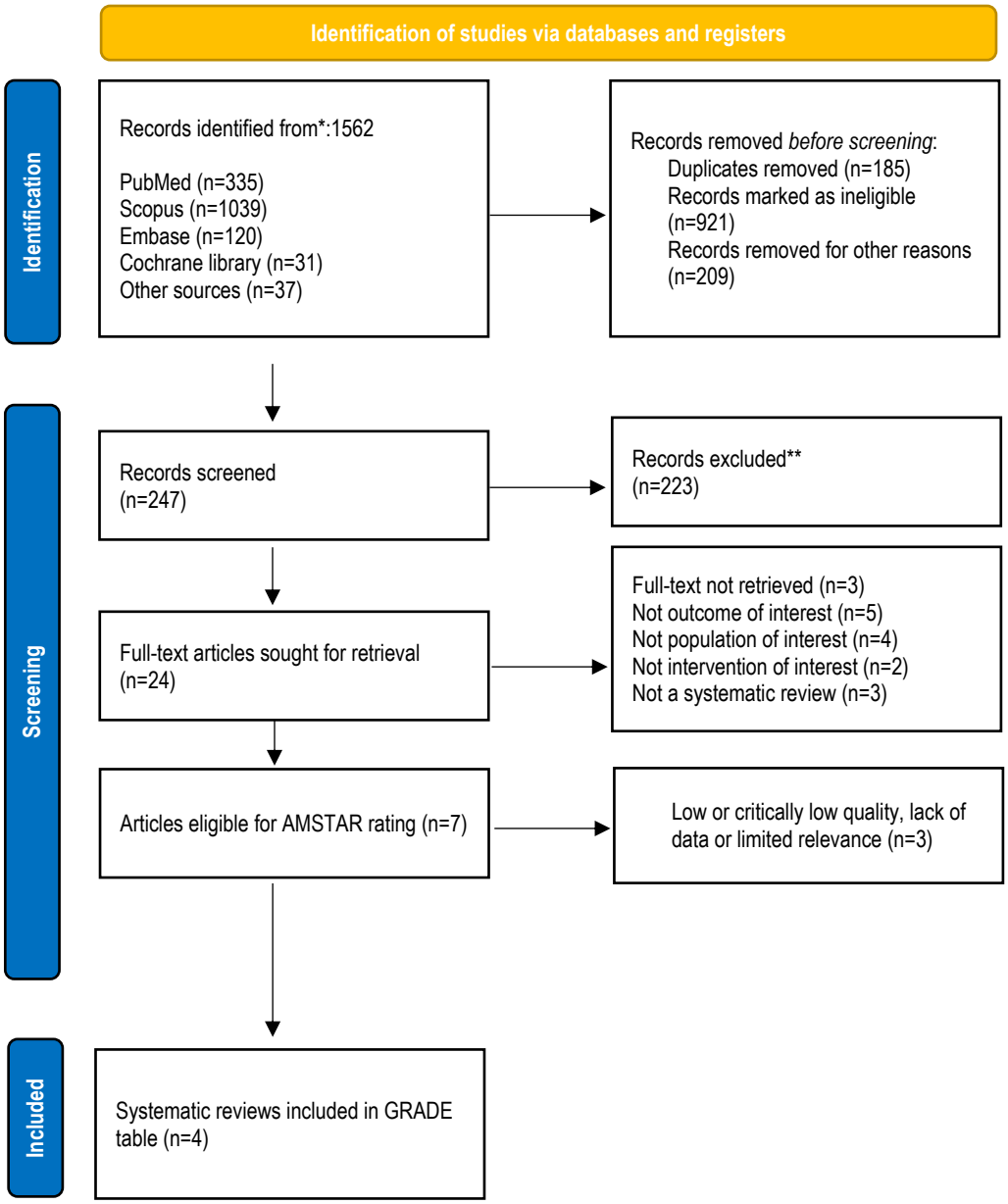
✓Indicates category selected, - Indicates category not selected.

QUESTION 2

Is brief, structured psychological intervention (e.g. CBT, PST) in non-specialist care settings better (more effective/as safe as) than treatment as usual, waitlist, no treatment in people with anxiety disorders (excluding SAD, specific phobias)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 2: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #2.



3.1.1. Included in GRADE tables/footnotes

1. Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. BMC Fam Pract. 2021;22(1):92. doi:10.1186/s12875-021-01445-5
2. Haller H, Breilmann P, Schröter M, Dobos G, Cramer H. A systematic review and meta-analysis of acceptance- and mindfulness-based interventions for DSM-5 anxiety disorders. Sci Rep. 2021;11(1):20385. doi:10.1038/s41598-021-99882-w
3. van Dis EAM, van Veen SC, Hagenaars MA, Batelaan NM, Bockting CLH, van den Heuvel RM, et al. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2020;77(3):265-73. doi:10.1001/jamapsychiatry.2019.3986
4. Papola D, Ostuzzi G, Tedeschi F, Gastaldon C, Purgato M, Del Giovane C, Pompoli A, Pauley D, Karyotaki E, Sijbrandij M, Furukawa TA, Cuijpers P, Barbui C. Comparative efficacy and acceptability of psychotherapies for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. Br J Psychiatry. 2021 Oct 6:1-13. doi: 10.1192/bjp.2021.148

3.1.2. Excluded from GRADE tables/footnotes

1. Zhang A, Borhneimer LA, Weaver A, Franklin C, Hai AH, Guz S, et al. Cognitive behavioral therapy for primary care depression and anxiety: a secondary meta-analytic review using robust variance estimation in meta-regression. J Behav Med. 2019;42(6):1117-41. doi:10.1007/s10865-019-00132-2
2. Li J, Cai Z, Li X, Du R, Shi Z, Hua Q, et al. Mindfulness-based therapy versus cognitive behavioral therapy for people with anxiety symptoms: a systematic review and meta-analysis of random controlled trials. Ann Palliat Med. 2021;10(7):7596-612. doi:10.21037/apm-21-1212
3. Barbui C, Purgato M, Abdulmalik J, Acarturk C, Eaton J, Gastaldon C, et al. Efficacy of psychosocial interventions for mental health outcomes in low-income and middle-income countries: an umbrella review. Lancet Psychiatry. 2020;7(2):162-72. doi:10.1016/S2215-0366(19)30511-5

Table 7: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 2	brief, structured psychological treatment	Reduction of symptoms	Parker et al. (2021); Van Dis et al. (2020); Papola et al. (2021)	Parker et al. (2021) and Van Dis et al. (2020) were chosen over Haller et al. (2021) and for post treatment symptom reduction because Parker et al. (2021) reviewed studies in non-specialist care settings (vs specialist or highly controlled care settings) and Van Dis et al. (2020) reported outcomes specific to GAD while others did not. Papola was selected over Van Dis et al. (2020) for PD outcomes because Papola was more recent and included more studies and participants.
		Adverse events	Haller et al. (2021)	Haller et al. (2021) was chosen for adverse events because Parker et al. (2021) and Van Dis et al. (2020) did not report adverse events.
		Acceptability profile (number of dropouts)	Haller et al. (2021); Papola et al. (2021)	Haller et al. (2021) was chosen for acceptability in adults with anxiety disorders because Parker et al. (2021) and Van Dis et al. (2020) did not report number of dropouts. Papola et al. (2021) was selected over Haller et al. (2021) for acceptability in adults with PD because it was a larger study concerning more participants and trials.
		Sustained response	Van Dis et al. (2020)	Van Dis et al. (2020) was chosen over Parker et al. (2021) for long-term symptom reduction because Parker et al (2021) did not report pooled effects for long-term symptom reduction.
		Functioning	No evidence	No evidence.

GAD: generalized anxiety disorder; PD: panic disorder

3.2. Narrative description of studies that contributed to GRADE analysis

Haller et al. (2021) conducted a meta-analysis systematically reviewed the evidence on standardized psychological interventions on anxiety disorders. In total, 23 RCTs were included in the review. Studies investigated patients diagnosed with GAD, SAD, and mixed anxiety diagnoses. Twelve RCTs investigated acceptance and commitment therapy (ACT) interventions, three mindfulness-based cognitive therapy (MBCT), and eight mindfulness-based stress reduction (MBSR). Individual- and group-based approaches varied as well as online and offline/in-person settings. Control interventions included treatment as usual/waitlist, psychoeducation, and relaxation. The median duration of the study treatments was 10 (4 to 16) weeks.

Parker et al. (2021) conducted a systematic review and meta-analysis of the effects of psychological and pharmacological interventions on adults with anxiety disorders treated in primary care settings. A total of 19 articles reporting 18 studies met all criteria and were included in our review. Two articles reported separate steps of the same study, and eight studies involved more than one active treatment condition. Across all studies, there were 28 comparisons of active treatment with a control group (placebo, waitlist control, or care as usual). In the included studies, 2 059 participants were randomized to an active treatment condition and 1 247 to a control condition. Thirteen studies investigated anxiety disorders specifically; four generalized anxiety disorder (22.2% of 18), four panic disorder with or without agoraphobia (22.2% of 18), and five investigated multiple anxiety disorders (including mixed anxiety/depression; 27.8% of 18). Psychological interventions were predominantly CBT (n = 13, 81.2% of 16) and provided on an individual basis.

Papola et al. (2021) conducted a systematic review and network meta-analysis of RCTs to examine the most effective and accepted interventions for panic disorder. A total of 136 studies were eligible for inclusion in the systematic review. Overall, 9559 participants were randomized to 10 different psychotherapies (behavioural therapy, CBT, cognitive therapy, EMDR, interpersonal therapy, physiological therapies, psychodynamic therapies, psychoeducation, supportive psychotherapy and third-wave CBT) and six different control conditions (antidepressants, attention or psychological placebo, benzodiazepines, placebo, treatment as usual, waiting list).

van Dis et al. (2020) conducted a systematic review and meta-analysis that aimed to assess the long-term outcomes after CBT (compared with care as usual, relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list) for anxiety disorders. In total, 69 published studies (reported in 73 records) met our inclusion criteria: 14 studies on GAD, 13 studies on PD, seven studies on SAD, three studies on specific phobia, 30 studies on post-traumatic stress disorder (PTSD), and two studies on obsessive compulsive disorder (OCD). A total of 4118 unique patients were enrolled (age and sex not available in the final analyses). The studies examined CBT (number of studies [k] = 42), exposure therapy, (k = 26), cognitive therapy (k = 10), cognitive reprocessing (k = 1), metacognitive therapy (k = 1), applied tension (k = 1), and ACT (k = 1). Comparison groups consisted of care as usual (k = 13), relaxation (k = 24), psychoeducation (k = 2), pill placebo (k = 5), supportive therapy (k = 14), waiting list (k = 12), and tension only (k = 1). Multiple treatment or comparison groups within one study were pooled together (k = 9). We found 41 studies reporting outcomes at one to six months, 34 studies at six to 12 months, and 24 studies at more than 12 months of follow-up.

3.3. Grading the Evidence

Table 8: Brief, Structured psychological interventions vs treatment as usual, waitlist, no treatment

Author(s): Brandon Gray and Biksegn Asrat
Question: Is brief, structured psychological intervention (e.g. CBT, Problem Solving Therapy) in non-specialist care settings better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?
Setting: non-specialist care settings
Reference List:
Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. BMC Fam Pract. 2021;22(1):92. doi:10.1186/s12875-021-01445-5

Haller H, Breilmann P, Schröter M, Dobos G, Cramer H. A systematic review and meta-analysis of acceptance- and mindfulness-based interventions for DSM-5 anxiety disorders. Sci Rep. 2021;11(1):20385. doi:10.1038/s41598-021-99882-w

van Dis EAM, van Veen SC, Hagenaars MA, Batelaan NM, Bockting CLH, van den Heuvel RM, et al. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2020;77(3):265-73. doi:10.1001/jamapsychiatry.2019.3986

Papola D, Ostuzzi G, Tedeschi F, Gastaldon C, Purgato M, Del Giovane C, Pompoli A, Pauley D, Karyotaki E, Sijbrandij M, Furukawa TA, Cuijpers P, Barbui C. Comparative efficacy and acceptability of psychotherapies for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. Br J Psychiatry. 2021 Oct 6:1-13. doi: 10.1192/bjp.2021.148

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	brief, structured psychological intervention	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures)												
10[b]	randomized trials	not serious	serious[c]	not serious	not serious	publication bias strongly suspected[d]	761	650	-	SMD **0.49 SD higher** (0.1 higher to 0.88 higher)[e]	⨁⨁⨁◯ Moderate	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD (assessed with multiple measures)												
14[f]	randomized trials	serious[g]	serious[h]	not serious	not serious	none	369	354	-	SMD **0.39 SD higher** (0.12 higher to 0.66 higher)	⨁⨁◯◯ Low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with PD (assessed with multiple measures)												
31	See NMA tables 2.2 and 2.3 below											
Adverse events in adults with mixed anxiety disorders												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	brief, structured psychological intervention	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
5[i]	randomized trials	not serious	not serious	serious[j]	very serious[k]	none	Safety data were reported insufficiently across studies, indicating adverse events (AE) in 5/204 participants in the psychotherapy groups vs 1/148 in the comparison group. Fourteen RCTs did not report any information on AEs or reasons for study withdrawal. Serious AEs were reported by one RCT in the intervention group (bypass surgery), which was highly likely not related to the study intervention. Minor AEs were equally distributed between experimental and control groups.				⨁◯◯◯ Very low	CRITICAL
Adverse events in adults with GAD												
0	no evidence								not estimable		-	CRITICAL
Adverse events in adults with PD												
0	no evidence								not estimable		-	CRITICAL

Acceptability profile in adults with mixed anxiety disorders (assessed with number of dropouts)

2[i]	randomized trials	not serious	not serious	serious[j]	very serious[k]	none	Dropouts were reported in a minority of studies and results were not pooled. Instead, studies indicated dropouts in 4/72 (5.6%) of participants in the intervention group versus 2/78 (2.6%) of participants in the comparison group.				⊕◯◯◯ Very low	IMPORTANT

Acceptability profile in adults with GAD

0	no evidence								not estimable		-	IMPORTANT

Acceptability profile in adults with PD

29	See NMA tables 3.4 and 3.5 below								not estimable		-	IMPORTANT

Sustained reduction of anxiety symptoms in adults with mixed anxiety disorders

0	no evidence								not estimable		-	IMPORTANT

Sustained reduction of anxiety symptoms in adults with GAD (follow-up: range 6 months to 12 months; assessed with: multiple measures)

11[f]	randomized trials	serious[g]	serious[l]	not serious	not serious	none	337	323	-	SMD **0.4 SD higher** (0.13 higher to 0.67 higher)	⊕⊕◯◯ Low	IMPORTANT

Sustained reduction of anxiety symptoms in adults with PD (follow-up: range 6 months to 12 months; assessed with: multiple measures)

9[f]	randomized trials	serious[g]	not serious	not serious	not serious	none	310	216	-	SMD **0.35 SD higher** (0.11 higher to 0.59 higher)[m]	⊕⊕⊕◯ Moderate	IMPORTANT

Functioning in adults with mixed anxiety disorders

0	no evidence								not estimable		-	IMPORTANT

Functioning in adults with GAD

0	no evidence								not estimable		-	IMPORTANT

Functioning in adults with PD

0	no evidence								not estimable		-	IMPORTANT

Notes. CI: confidence interval; GAD: generalized anxiety disorder; NMA: network meta-analyses; PD: panic disorder; RR: risk ratio; SMD: standardized mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Parker et al. (2021).

c. I squared = 81.25%; p = 0.00. The effects of one moderator (treatment provider) accounted for 53% of heterogeneity but the remainder could not be explained with certainty.

d. Egger's regression test showed significant funnel plot asymmetry (z = 3.70, p < 0.001), indicating possible publication bias.

e. This effect pools studies comparing psychological interventions vs treatment as usual and waitlist combined. Parker et al. (2021) also reported sub analyses of psychological interventions vs care as usual and vs waitlist individually, which also confirm these main findings. Subgroup analyses also compared specialist providers vs care as usual and waitlist and non-specialist providers vs care as usual and waitlist, with specialist providers demonstrating much larger effects.

f. Van Dis et al. (2020).

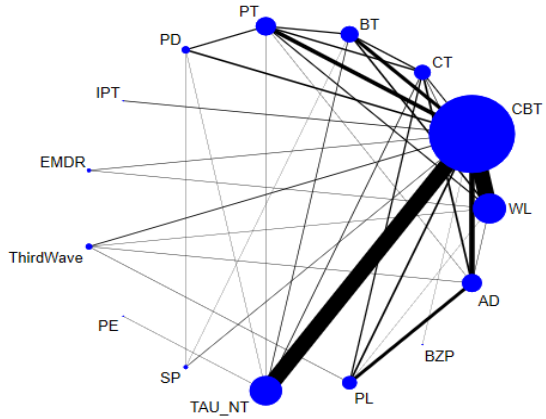
g. Approximately 50% of studies are at risk of bias due to incomplete outcome data (Figure 2).

h. I squared = 67%.
i. Haller et al. (2021).
j. Studies included participants with excluded diagnoses.
k. Sample size and confidence intervals indicate potential imprecision.
l. I squared = 59.00%.
m. Van Dis et al. (2020) also examined relapse rates but did not pool results and instead presented outcomes by study. Overall, relapse rates were relatively low in three of seven comparisons, relapse occurred after successful CBT and relapse rates ranged from 0% to 14%. In total, relapse was reported in 3/77 (3.9%) participants in the intervention group versus 0/39 (0.00%) in the comparison group.

Table 8.1 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: psychological interventions
Comparator (reference): waitlist
Outcome: efficacy (symptom reduction)
Setting(s): non-specialist care settings; specialist care settings
Reference: Papola et al. (2021)

Geometry of the Network*



	Odds ratio** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of studies
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
CBT	-1.03[a] (-1.21 to -0.85)	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	⨁⨁⨁⨁ High	78.3%	31 RCTs

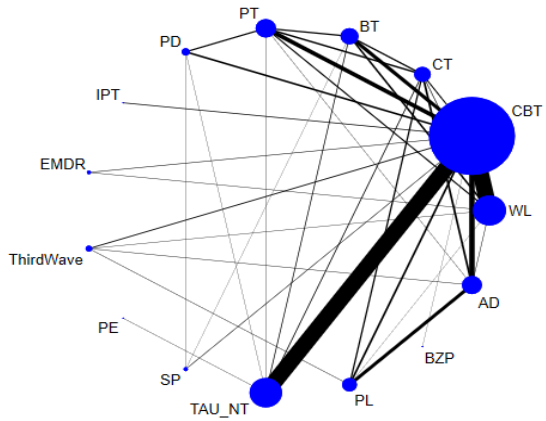
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CBT: cognitive behavioural therapy; CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking.

Explanations
a. For this comparison, the effect favours the intervention.

Table 8.2 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with PD
Interventions: psychological interventions
Comparator (reference): treatment as usual
Outcome: efficacy (symptom reduction)
Setting(s): non-specialist care settings; specialist care settings
Reference: Papola et al. (2021)

Geometry of the Network*



	Odds ratio** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of studies
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
CBT	-0.67[a] (-0.95 to -0.39)	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	78.3%	12 RCTs

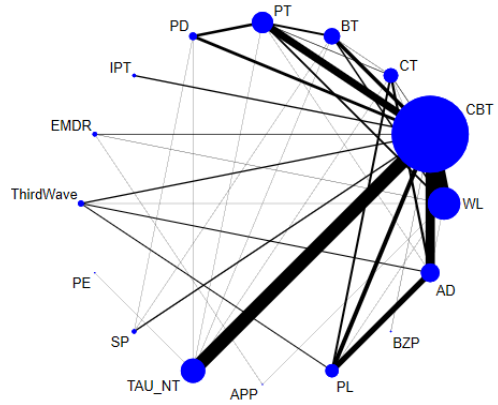
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CBT: cognitive behavioural therapy; CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking.

Explanations
a. For this comparison, the effect favours the intervention.

Table 8.3 Bayesian NMA-SoF table

Patient or population: adults with PD
Interventions: psychological interventions
Comparator (reference): waitlist
Outcome: acceptability (dropouts)
Setting(s): non-specialist care settings; specialist care settings
Reference: Papola et al. (2021)

Geometry of the Network*



	Risk ratio** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of studies
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
CBT	0.81[a] (0.65 to 1.00)	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	42.1%	29 RCTs

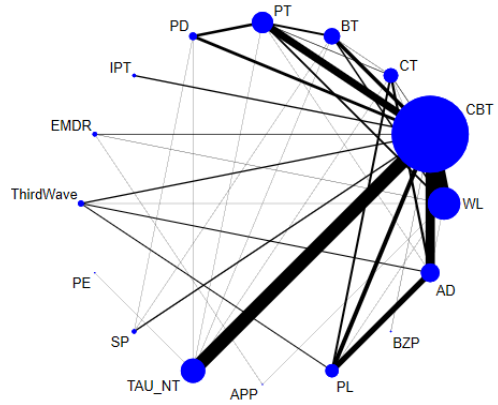
NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CBT: cognitive behavioural therapy; CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking.

Explanations
a. For this comparison, the effect favours the comparison.

Table 8.4 Bayesian NMA-SoF table

Patient or population: adults with PD
Interventions: psychological interventions
Comparator (reference): treatment as usual
Outcome: acceptability (dropouts)
Setting(s): non-specialist care settings; specialist care settings
Reference: Papola et al. (2021)

Geometry of the Network*



	Risk ratio** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of studies
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
CBT	0.83[a] (0.64 to 1.07)	Some concerns	Undetected	Some concerns	No concerns	No concerns	No concerns	⊕⊕⊕◯ Moderate	42.1%	8 RCTs

NMA-SoF table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio. CBT: cognitive behavioural therapy; CI: Confidence intervals; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking.

Explanations
a. For this comparison, the effect favours the comparison.

3.4. Additional evidence not mentioned in GRADE tables

No additional evidence.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 9: Summary of findings table

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence
Table 2 (Psychological interventions vs TAU, WL, no treatment)	Parker et al. (2021)	Reduction of anxiety symptoms (mixed anxiety disorders)	SMD **0.49 SD higher** (0.1 higher to 0.88 higher)	1411 (10 RCTs)	⊕⊕⊕◯ Moderate
	Van Dis et al. (2020)	Reduction of anxiety symptoms post- treatment in adults with GAD	SMD **0.39 SD higher** (0.12 higher to 0.66 higher)	723 (14 RCTs)	⊕⊕◯◯ Low
	Papola et al. (2021)	Reduction of anxiety symptoms post- treatment in adults with PD (compared to TAU)	SMD **0.67 SD lower** (0.95 lower to 0.39 lower)[b]	12 RCTs	⊕⊕⊕◯ Moderate
	Haller et al. (2021)	Adverse events in adults with mixed anxiety disorders	Effects reported are based on 352 participants from five RCTs. Safety data were reported insufficiently across studies, indicating adverse events (AE) in 5/204 participants in the psychotherapy groups vs 1/148 in the comparison group. Fourteen RCTs did not report any information on AEs or reasons for study withdrawal. Serious AEs were reported by one RCT in the intervention group (bypass surgery), which was highly likely not related to the study intervention. Minor AEs were equally distributed.		⊕◯◯◯ Very low

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence
	Haller et al. (2021)	Acceptability profile in adults with mixed anxiety disorders	Effects are based on 150 participants from 2 RCTs. Dropouts were reported in a minority of studies and results were not pooled. Instead, studies indicated dropouts in 4/72 (5.6%) of participants in the intervention group versus 2/78 (2.6%) of participants in the comparison group.		⊕◯◯◯ Very low
	Papola et al. (2021)	Acceptability profile in adults with PD (compared to TAU)	RR 0.83 higher (0.64 higher to 1.07 higher)	8 RCTs	⊕⊕⊕◯ Moderate
	Van Dis et al. (2020)	Sustained reduction of anxiety symptoms in adults with GAD	SMD **0.4 SD higher** (0.13 higher to 0.67 higher)	660 (11 RCTs)	⊕⊕◯◯ Low
	Van Dis et al. (2020)	Sustained reduction of anxiety symptoms in adults with PD	SMD **0.35 SD higher** (0.11 higher to 0.59 higher)	526 (9 RCTs)	⊕⊕⊕◯ Moderate

Notes. AE: adverse effect; CI: confidence interval; PD: panic disorder; RR: risk ratio; SMD: standardized mean difference; TAU: treatment as ususla; WL: waitlist

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. For this effect, negative values favour the intervention.

4.2. Evidence to Decision

Table 10: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	
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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	Evidence from 10 RCTs suggested a moderate, significant benefit of **structured psychological treatment** (e.g. CBT) on anxiety symptoms in **adults with mixed anxiety disorders** relative to treatment as usual, waitlist, no treatment. Evidence from 14 RCTs suggested a moderate, significant benefit of **structured psychological treatment** (e.g. CBT) on anxiety symptoms in **adults with GAD** relative to treatment as usual, waitlist, no treatment. Evidence from 12 RCTs suggested a moderate, significant benefit of **structured psychological treatment** (e.g. CBT) on anxiety symptoms in **adults with PD** relative to treatment as usual, waitlist, no treatment.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	Generally, data were reported insufficiently across studies on anxiety disorders generally, indicating adverse events (AE) in 5/204 participants in the psychotherapy groups vs 1/148 in the comparison group. Fourteen RCTs did not report any information on AEs or reasons for study withdrawal. Serious AEs were reported by one RCT in the intervention group (bypass surgery), which was highly likely not related to the study intervention. Minor AEs were equally distributed between experimental and control groups. Evidence from eight RCTs suggested a moderate, quality evidence indicated no difference in risk of dropout in **structured psychological treatment** (e.g. CBT) for **adults with PD** relative to treatment as usual, waitlist, no treatment.	No additional considerations.

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 overall certainty of the evidence for brief, structured psychological treatment was MODERATE. Certainty of the evidence for brief, structured psychological treatment vs TAU, WL, and no treatment for **adults with mixed anxiety disorders** was MODERATE due to inconsistency and risk of publication bias. Certainty of the evidence for brief, structured psychological treatment vs TAU, WL, and no treatment for **adults with GAD** was LOW due to inconsistency and risk of bias. Certainty of the evidence for brief, structured psychological treatment vs TAU, WL, and no treatment for **adults with PD** was MODERATE due to risk of bias.	No additional considerations.

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	A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	In relation to psychological interventions, the promotion of people seeking treatment's capacities and skills is a component of most brief psychological interventions that has value beyond the reduction of anxiety symptoms. There are also additional valuable aspects in teaching general health workers psychological interventions because they contribute to important interpersonal skills, such as listening, problem exploration, linking physical and psychological complaints, and involving patients in treatment decisions – making the health worker a better health worker.

Criteria, questions		Judgement	Research evidence	Additional considerations
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, considering 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	Taken together, the effects of brief, structured psychological treatment vs TAU, WL, and no treatment for adults with anxiety disorders were moderate, with moderate quality evidence. The undesirable effects were minimally reported but data indicated no difference in acceptability. **Thus, the effects favour brief, structured psychological treatment.**	No additional considerations
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more 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**	There was no direct evidence to evaluate resource requirements. However, a recent global study described the investment case for scaling up the response to public health and economic burden of common mental disorders, including depression and anxiety disorders. Results indicated the benefit to cost ratios for anxiety	Anecdotal evidence indicates that in non-specialist care settings, brief psychological treatment can be human resource-intensive and requires substantial provider time, training, and supervision.

Criteria, questions		Judgement	Research evidence	Additional considerations
		☐ Don't know	disorders ranged from 3.3 to 4.0, indicating a substantial return on investment in increased economic productivity and improved health *(21)*.	
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**	No reviews examining resource requirements were identified.	No 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?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison	Clinical experience among GDG members indicates the cost effectiveness varies across countries and contexts.	Gajic-Veijanoski et al. (2018) reported CBT represented good value for money at different country-specific willingness-to-pay thresholds for the treatment of GAD. The long-term cost-effectiveness of the group versus individual format was unclear.

Criteria, questions	Judgement	Research evidence	Additional considerations
• Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Probably favours the intervention ☐ Favours the intervention ☒ **Varies** ☐ No included studies		Mutayambizi-Mafunda et al. (2022) conducted a systematic review of economic evaluations of psychological interventions for common mental disorders in LMICs. The review included 26 studies from mostly Asia (12) and Africa (9). Majority were Cost-Effectiveness Analyses (CEAs) (12), some were Cost-Utility Analyses (CUAs) (5), with one Cost-Benefit Analysis (CBA), or combinations of economic evaluations (8). Psychological treatments involved a variety of therapies including BA (3/26), CBT(2/26), IPT (2/26), Motivational Interviewing (1/26), PST(3/26), psychoeducation (1/26), various blends of these therapies (12/26), and some were unclear or unspecified (2/26). Individualized treatments were the most evident (17/26), followed by group treatments (7/26). A few blended individual and group treatments (2/26). Most interventions were considered either cost-effective or potentially cost-effective (22),

Criteria, questions	Judgement	Research evidence	Additional considerations
			with three interventions not cost-effective (i.e the Youth Readiness Intervention, Mcbain et al., 2016; a counselling intervention for perinatal depression based on CBT principles, Lund et al., 2020; and a multidisciplinary rehabilitation programme involving combined physiotherapy, biofeedback-supported psychotherapy and social support, Chang et al., 2018). The use of volunteers as non-specialists' workers also supported low-cost programming contributing to cost-effectiveness. Most studies where delivery was task-shifted to lay counsellors and where booster sessions after treatment were offered reported being cost-effective.

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? 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	The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available, and non-discriminatory: • Accessibility, physical/practical considerations. • time & travel constraints. • Accessibility, informational barriers. • Affordability - medication and treatment costs. These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials). • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			Low resource settings - affordability/cost considerations exacerbated.	
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e., the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	In addition, the qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 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.**	Specific to brief structured psychological interventions, the context may play a role in the feasibility of brief interventions and may depend on factors such as health system capacities and human resources.

Criteria, questions		Judgement	Research evidence	Additional considerations
			• **Participant education and literacy requires verbal explanations/tasks.** • **Logistical issues** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted several 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	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility. Mitigating steps to improve sociocultural acceptability include: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma. • Train acceptable counsellors for the local settings and target groups Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility, and fidelity.	

Notes. BA: behavioural activation; CBT: cognitive behavioural therapy; IPT: interpersonal therapy; LMICs: low- and middle-income countries; MNS: mental, neurological and substance use.

4.3. Summary of judgements

Table 11: Summary of judgements

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	- Favours no intervention	- Probably favours no intervention	- Does not favour either	- Probably favours intervention	✓ **Favours 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	Don't know	✓ **Varies**	- Favours no intervention	- Probably favours no intervention	- Does not favour either	- Probably favours intervention	- Favours 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

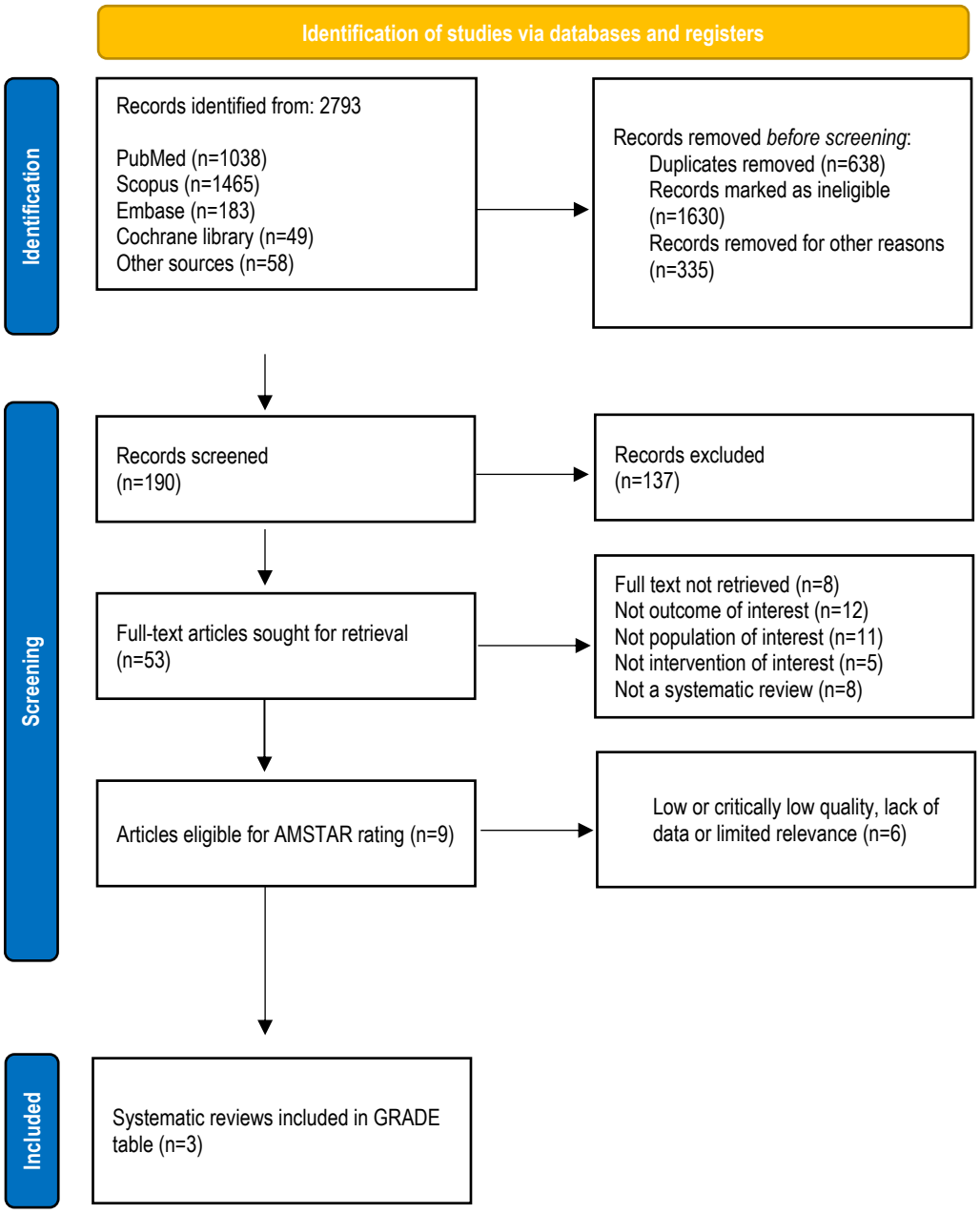
✓Indicates category selected, - Indicates category not selected.

QUESTION 3

For adults and with anxiety disorders (excluding social phobia, SAD), what is the comparative effectiveness of different formats of psychological interventions?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 3: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #3



3.1.1. Included in GRADE tables/footnotes

1. Barkowski S, Schwartze D, Strauss B, Burlingame GM, Rosendahl J. Efficacy of group psychotherapy for anxiety disorders: A systematic review and meta-analysis. Psychotherapy research : journal of the Society for Psychotherapy Research. 2020;30(8):965-82. doi:10.1080/10503307.2020.1729440
2. Pauley D, Cuijpers P, Papola D, Miguel C, Karyotaki E. Two decades of digital interventions for anxiety disorders: A systematic review and meta-analysis of treatment effectiveness. Psychol Med. 2021: 1-13. doi: 10.1017/S0033291721001999
3. Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. BMC Fam Pract. 2021;22(1):92. doi:10.1186/s12875-021-01445-5

3.1.2. Excluded from GRADE tables/footnotes

1. Saramago P, Gega L, Marshall D, Nikolaidis GF, Jankovic D, Melton H, et al. Digital Interventions for Generalized Anxiety Disorder (GAD): Systematic Review and Network Meta-Analysis. Front Psychiatry. 2021;12:726222. doi:10.3389/fpsyt.2021.726222
2. Krzyzaniak N, Greenwood H, Scott AM, Peiris R, Cardona M, Clark J, et al. The effectiveness of telehealth versus face-to face interventions for anxiety disorders: A systematic review and meta-analysis. Journal of telemedicine and telecare. 2021:1357633x211053738:1-12. doi:10.1177/1357633X211053738
3. Currie CL, Larouche R, Voss ML, Trottier M, Spiwak R, Higa E, et al. Effectiveness of Live Health Professional-Led Group eHealth Interventions for Adult Mental Health: Systematic Review of Randomized Controlled Trials. J Med Internet Res. 2022;24(1):e27939:1-21. doi:10.2196/27939
4. McCall HC, Hadjistavropoulos HD, Sundström CRF. Exploring the role of persuasive design in unguided internet-delivered cognitive behavioral therapy for depression and anxiety among adults: Systematic review, meta-analysis, and meta-regression. J Med Internet Res. 2021;23(4):1-24. doi:10.2196/26939
5. Coto-Lesmes R, Fernández-Rodríguez C, González-Fernández S. Acceptance and Commitment Therapy in group format for anxiety and depression. A systematic review. J Affective Disord. 2020;263:107-20. doi:10.1016/j.jad.2019.11.154
6. Fischer R, Bortolini T, Karl JA, Zilberberg M, Robinson K, Rabelo A, et al. Rapid Review and Meta-Meta-Analysis of Self-Guided Interventions to Address Anxiety, Depression, and Stress During COVID-19 Social Distancing. Front Psychol. 2020;11:563876. doi:10.3389/fpsyg.2020.563876

Table 12: Example PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX3.1	Group interventions / individual interventions	Reduction of symptoms	Barkowski et al. (2020)	Barkowski et al. (2020) was chosen for symptom reduction because it was the only recent high-quality review that compares group vs individual treatment in the population of interest.
		Adverse effects	No evidence.	No evidence
		Acceptability profile	Barkowski et al. (2020)	Barkowski et al. (2020) was chosen for adverse effects because it was the only a recent high-quality review that compares group vs individual treatment in the population of interest.
		Sustained response	No evidence	No evidence.
		Functioning	No evidence	No evidence.
ANX3.2	Unguided self-help / guided self-help	Reduction of symptoms	Pauley et al. (2021);	Pauley et al. (2021) was chosen because it is the only recent high-quality review identified that compares guided and unguided self-help interventions.
		Adverse effects	No evidence.	No evidence.
		Acceptability profile	No evidence.	No evidence.
		Sustained response	No evidence.	No evidence.
		Functioning	No evidence.	No evidence.
ANX3.3	Non-specialist vs specialist providers of face-to-face interventions	Reduction of symptoms	Parker et al. (2021)	Parker et al. (2021) was chosen for symptom reduction because it was the only recent high-quality review that reported outcomes specialist and non-specialist providers providing face-to-face interventions for symptom reduction in adults with anxiety disorders in settings of interest.
		Adverse effects	No evidence.	No evidence
		Acceptability profile (number of dropouts)	No evidence.	No evidence.
		Sustained response	No evidence	No evidence.
		Functioning	No evidence	No evidence.

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX3.4	Digital interventions / face-to-face interventions	Reduction of symptoms	Pauley et al. (2021)	Pauley et al. (2021) was chosen because it was the only recent high-quality review that directly compared digital interventions to face-to-face interventions.
		Adverse events	No evidence	No evidence.
		Acceptability profile	No evidence	No evidence.
		Sustained response	No evidence.	No evidence.
		Functioning	No evidence	No evidence.

3.2. Narrative description of studies that contributed to GRADE analysis

Review sub-question 1: Group psychological interventions vs individual psychological interventions for adults with anxiety disorders

Barkowski et al. (2020) evaluated the efficacy of group psychotherapy in the treatment of anxiety disorders through meta-analysis. The review examined 57 eligible studies (k = 76 comparisons) including 3656 participants receiving group psychotherapy or an alternative treatment for GAD, SAD, and panic disorder.

In total, thirty-four studies (59.6%) reported on SAD patients, 13 (22.8%) on PD patients, five (8.8%) on GAD patients and five (8.8%) on mixed anxiety disorder diagnoses. Sixty-seven group psychotherapeutic interventions were reported, n= 57 of which followed a full CBT approach, n = 6 provided for exposure treatment alone and n = 4 for a different treatment approach (n = 1 cognitive therapy, n = 1 psychodynamic psychotherapy, n =1 interpersonal psychotherapy and n = 1 social skills training). These interventions were directly compared to no-treatment controls (k = 48), common factor controls (k = 12), individual interventions (k = 8), and pharmacotherapy (k = 8). In total, 1922 patients received a group psychotherapeutic treatment and 1734 were allocated to a control group.

Review sub-question 2: Unguided self-help vs guided self-help psychological interventions for adults with anxiety disorders

Pauley et al. (2021) conducted a systematic review and meta-analysis that examined the effectiveness of digital interventions across all anxiety disorders and specific to each disorder vs waitlist and care-as-usual controls.

In total, 47 randomized controlled trials (53 comparisons; 4958 participants) contributed to the meta-analysis. Among the 47 included studies, seven studies had multiple trial arms which were merged for analysis. In four studies, the control group was equally split and shared between guided and unguided intervention arms. The 47 studies resulted in 4958 participants (2808 treatment group and 2150 control group) and 53 comparisons quantified in analysis.

Review sub-question 3: Specialist vs non-specialist providers of face-to-face psychological interventions for adults with anxiety disorders

Parker et al. (2021) conducted a systematic review and meta-analysis of the effects of psychological and pharmacological interventions on adults with anxiety disorders treated in primary care settings.

A total of 19 articles reporting 18 studies met all criteria and were included in our review. Two articles reported separate steps of the same study, and eight studies involved more than one active treatment condition. Across all studies, there were 28 comparisons of active treatment with a control group (placebo, waitlist control, or care as usual CAU). In the included studies, 2,059 participants were randomized to an active treatment condition and 1247 to a control condition. Thirteen studies investigated anxiety disorders specifically; four generalized anxiety disorder (22.2% of 18), four panic disorder with or without agoraphobia (22.2% of 18), and five investigated multiple anxiety disorders (including mixed anxiety/depression; 27.8% of 18).

Psychological interventions were predominantly CBT (n = 13, 81.2% of 16) and provided on an individual basis.

Review sub-question 4: Digital psychological interventions vs face-to-face psychological interventions

Pauley et al. (2021) conducted a systematic review and meta-analysis that examined the effectiveness of digital interventions across all anxiety disorders and specific to each disorder vs waitlist and care-as-usual controls.

In total, 47 randomized controlled trials (53 comparisons; 4958 participants) contributed to the meta-analysis. Among the 47 included studies, seven studies had multiple trial arms which were merged for analysis. In four studies, the control group was equally split and shared between guided and unguided intervention arms. The 47 studies resulted in 4958 participants (2808 treatment group and 2150 control group) and 53 comparisons quantified in analysis.

3.3. Grading the Evidence

Table 13.1: Review sub-question: Group psychological interventions vs individual psychological interventions for adults with anxiety disorders
Author(s): Brandon Gray and Biksegn Asrat
Question: Group psychological interventions compared to individual psychological interventions for adults with anxiety disorders (excluding SAD, specific phobias)
Setting: Non-specialist care settings
Reference List:
Barkowski S, Schwartze D, Strauss B, Burlingame GM, Rosendahl J. Efficacy of group psychotherapy for anxiety disorders: A systematic review and meta-analysis. Psychother Res. 2020;30(8):965-82. doi:10.1080/10503307.2020.1729440

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	group psychological treatment	individual psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures of disorder specific symptoms)												
7[b]	RCT	not serious	serious[c]	serious[d]	not serious	none	188	192	-	SMD **0.24 SD higher** (0.09 lower to 0.57 higher)	⨁⨁◯◯ Low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD												
0	no evidence								-	**0** (0 to 0)	-	CRITICAL
Reduction of anxiety symptoms post treatment in adults with PD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	group psychological treatment	individual psychological treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence								not estimable		-	CRITICAL
Adverse effects in adults with mixed anxiety disorders												
0	no evidence								not estimable		-	CRITICAL
Adverse effects in adults with GAD												
0	no evidence								not estimable		-	IMPORTANT
Adverse effects in adults with PD												
0	no evidence								-	**0** (0 to 0)	-	IMPORTANT
Acceptability profile in adults with mixed anxiety disorders (assessed with number of dropouts)												
7[b,e]	RCT	not serious	serious	serious[d]	not serious	none			**RR 1.58** (1.00 to 2.49)	**2 fewer per 1,000** (from 2 fewer to 1 fewer)[f]	⨁⨁◯◯ Low	IMPORTANT
Acceptability profile in adults with GAD												
0	no evidence											IMPORTANT

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	group psychological treatment	individual psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Acceptability profile in adults with PD												
0	no evidence											IMPORTANT
Sustained response in adults with mixed anxiety disorders												
0	no evidence											IMPORTANT
Sustained response in adults with GAD												
0	no evidence											IMPORTANT
Sustained response in adults with PD												
0	no evidence											IMPORTANT
Functioning in adults with mixed disorders												
0	no evidence								-		-	IMPORTANT
Functioning in adults with GAD												
0	no evidence										-	IMPORTANT
Functioning in adults with PD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	group psychological treatment	individual psychological treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence										-	IMPORTANT
0	no evidence								not estimable		-	IMPORTANT

Notes. CI: confidence interval; GAD: generalized anxiety disorder; PD: panic disorder; RR: risk ratio; RCT: randomized controlled trial; SMD: standardized mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Barkowski et al. (2020).

c. I squared = 64.7%.

d. Study samples included participants with excluded disorders.

e. Raw data on dropout by group is not reported in the study or supplementary materials. Authors instead reported a trend emerged for higher dropout rates in group psychotherapy (25.1% [15.8%; 34.4%]) compared to individual psychotherapy (15.3% [10.8%; 19.9%]; RR = 1.58 [1.00; 2.49]; p = .050; k = 7). There was no significant difference between dropout rates of group psychotherapy (21.2% [14.0%; 28.4%]) and common factor control groups (18.7% [10.4%; 27.1%]; RR = 0.91 [0.67; 1.22]; p = .520, k = 10) or group psychotherapy (18.7% [10.0%, 27.4%]) and pharmacotherapy (25.5% [15.9%; 35.0%]; RR = 0.76 [0.55; 1.03]; p = .081, k = 8).

f. For this outcome, positive effects are reported favouring individual therapy (higher dropout rates in group psychotherapy relative to individual).

Table 13.2: Review sub-question: Unguided self-help vs guided self-help psychological interventions for adults with anxiety disorders

Author(s): Brandon Gray and Biksegn Asrat
Question: Unguided self-help psychological interventions compared to guided self-help psychological interventions for adults with anxiety disorders (excluding SAD, specific phobias)
Setting: Non-specialist care settings
Reference List:
Pauley D, Cuijpers P, Papola D, Miguel C, Karyotaki E. Two decades of digital interventions for anxiety disorders: A systematic review and meta-analysis of treatment effectiveness. Psychol Med. 2021: 1-13. doi: 10.1017/S0033291721001999

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	unguided self-help psychological treatment	guided self-help psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with: multiple measures of anxiety symptoms)												
47[b]	randomized trials	not serious	serious[c]	serious[d]	not serious	none	Authors reported the effects of guided interventions vs treatment as usual, waitlist or no treatment (N = 3467; k = 42; g = 0.84, 95% CI: 0.71-0.98) and unguided interventions vs treatment as usual, waitlist or no treatment (N = 1491; k = 11; g = 0.64, 95% CI: 0.37-0.90) were not significantly different (p = 0.177).				⨁⨁◯◯ Low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD												
0	no evidence											CRITICAL
Reduction of anxiety symptoms post treatment in adults with PD												
0	no evidence											CRITICAL
Adverse effects in adults with mixed anxiety disorders												
0	no evidence											CRITICAL

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	unguided self-help psychological treatment	guided self-help psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Adverse effects in adults with GAD												
0	no evidence											CRITICAL
Adverse effects in adults with PD												
0	no evidence											CRITICAL
Sustained reduction of anxiety symptoms in adults with mixed anxiety disorders (follow-up: range 6 months to 12 months; assessed with: multiple anxiety disorder specific measures)												
0	no evidence											IMPORTANT
Sustained reduction of anxiety symptoms in adults with GAD												
0	no evidence											IMPORTANT
Sustained reduction of anxiety symptoms in adults with PD												
0	no evidence											IMPORTANT
Acceptability profile in adults with mixed anxiety disorders (assessed with: number of dropouts)												
0	no evidence											IMPORTANT
Acceptability profile in adults with GAD												
0	no evidence											IMPORTANT
Acceptability profile in adults with PD												
0	no evidence											IMPORTANT
Functioning in adults with mixed anxiety disorders (assessed with: quality of life)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	unguided self-help psychological treatment	guided self-help psychological treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence											IMPORTANT
Functioning in adults with GAD												
0	no evidence											IMPORTANT
Functioning in adults with PD												
0	no evidence											IMPORTANT

Notes. CI: confidence interval; GAD: generalized anxiety disorder; PD: panic disorder; RR: risk ratio; RCT: randomized controlled trial; SMD: standardized mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Pauley et al. (2021).

c. I squared ranged from 72-77% in guided vs unguided analysis.

d. Study samples included participants with excluded anxiety disorders.

3.4. Additional evidence not mentioned in GRADE table 2.2

Olthuis et al. (2016) conducted a Cochrane systematic review and meta-analysis to assess the effects of therapist-supported Internet CBT (iCBT) on remission of anxiety disorder diagnosis and reduction of anxiety symptoms in adults as compared to waiting list control, unguided CBT, or face-to-face CBT. However, this review was not identified in the literature review because it was published prior to the search's timeframe.

In total, 38 studies (3214 participants) were included . The studies examined social phobia (11 trials), panic disorder with or without agoraphobia (8 trials), GAD (5 trials), PTSD (2 trials), OCD (2 trials), and specific phobia (2 trials). Eight remaining studies included a range of anxiety disorder diagnoses. Studies were conducted in Sweden (18 trials), Australia (14 trials), Switzerland (3 trials), the Netherlands (2 trials), and the USA (1 trial) and investigated a variety of iCBT protocols. Three primary comparisons were identified, therapist-supported iCBT versus waiting list control, therapist-supported versus unguided iCBT, and therapist-supported iCBT versus face-to-face CBT.

Very low-quality evidence suggested that **guided interventions demonstrated a small, significant benefit on sustained reduction of anxiety symptoms (SMD 0.30 SD Lower; 95% CI: 0.58 lower to 0.01 lower) in adults with mixed anxiety disorders compared to unguided interventions and no difference in dropout**.

Table 13.3: Review sub-question: Specialist vs non-specialist providers of psychological interventions for adults with anxiety disorders

Author(s): Brandon Gray and Biksegn Asrat
Question: Specialist vs non-specialist providers of psychological interventions for adults with anxiety disorders (excluding social anxiety disorder, specific phobias)
Setting: non-specialized care settings
Reference List:
Parker EL, Banfield M, Fassnacht DB, Hatfield T, Kyrios M. Contemporary treatment of anxiety in primary care: a systematic review and meta-analysis of outcomes in countries with universal healthcare. BMC Fam Pract. 2021;22(1):92. doi:10.1186/s12875-021-01445-5

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	self-help psychological interventions	face-to-face interventions	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures of anxiety symptoms)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	self-help psychological interventions	face-to-face interventions	Relative (95% CI)	Absolute (95% CI)		
9[b]	RCT	not serious	not serious[c]	serious	not serious	Publication bias suspected[d]	Treatment provided by a non-specialist compared with TAU (7 studies) did not produce a significant effect on anxiety symptoms (g = 0.10, 95%CI = -0.16-0.35; p = 0.468). However, compared with waitlist (n = 2 studies) control a large effect was found (g = 0.80, 95%CI = 0.31 – 1.28). Treatment provided by a specialist was associated with large effects regardless of the comparison group (TAU = 2 studies: g = 0.76, 95%CI = 0.27 – 1.25; waitlist = 3 studies: g = 1.46, 95%CI = 0.96 – 1.96).				⊕⊕◯◯ Low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD												
0	no evidence											CRITICAL
Reduction of anxiety symptoms post treatment in adults with PD												
0	no evidence											CRITICAL
Adverse effects in adults with mixed anxiety disorders												
0[b]	no evidence											CRITICAL
Adverse effects in adults with GAD												
0	no evidence											CRITICAL
Adverse effects in adults with PD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	self-help psychological interventions	face-to-face interventions	Relative (95% CI)	Absolute (95% CI)		
0	no evidence											CRITICAL
Acceptability profile in adults with mixed anxiety disorders (assessed with adherence and patient satisfaction)												
0	no evidence											IMPORTANT
Acceptability profile in adults with GAD												
0	no evidence											IMPORTANT
Acceptability profile in adults with PD												
0	no evidence											IMPORTANT
Sustained response in adults with mixed anxiety disorders												
0	no evidence											IMPORTANT
Sustained response in adults with GAD												
0	no evidence											IMPORTANT
Sustained response in adults with PD												
0	no evidence											IMPORTANT
Functioning in adults with mixed anxiety disorders												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	self-help psychological interventions	face-to-face interventions	Relative (95% CI)	Absolute (95% CI)		
0	no evidence											IMPORTANT
Functioning in adults with GAD												
0	no evidence											IMPORTANT
Functioning in adults with PD												
0	no evidence											IMPORTANT

Notes. CI: confidence interval; GAD: general anxiety disorder; PD: panic disorder; RCT: randomized controlled trial; SMD**:** standardized mean difference; TAU: treatment as usual

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Pauley et al. (2021).

c. I squared not reported for this sub-analysis.

d. Egger's regression test showed significant funnel plot asymmetry ($z = 3.70$, $p < 0.001$), indicating possible publication bias.

e. For this outcome, the effect favoured face-to-face interventions.

3.5. Additional evidence not mentioned in GRADE table 2.3

No additional considerations.

Table 2.4: Review sub-question: Digital psychological intervention vs face-to-face psychological intervention

Author(s): Brandon Gray and Biksegn Asrat
Question: Digital psychological intervention compared to face-to-face psychological intervention for adults with anxiety disorders (excluding SAD, specific phobias)
Setting: non-specialist care settings
Reference List:
Pauley D, Cuijpers P, Papola D, Miguel C, Karyotaki E. Two decades of digital interventions for anxiety disorders: A systematic review and meta-analysis of treatment effectiveness. Psychol Med. 2021: 1-13. doi:10.1017/S0033291721001999

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	digital psychological treatment	face-to-face psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures of anxiety symptoms)												
9[b]	randomized trials	not serious	not serious	serious[c]	not serious	none	683		-	SMD **0.14 SD higher** (0.01 lower to 0.3 higher)[d]	⨁⨁⨁◯ Moderate	CRITICAL
Reduction of anxiety symptoms in adults with GAD												
0	no evidence								not estimable		-	CRITICAL
Reduction of anxiety symptoms in adults with PD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	digital psychological treatment	face-to-face psychological treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence								not estimable		-	CRITICAL

Adverse effects in adults with mixed anxiety disorders

0[e]	no evidence						No studies specifically investigated the harms of iCBT. Furthermore, none of the studies examined in this meta-analysis made mention of harm or negative effects experienced by participants.				-	CRITICAL

Adverse effects in adults with GAD

0	no evidence								not estimable		-	CRITICAL

Adverse effects in adults with PD

0	no evidence								not estimable		-	CRITICAL

Acceptability profile in adults with mixed anxiety disorders (assessed with number of dropouts)

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	digital psychological treatment	face-to-face psychological treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence										⨁⨁⨁◯ Moderate	IMPORTANT
Acceptability profile in adults with GAD												
0	no evidence								not estimable		-	IMPORTANT
Acceptability profile in adults with PD												
0	no evidence								not estimable		-	IMPORTANT
Sustained reduction of anxiety symptoms in adults with mixed anxiety disorders												
0	no evidence											

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	digital psychological treatment	face-to-face psychological treatment	Relative (95% CI)	Absolute (95% CI)		
Sustained reduction of anxiety symptoms in adults with GAD												
0	no evidence											IMPORTANT
Sustained reduction of anxiety symptoms in adults with PD												
0	no evidence											
Functioning in adults with mixed anxiety disorders												
0	no evidence								not estimable		-	IMPORTANT
Functioning in adults with GAD												
0	no evidence								not estimable		-	IMPORTANT
Functioning in adults with PD												
0	no evidence								not estimable		-	IMPORTANT

Notes. CI**:** confidence interval; GAD: general anxiety disorder; PD: panic disorder; SMD**:** standardized mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.
b. Pauley et al. (2021).
c. Study samples included participants with excluded disorders.
d. For this outcome, positive effects are reported favouring digital interventions.

3.6. Additional evidence not mentioned in GRADE table 2.4

Andrews et al. (2018) updated a 2010 meta-analysis examined the effectiveness of iCBT for anxiety disorders that was not identified in the literature review because it was published prior to the search's timeframe. Two of the 22 studies in the original meta-analysis contained multiple relevant arms, which were analysed as separate trials. 31 additional studies were identified following the full-text screen, making 53 randomized controlled studies in total. As studies with multiple relevant arms were treated as separate trials, a total of 64 efficacy trials were analysed. The control conditions varied from wait list in which treatment was deferred for a period (usually three months), to psychological placebos (information and discussion groups about the disorder in question; pseudo-active interventions) to care as usual in which the previous treatment was continued or changed, provided face to face or i CBT was not introduced. The search also identified nine studies comparing face to face CBT with iCBT, three studies comparing iCBT to bibliotherapy and eight effectiveness studies of the benefits of iCBT when used in routine practice − these were used for separate analyses. Authors reported that **adherence in the iCBT and bibliotherapy self-help conditions were comparable, and there was no significant difference between the iCBT and face to face CBT conditions.**

4. From Evidence to Recommendations

4.1. Summary of findings

Table 14: Summary of findings table

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
Table 2.1 (Group vs Individual Psychological intervention)	Barkowski et al. (2020)	Reduction of anxiety symptoms in adults with mixed anxiety disorders	SMD 0.24 SD higher (0.09 lower to 0.57 higher)[b]	380 (7 RCTs)	⨁⨁◯◯ Low
	Barkowski et al. (2020)	Acceptability profile in adults with mixed anxiety disorders	**RR 1.58** (1.00 to 2.49)	380 (7 RCTs)	⨁⨁◯◯ Low
Table 2.2 (Unguided vs Guided intervention)	Pauley et al. (2021)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders	Effects are based on 47 RCTs. Authors reported the effects of guided interventions vs treatment as usual, waitlist or no treatment (N = 3467; k = 42; g = 0.84, 95% CI: 0.71-0.98) and unguided interventions vs treatment as usual, waitlist or no treatment (N = 1491; k = 11; g = 0.64, 95% CI: 0.37-0.90) were not significantly different (p = 0.177).		⨁⨁◯◯ Low

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
Table 2.3 (Specialist vs non-specialist providers of psychological interventions)	Parker et al. (2021)	Reduction of symptoms post treatment in adults with mixed anxiety disorders	Evidence is based on nine RCTs. Treatment provided by a non-specialist compared with TAU (7 studies) did not produce a significant effect on anxiety symptoms (g = 0.10, 95%CI = -0.16-0.35; p = 0.468). However, compared with waitlist (n = 2 studies) control a large effect was found (g = 0.80, 95%CI = 0.31 – 1.28). Treatment provided by a specialist was associated with large effects regardless of the comparison group (TAU = 2 studies: g = 0.76, 95%CI = 0.27 – 1.25; waitlist = 3 studies: g = 1.46, 95%CI = 0.96 – 1.96).		⊕⊕◯◯ Low
Table 2.4 (Digital vs face-to-face interventions)	Pauley et al. (2021)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders	SMD 0.14 SD higher (0.01 lower to 0.3 higher)[f]	683 (9 RCTs)	⊕⊕⊕◯ Moderate

Notes. CI: confidence interval; RR: risk ratio; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; TAU: treatment as usual

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.
b. For this effect, positive outcomes favour guided interventions.
c. For this outcome, negative effects are reported favouring guided interventions
d. For this outcome, effects favoured unguided interventions.
e. For this outcome, the effect favoured face-to-face interventions.
f. For this outcome, positive effects are reported favouring digital interventions.

4.2. Evidence to Decision

Table 15: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☒ **Trivial** ☐ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	**<u>Group vs Individual</u>** Evidence from seven RCTs suggested no significant difference of group psychological treatment on anxiety symptom reduction in adults with mixed anxiety disorders relative to individual psychological treatment**.** **<u>Guided vs unguided self-help</u>** Evidence from 47 RCTs suggested no significant difference in the reduction of anxiety symptoms in adults with mixed anxiety disorders between guided self-help and unguided self-help. **<u>Specialist vs non-specialist providers</u>** Evidence from nine RCTs suggested both specialist providers and non-specialist providers demonstrated large, significant benefits on reduction of symptoms in adults with mixed anxiety disorders when compared to waitlist controls. When compared to active controls (i.e. treatment as usual), specialists providers demonstrated a large, significant benefit on anxiety symptom reduction while non-specialists demonstrated a small, non-significant benefit on anxiety symptom reduction. However, it must be noted this was not a direct comparison and so conclusions that can be made are limited.	In Olthuis et al.'s (2016) review, Evidence from three RCTs suggested a small, significant difference in the sustained reduction of anxiety symptoms at follow-up in adults with mixed anxiety disorders between **guided self-help** and **unguided self-help.**

Criteria, questions		Judgement	Research evidence	Additional considerations
			<u>Digital vs face-to-face</u> Evidence from nine RCTs suggested no significant difference in the reduction of symptoms for adults with mixed anxiety disorders between face-to-face interventions and digital interventions.	
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	**<u>Group vs individual psychological</u>** Evidence from seven RCTs suggested a significant difference between groups in dropout rates, with group psychological treatment demonstrating increased dropouts relative to individual psychological treatment**.** **<u>Guided vs unguided self-help</u>** Evidence from four RCTs suggested a significant difference between guided and unguided self-help in dropout rates, with unguided self-help demonstrating increased dropouts relative to guided self-help. **<u>Specialist vs non-specialist providers</u>** No evidence was reported on undesirable effects in this comparison. **<u>Digital vs face-to-face psychological</u>** No evidence was reported on undesirable effects.	In Olthuis et al.'s (2016) review, evidence from three RCTs suggested no difference in dropout in adults with mixed anxiety disorders between **guided self-help** and **unguided self-help.** In Andrews et al.'s (2018) review, evidence from 52 RCTs suggested no difference in treatment adherence among adults with mixed anxiety disorders between **digital** and **face to face** psychological treatment.

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 overall certainty of the evidence was LOW. Certainty of the evidence for **group vs individual psychological interventions** was LOW. Certainty of the evidence for **guided vs unguided** self-help was LOW. Certainty of the evidence for **specialist vs non-specialist providers** was LOW due to indirectness. Certainty of the evidence for **digital vs face-to-face psychological interventions** was MODERATE due to risk of publication bias.	No 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	A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services.	The promotion of people seeking treatment's capacities and skills is a component of most brief psychological interventions that has value beyond the reduction of anxiety symptoms. There are also additional valuable aspects

Criteria, questions	Judgement	Research evidence	Additional considerations
	☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	in teaching general health workers psychological interventions because they contribute to important interpersonal skills, such as listening, problem exploration, linking physical and psychological complaints, and involving patients in treatment decisions – making the health worker a better health worker. Because the current evidence shows that treatment format has limited impact on desired outcomes, the values and preferences that affect treatment access and delivery are of particular importance. Given global treatment gaps, there is value in identifying formats of delivery that promote health equity.

Criteria, questions		Judgement	Research evidence	Additional considerations
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, considering 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	**<u>Group vs individual</u>** Taken together, low quality evidence indicated the effects of group vs individual psychological treatment were similar in the reduction of anxiety symptoms post treatment, while group psychological treatment demonstrated a greater risk for dropout. **Thus, the effects probably favour individual psychological treatment.** **<u>Guided vs unguided self-help</u>** Low quality evidence indicated the effects of guided self-help vs unguided self-help were similar in reduction of anxiety symptoms post treatment. **Thus, considering the evidence and additional considerations, the effects are similar but may favour guided self-help.** **<u>Specialist vs non-specialist providers</u>** Low quality indirect evidence indicated the effects of specialist and non-specialist provided psychological treatment were similar in comparison to waitlist controls, while specialist providers demonstrated a large benefit when compared to active controls (TAU) while non-specialist providers demonstrated no difference compared to active controls (TAU). There was no evidence on adverse effects. **Thus, the**	In Olthuis et al.'s (2016) review, guided interventions demonstrated a small benefit in the sustained reduction of anxiety symptoms at follow up compared to unguided.

Criteria, questions		Judgement	Research evidence	Additional considerations
			effects probably favour specialist provided psychological interventions. **<u>Digital vs face-to-face</u>** Moderate quality evidence indicated the effects of digital vs. face-to-face psychological treatment were similar in the reduction of anxiety symptoms. **Thus, the effects do not favour either digital or face-to-face psychological treatment.**	
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. However, a recent global study described the investment case for scaling up the response to public health and economic burden of common mental disorders, including depression and anxiety disorders. Results indicated the benefit to cost ratios for anxiety disorders ranged from 3.3 to 4.0, indicating a substantial return on investment in increased economic productivity and improved health *(21)*.	Although a variety of low intensity interventions help make mental health care more widely available, anecdotal evidence indicates certain resources requirements can impact format of delivery: 1. IT-based interventions require access to computers and/or smart phones, which can reduce accessibility for low-income individuals or those living in poverty. 2. Self-help books require sufficient literacy skills, which can be very low in low-income countries.

Criteria, questions		Judgement	Research evidence	Additional considerations
				3. Delivering interventions via mobile telephone support may be more feasible in low-income settings; however, the very poor may not have access to mobile telephones. 4. Lay therapists tend not to be members of national associations that regulate the quality and quantity of training and supervision; therefore, care delivered by lay therapists may be more difficult to regulate.
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.	No additional considerations.

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	Two systematic reviews of cost-effectiveness for treating anxiety disorders (including those excluded in this question) that were published outside of the review period were known to the evidence review team (Ophuis et al., 2017; Gajic-Veijanoski et al. 2018). Ophuis et al. (2017) indicated that studies comparing iCBT to control groups (WL, TAU, no treatment) indicated iCBT was more cost effective than controls but Gajic-Veijanoski et al. (2018) reported CBT represented good value for money at different country-specific willingness-to-pay thresholds for the treatment of GAD. The long-term cost-effectiveness of the group versus individual format was unclear. Other formats were not examined. A third review published after the review period, Mutayambizi-Mafunda et al. (2022), conducted a systematic review of economic evaluations of psychological interventions for common mental disorders in LMICs. The review included 26 studies from mostly Asia (12) and Africa (9). Majority were Cost-Effectiveness Analyses (CEAs) (12), some were Cost-Utility Analyses (CUAs) (5), with one Cost-Benefit Analysis (CBA), or combinations of economic evaluations (8). Psychological treatments involved a variety of therapies including BA (3/26), Cognitive Behavioural Therapy	Cost effectiveness may vary across settings depending on health system capacities and resources.

Criteria, questions	Judgement	Research evidence	Additional considerations
		(CBT)(2/26), Interpersonal Therapy (IPT) (2/26), Motivational Interviewing (1/26), PST(PST) (3/26), psychoeducation (1/26), various blends of these therapies (12/26), and some were unclear or unspecified (2/26). Individualized treatments were the most evident (17/26), followed by group treatments (7/26). A few blended individual and group treatments (2/26). Most interventions were considered either cost-effective or potentially cost-effective (22), with 3 interventions not cost-effective (i.e the Youth Readiness Intervention, Mcbain et al., 2016; a counselling intervention for perinatal depression based on CBT principles, Lund et al., 2020; and a multidisciplinary rehabilitation programme involving combined physiotherapy, biofeedback-supported psychotherapy and social support, Chang et al., 2018). The use of volunteers as non-specialist workers also supported low-cost programming contributing to cost-effectiveness. Most studies where delivery was task-shifted to lay counsellors and where booster sessions after treatment were offered reported being cost-effective.	

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? 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	Additionally, the qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available, and non-discriminatory: • Accessibility, physical/practical considerations. • time & travel constraints. • Accessibility, informational barriers. • Affordability - medication and treatment costs. These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials). • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities Low resource settings - affordability/cost considerations exacerbated.	Although a variety of low intensity interventions help make mental health care more widely available, certain issues can impact vertical health equity: 1. IT-based interventions require access to computers and/or smart phones, which can reduce accessibility for low-income individuals or those living in poverty. 2. Self-help books require sufficient literacy skills, which can be very low in low-income countries. 3. Delivering interventions via mobile telephone support may be more feasible in low-income settings; however, the very poor may not have access to mobile telephones.

Criteria, questions		Judgement	Research evidence	Additional considerations
				4. Lay therapists tend not to be members of national associations that regulate the quality and quantity of training and supervision; therefore, care delivered by lay therapists may be more difficult to regulate.
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	The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 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.**	Feasibility may vary by context and by format of the intervention applied.

Criteria, questions		Judgement	Research evidence	Additional considerations
			• **Logistical issues** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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 groups or organization's autonomy, i.e.,	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted several 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 consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		age, sex and language have been highlighted as important to acceptability and accessibility. Mitigating steps to improve sociocultural acceptability include: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma. • Train acceptable counsellors for the local settings and target groups. Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility, and fidelity.	

Notes. CBT: cognitive behavioural therapy; iCBT: internet-based cognitive behavioural therapy; MNS: mental, neurological and substance use; RCT: randomized controlled trial; TAU: treatment as usual; WL: waitlist

4.3. Summary of judgements

Table 16: Summary of judgements

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	- Favours no intervention	- Probably favours no intervention	✓ **Does not favour either**	- Probably favours intervention	- Favours 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	Don't know	✓ **Varies**	- Favours no intervention	- Probably favours no intervention	- Does not favour either	Probably favours intervention	- Favours 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

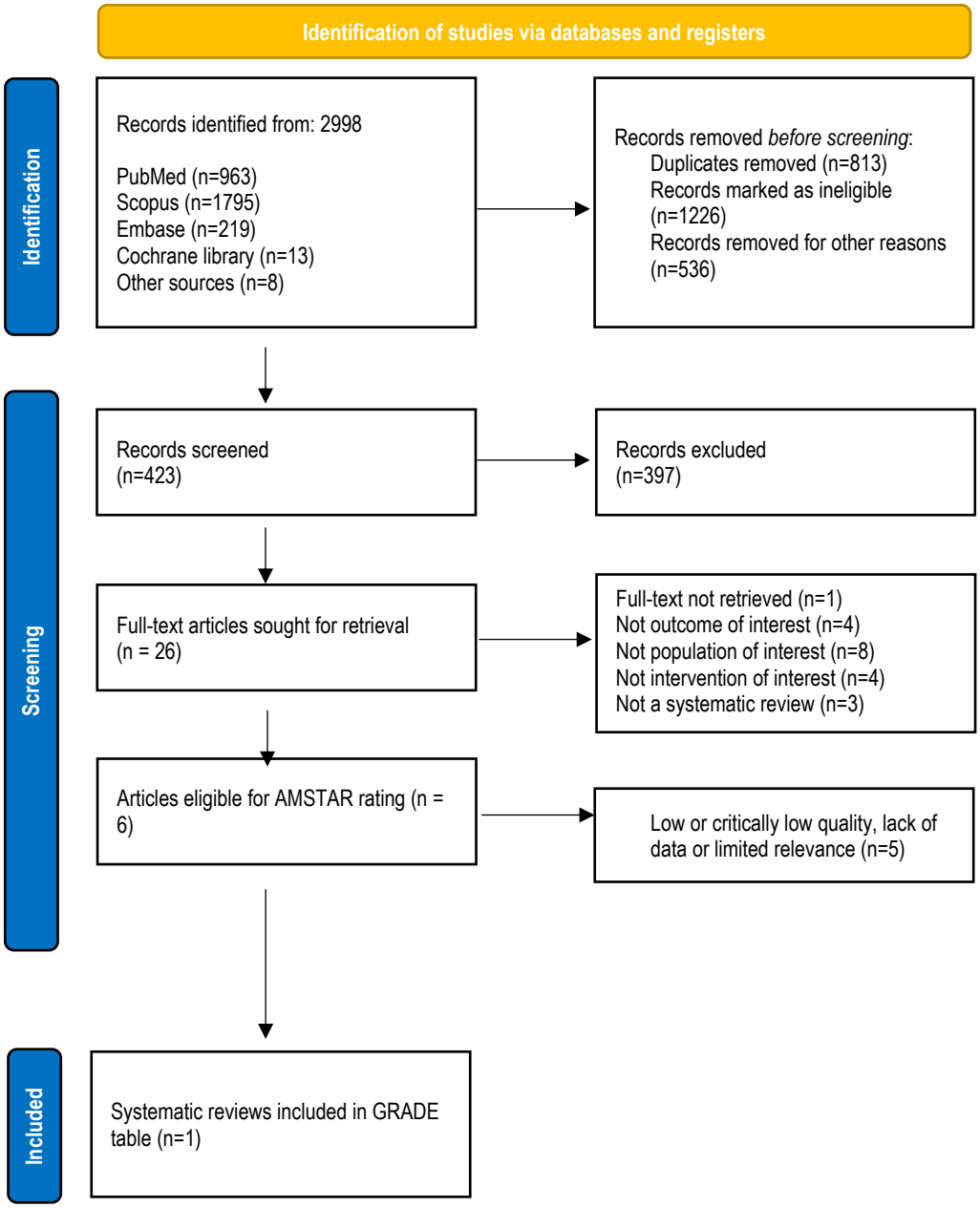
✓Indicates category selected, - Indicates category not selected.

QUESTION 4

Are stress management techniques better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 4: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #4



3.1.1. Included in GRADE tables/footnotes

1. Kim HS, Kim EJ. Effects of Relaxation Therapy on Anxiety Disorders: A Systematic Review and Meta-analysis. Arch Psychiatr Nurs. 2019;32(2):278-84. doi:10.1016/j.apnu.2017.11.015.

3.1.2. Excluded from GRADE tables/footnotes

1. Montero-Marin J, Garcia-Campayo J, Pérez-Yus MC, Zabaleta-Del-Olmo E, Cuijpers P. Meditation techniques v. relaxation therapies when treating anxiety: a meta-analytic review. Psychol Med. 2019;49(13):2118-33. doi:10.1017/S0033291719001600
2. So WWY, Lu EY, Cheung WM, Tsang HWH. Comparing mindful and non-mindful exercises on alleviating anxiety symptoms: A systematic review and meta-analysis. Int J Environ Res Public Health. 2020;17(22):1-16. doi:10.3390/ijerph17228692
3. de Abreu Costa M, D'Alò de Oliveira GS, Tatton-Ramos T, Manfro GG, Salum GA. Anxiety and Stress-Related Disorders and Mindfulness-Based Interventions: a Systematic Review and Multilevel Meta-analysis and Meta-Regression of Multiple Outcomes. Mindfulness. 2019; 10(6). doi:10.1007/s12671-018-1058-1
4. Vollbehr NK, Bartels-Velthuis AA, Nauta MH, Castelein S, Steenhuis LA, Hoenders HJR, et al. Hatha yoga for acute, chronic and/or treatment-resistant mood and anxiety disorders: A systematic review and meta-analysis. PLoS ONE. 2018;13(10):1-28. doi:10.1371/journal.pone.0204925
5. Cole AK, Pearson T, Knowlton M. Comparing Aerobic Exercise with Yoga in Anxiety Reduction: An Integrative Review. Issues Ment Health Nurs. 2021: 282-287. doi:10.1080/01612840.2021.1965269

Table 1: Example PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 4	Stress management techniques (relaxation, mindfulness) / treatment as usual, waitlist, no treatment	Reduction of symptoms	Kim et al. (2019)	Kim et al. (2019) was chosen for symptom reduction because it was the only recent high-quality review that reviewed trials on stress management techniques of interest.
		Adverse effects	No evidence	No evidence
		Acceptability profile (number of dropouts)	No evidence	No evidence
		Sustained response	No evidence	No evidence
		Functioning	No evidence	No evidence
		Reduction of symptoms	No evidence	No evidence

3.2. Narrative description of studies that contributed to GRADE analysis

Kim et al. (2019) conducted a systematic review and meta-analysis to explore the effect of relaxation techniques applied to people with anxiety disorders. Sixteen studies were included. These studies were published between 1988 and 2014. The pooled sample was composed of 856 subjects, of which 431 were allocated to experimental training groups, while 425 were in control groups. For the treatment group, only two types of intervention were utilized in all the selected studies: Applied Relaxation (AR) was used in nine studies, and Mindfulness-Based Stress Reduction (MBSR) was used in 7 studies. Regarding the comparison group, 12 studies utilized treatment-as-usual , while four studies utilized CBT. The number of intervention sessions ranged from eight to 48, and the duration of each session ranged from 20 to 150 min. Six studies examined the effect of relaxation on subjects with GAD; four with PD; two with SAD. In four studies subjects were not separated by subtypes of diagnosis, instead administrating relaxation to subjects with all types of anxiety disorders. Anxiety symptoms were measured using valid and reliable instruments in all selected studies. The most used instruments were the Beck Anxiety Inventory (BAI) and the Hamilton Rating Scale for Anxiety (HAMA).

3.3. Grading the Evidence

Table 2: Stress management vs treatment as usual, waitlist, no treatment

Author(s): Brandon Gray and Biksegn Asrat
Question: Are stress management techniques better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?
Setting: non-specialist care settings
Reference List:
Kim HS, Kim EJ. Effects of Relaxation Therapy on Anxiety Disorders: A Systematic Review and Meta-analysis. Arch Psychiatr Nurs. 2019;32(2):278-84. doi:10.1016/j.apnu.2017.11.015

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress management techniques	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures)												
16[b]	randomized trials	not serious[c]	serious[d]	serious[e]	not serious	none	431	425	-	SMD **0.62 SD higher** (0.42 higher to 0.81 higher)[f]	⨁⨁◯◯ Low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders – *AR only* (assessed with multiple measures)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress management techniques	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
9[b]	randomized trials	not serious[c]	serious[d]	serious[e]	not serious	none	173	167	-	SMD **0.63 SD higher** (0.38 higher to 0.88 higher)	⨁⨁◯◯ Low	CRITICAL

Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders – *MBSR only* (assessed with multiple measures)

7[b]	randomized trials	not serious[c]	serious[d]	serious[e]	not serious	none	258	258	-	SMD **0.62 SD higher** (0.31 higher to 0.93 higher)	⨁⨁◯◯ Low	CRITICAL

Reduction of anxiety symptoms post treatment in adults with GAD (assessed with multiple measures)

6[b]	randomized trials	not serious[c]	serious[d]	not serious	serious[g]	none	162	149	-	SMD **0.57 SD higher** (0.28 higher to 0.87 higher)	⨁⨁◯◯ Low	CRITICAL

Reduction of anxiety symptoms post treatment in adults with PD (assessed with multiple measures)

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress management techniques	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
4[b]	randomized trials	not serious[c]	serious[d]	not serious	serious[g]	none	59	59	-	SMD **0.69 SD higher** (0.32 higher to 1.05 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse effects in adults with mixed anxiety disorders												
0	no evidence								not estimable		-	CRITICAL
Adverse effects in adults with GAD												
0	no evidence								not estimable		-	CRITICAL
Adverse effects in adults with PD												
0	no evidence								not estimable		-	CRITICAL
Acceptability profile in adults with mixed anxiety disorders												
0	no evidence								-	**0** (0 to 0)	-	IMPORTANT
Acceptability profile in adults with GAD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress management techniques	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence								not estimable		-	IMPORTANT
Acceptability profile in adults with PD												
0	no evidence								not estimable		-	IMPORTANT
Sustained response in adults with mixed anxiety disorders												
0	no evidence								-	**0** (0 to 0)	-	IMPORTANT
Sustained response in adults with GAD												
0	no evidence								not estimable		-	IMPORTANT
Sustained response in adults with PD												
0	no evidence								not estimable		-	IMPORTANT
Functioning in adults with mixed anxiety disorders												
0	no evidence								-	**0** (0 to 0)	-	IMPORTANT
Functioning in adults with GAD												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stress management techniques	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence								not estimable		-	IMPORTANT

Functioning in adults with PD

0	no evidence								not estimable		-	IMPORTANT

Notes. AR: applied relaxation; CI: confidence interval; GAD: generalized anxiety disorder; PD: panic disorder; MBSR: mindfulness-based stress reduction; SMD: standardized mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Kim et al. (2019).

c. Risk of bias not reported in the study.

d. I squared = 48.84%.

e. Study samples included participants with excluded disorders.

f. Kim et al. (2019) also conducted subgroup analyses of applied relaxation vs control and mindfulness-based techniques vs control and found SMD's of 0.63 (95% CI = 0.38 to 0.88) and 0.62 (95% CI 0.42 to 0.81), indicating no difference in effect between these two stress management techniques.

g. Sample size and confidence intervals indicated potential imprecision.

3.4. Additional evidence not mentioned in GRADE tables

No additional evidence.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 3: Summary of findings table

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
Table 2 (Stress management vs TAU, WL, no treatment)	Kim et al. (2019)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders	SMD **0.62 SD higher** (0.42 higher to 0.81 higher)	856 (16 RCTs)	⨁⨁◯◯ Low
	Kim et al. (2019)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders: *AR only*	SMD **0.63 SD higher** (0.38 higher to 0.88 higher)	340 (9 RCTs)	⨁⨁◯◯ Low
	Kim et al. (2019)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders: *MBSR only*	SMD **0.62 SD higher** (0.31 higher to 0.93 higher)	516 (7 RCTs)	⨁⨁◯◯ Low
	Kim et al. (2019)	Reduction of anxiety symptoms post treatment in adults with GAD	SMD **0.57 SD higher** (0.28 higher to 0.87 higher)	311 (6 RCTs)	⨁⨁◯◯ Low

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
	Kim et al. (2019)	Reduction of anxiety symptoms post treatment in adults with PD	SMD **0.69 SD higher** (0.32 higher to 1.05 higher)	118 (4 RCTs)	⨁⨁◯◯ Low

Notes. CI: confidence interval; GAD: generalized anxiety disorder; RCT: randomized controlled trial; PD: panic disorder; RR: risk ratio; SD: standard deviation; SMD: standardized mean difference; TAU: treatment as usual; WL: waitlist

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

4.2 Evidence to Decision

Table 4: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations.

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	Evidence from 16 RCTs suggested a moderate, significant benefit of stress management techniques on anxiety symptom reduction in **adults with mixed anxiety disorders**. Evidence from nine RCTs suggested a moderate, significant benefit of AR techniques on anxiety symptom reduction in **adults with mixed anxiety disorders**. Evidence from nice RCTs suggested a moderate, significant benefit of MBSR techniques on anxiety symptom reduction in **adults with mixed anxiety disorders**. Evidence from six RCTs suggested a moderate, significant benefit of stress management techniques on anxiety symptom reduction in **adults with GAD**. Evidence from four RCTs suggested a moderate, significant benefit of stress management techniques on anxiety symptom reduction in **adults with PD.**	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☐ Varies ☒ **Don't know**	No reviews examining undesirable effects were identified.	No 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 overall certainty of the evidence for stress management was LOW. Certainty of the evidence for stress management techniques for **adults with mixed anxiety disorders** was LOW. Certainty of the evidence for stress management techniques for **adults with GAD** was LOW. Certainty of the evidence for stress management techniques for **adults with PD** was LOW.	No additional considerations.

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	The qualitative systematic review (Gronholm et al., 2023) also assessed values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	The intervention is consistent with the value of promotion of individual and family members' capacity and skills and the value of increasing access to care with low-intensity interventions.
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, considering 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:	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the	Low quality evidence indicated a moderately sized benefit of stress management vs TAU, WL, and no treatment on anxiety symptoms post treatment in adults with anxiety disorders. Reviews examining undesirable effects were not identified. **Thus, the effects favour stress management.**	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	- 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)?	intervention or the comparison ☒ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ Don't know		
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 fewer resources are required? • How large is the difference in each item of resource use for which more 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**	No reviews identified directly examined resource requirements.	Anecdotal evidence indicates in many settings, stress management techniques can often be delivered with minimal training and by non-specialist providers.
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**	No reviews identified directly examined resource requirements.	No additional considerations.

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 were identified.	Anecdotal evidence indicates that in many settings, stress management techniques can often be delivered with minimal training and by non-specialist providers. .
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)?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☒ **Probably increased** ☐ Increased ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available, and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	• 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?		• Affordability - medication and treatment costs These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials) • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities 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	The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 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.**	The feasibility of this intervention in nonspecialized health care settings depends on the time that the provider has available as the intervention. In situations where there is sufficient staff, such as when community paraprofessional health workers (e.g. community health workers, midwives, health workers) are available. This intervention is likely to be feasible in non-specialized health care settings.

Criteria, questions		Judgement	Research evidence	Additional considerations
			• **Participant education and literacy requires verbal explanations/tasks.** • **Logistical issues** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted several considerations which would impact the right to health and access to healthcare. (e.g. stigma and discrimination and lack of confidentiality could affect the help-seeking among service users). • The importance of sociocultural acceptability of MNS interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	• How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		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: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma. • Train acceptable counsellors for the local settings and target groups. Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility and fidelity.	

Notes. AR: applied relaxation; GAD: generalized anxiety disorder; MBSR: mindfulness-based stress reduction; MNS: mental, neurological and substance use; PD: panic disorder; RCT: randomized controlled trial; TAU: treatment as usual; WL: waitlist

4.3. Summary of judgements

Table 5: Summary of judgements

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	- Favours no intervention	- Probably favours no intervention	- Does not favour either	✓ **Probably favours intervention**	- Favours 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	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours 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

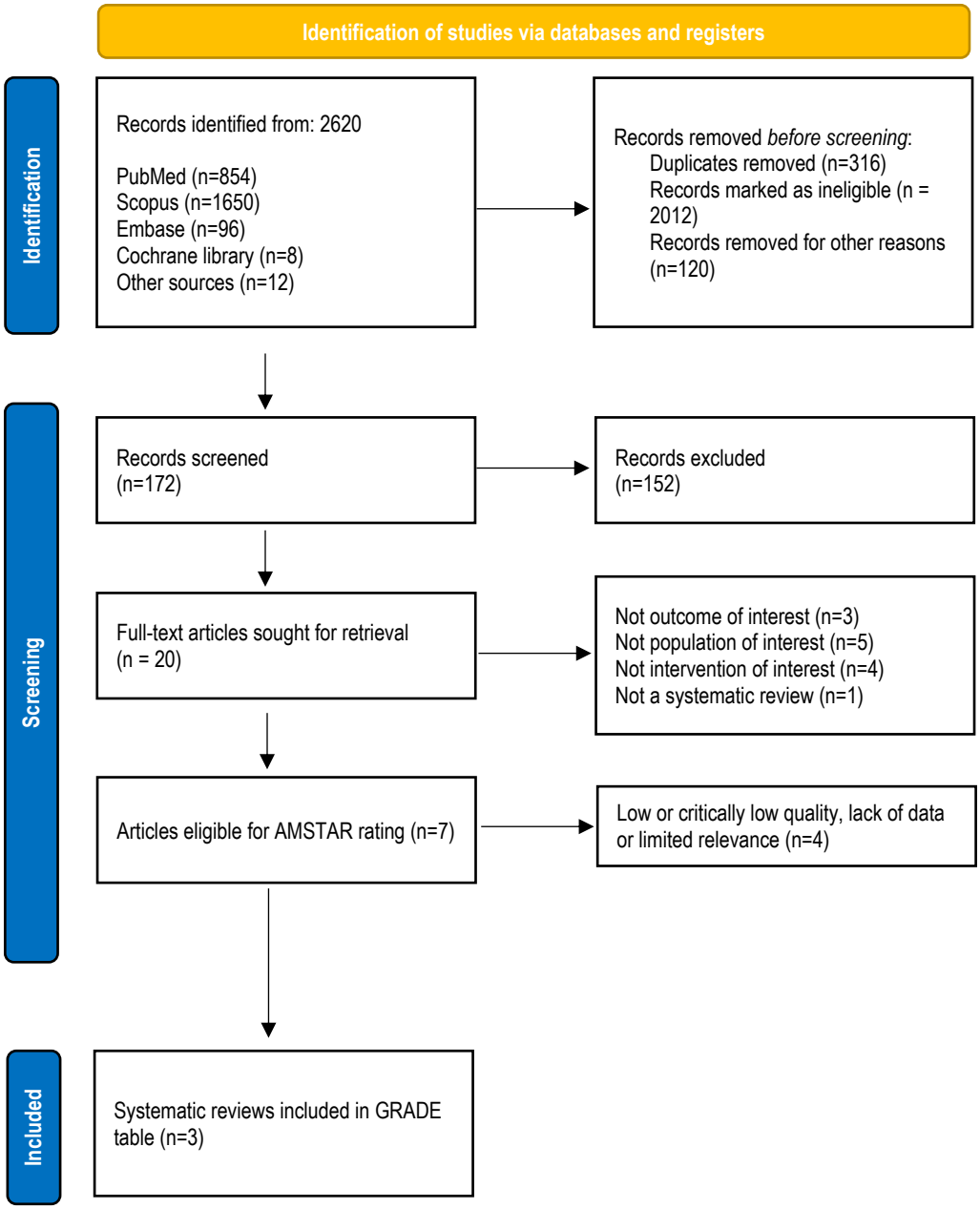
✓Indicates category selected, - Indicates category not selected.

QUESTION 5

Is advice on physical activity better (more effective/as safe as) than treatment as usual, waitlist, no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 5: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #5



3.1.1. Included in GRADE tables/footnotes

1. Ramos-Sanchez CP, Schuch FB, Seedat S, Louw QA, Stubbs B, Rosenbaum S, et al. The anxiolytic effects of exercise for people with anxiety and related disorders: An update of the available meta-analytic evidence. Psychiatry Res. 2021;302. doi:10.1016/j.psychres.2021.114046
2. Vancampfort D, Sánchez CP, Hallgren M, Schuch F, Firth J, Rosenbaum S, Van Damme T, Stubbs B. Dropout from exercise randomized controlled trials among people with anxiety and stress-related disorders: a meta-analysis and meta-regression. J Affect Disord. 2021;282:996-1004. doi:10.1016/j.jad.2021.01.003
3. Machado S, Telles G, Magalhaes F, Teixeira D, Amatriain-Fernández S, Budde H, et al. Can regular physical exercise be a treatment for panic disorder? A systematic review. Expert Rev Neurother. 2022;22(1):53-64. doi:10.1080/14737175.2021.2005581

3.1.2. Excluded from GRADE tables/footnotes

1. Moreno-Peral P, Pino-Postigo A, Conejo-Cerón S, Bellón D, Rodríguez-Martín B, Martínez-Vizcaíno V, et al. Effectiveness of Physical Activity in Primary Prevention of Anxiety: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Environ Res Public Health. 2022;19(3):1813. doi:10.3390/ijerph19031813
2. Frederiksen KP, Stavestrand SH, Venemyr SK, Sirevåg K, Hovland A. Physical exercise as an add-on treatment to cognitive behavioural therapy for anxiety: A systematic review. Behav Cognitive Psychother. 2021;49(5):626-40. doi:10.1017/S1352465821000126
3. Carneiro L, Rosenbaum S, Ward PB, Clemente FM, Ramirez-Campillo R, Monteiro-Júnior RS, et al. Web-based exercise interventions for patients with depressive and anxiety disorders: a systematic review of randomized controlled trials. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). 2021:2021-2026. doi:10.1590/1516-4446-2021-2026
4. Ashdown-Franks G, Firth J, Carney R, Carvalho AF, Hallgren M, Koyanagi A, et al. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. Sports Med. 2020;50(1):151-70. doi:10.1007/s40279-019-01187-6

Table 16: Example PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 5	Advice on physical activity / treatment as usual, waitlist, no treatment	Reduction of symptoms	Ramos-Sanchez et al. (2021)	Ramos-Sanchez et al. (2021) was selected over Vancampfort et al. (2021) and Machado et al. (2022) for symptom reduction because Machado et al. (2022) did not report pooled effects and only concerned adults with PD while Vancampfort et al. (2021) did not report on symptom reduction.
		Adverse effects	Ramos-Sanchez et al. (2021)	Ramos-Sanchez et al. (2021) was the only review that reported on adverse effects.
		Acceptability profile	Vancampfort et al. (2021)	Vancampfort et al. (2021) was selected over and Machado et al. (2022) for adverse effects because Machado et al. (2022) did not report pooled effects and only concerned adults with panic disorder.
		Sustained response	Machado et al. (2022)	Machado et al. (2022) was the only review that reported on long-term symptom reduction.
		Functioning	No evidence.	No evidence.

3.2. Narrative description of studies that contributed to GRADE analysis

Ramos-Sanchez et al. (2021) conducted a systematic review and meta-analysis of studies evaluating the effects of exercise on anxiety and stress symptoms in adults with anxiety and related disorders. Across the 13 RCTs, a total of 731 participants were included in the analysis, 376 and 355 assigned to exercise and control group, respectively. Anxiety and related disorders included in these studies were OCD, PD, PTSD, GAD, or a combination of diagnoses. Regarding the exercise modality, eight studies used aerobic exercise as an intervention, two used resistance training, and three combined aerobic and resistance training. Regarding the setting in which the studies were carried out, twelve included outpatient settings or were community-based and only one included an inpatient sample. In 10 studies, expert exercise professionals delivered the intervention, four studies included a home-based component.

Vancampfort et al. (2021) conducted a meta-analysis to investigate the prevalence and predictors of dropout rates among adults with anxiety and stress-related disorders participating in exercise RCTs. Overall, there were 14 unique RCTs, providing dropout data from a total of 16 exercise interventions, included in the review. Most of the studies investigated aerobic exercise (N = 8), two strength training and another three mixed strength and aerobic training. Three RCTs explored active body - mind interventions such as yoga or tai chi. Four RCT's used controlled motivation strategies and seven autonomous motivation strategies. One RCT use a mixed controlled and autonomous motivation strategy. Seven exercise interventions were supervised by exercise experts. Nine interventions were supervised during the entire study period. The duration of the interventions was on average eight weeks (range = 2 to 12 weeks), and most studies (N = 8) adopted a frequency of three sessions per week (range = 1 to 5). The exercise intensity was low in three studies and in the other interventions moderate-to-vigorous.

Machado et al. (2022) conducted a systematic review aims to assess the effects of regular exercise interventions on panic severity, global anxiety, and depression symptoms of adults with panic disorder. In total eight studies were included in the review. Regarding regular exercise programs, exercise groups had sample sizes between five and 39, among studies. Participants' average age was between 30 and 40 years old. Four out of eight studies developed home-based exercise programs mainly requiring walking and running, although Ma et al. also used other activities (dance, tai-chi, yoga). Furthermore, most programs developed aerobic training activities, although only two studies utilized multimodal programs encompassing other procedures such as strength training, sports, dance, among others. Intervention length was quite similar among studies, ranging from six to 12. The session duration was either 30 or 45 minutes, except in the program of one study where each session lasted 90 minutes. Most programs included three sessions per week, although two studies included home-based programs that stimulated participants to work out five times per week. Finally, exercise intensity was labelled as moderate or vigorous in all included trials, although only two trials clearly defined aerobic training intensity. Three of the included trials, exercise was combined with other interventions procedures such as group CBT and paroxetine or placebo pills. Furthermore, there was a wide range of control interventions in the studies included, namely traditional care, clomipramine treatment or placebo pills, CBT, relaxation training, educational meetings, and movement sessions. In six studies patients were individually supervised during exercise sessions, however both supervised and non-supervised studies showed significant results.

3.3. Grading the Evidence

Table 17: Advice on physical activity vs treatment as usual, waitlist, no treatment

Author(s): Brandon Gray and Biksegn Asrat
Question: Is advice on physical activity better (more effective/as safe as) than treatment as usual, waitlist no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?
Setting: non-specialist care settings
Reference List:
Ramos-Sanchez CP, Schuch FB, Seedat S, Louw QA, Stubbs B, Rosenbaum S, et al. The anxiolytic effects of exercise for people with anxiety and related disorders: An update of the available meta-analytic evidence. Psychiatry Res. 2021;302. doi:10.1016/j.psychres.2021.114046

Vancampfort D, Sánchez CP, Hallgren M, Schuch F, Firth J, Rosenbaum S, Van Damme T, Stubbs B. Dropout from exercise randomized controlled trials among people with anxiety and stress-related disorders: a meta-analysis and meta-regression. J Affect Disord. 2021;282:996-1004. doi:10.1016/j.jad.2021.01.003

Machado S, Telles G, Magalhaes F, Teixeira D, Amatriain-Fernández S, Budde H, et al. Can regular physical exercise be a treatment for panic disorder? A systematic review. Expert Rev Neurother. 2022;22(1):53-64. doi:10.1080/14737175.2021.2005581

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	advice on physical activity	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders (assessed with multiple measures of anxiety symptoms)												
13[b]	randomized trials	serious[c]	serious[d]	serious[e]	not serious	none	376	355	-	SMD **0.425 SD lower** (0.67 lower to 0.17 lower)[f]	⨁◯◯◯ Very low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD (assessed with multiple measures of anxiety symptoms)												
1[b]	randomized trials	not serious	not serious	not serious	extremely serious[g]	none	10	10	-	SMD **0.533 SD lower** (1.425 lower to 0.358 higher)[f]	⨁◯◯◯ Very low	CRITICAL
Reduction of anxiety symptoms post treatment in adults with PD (assessed with multiple measures of anxiety symptoms)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	advice on physical activity	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
2[b]	randomized trials	not serious	serious[h]	not serious	extremely serious[g]	none	21	20	-	SMD **0.919 SD lower** (-2.077 lower to 0.238 higher)[f]	⨁◯◯◯ Very low	CRITICAL
Adverse effects in adults with mixed anxiety disorders (assessed with adverse events)												
6[b,i]	randomized trials	serious[c]	serious[d]	serious[e]	not serious	none	0/218 (0.0%)	0/210 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Adverse effects in adults with GAD												
0									not estimable		-	CRITICAL
Adverse effects in adults with PD												
0									not estimable		-	CRITICAL
Acceptability profile in adults with mixed anxiety disorders (assessed with number of dropouts)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	advice on physical activity	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
16[j]	randomized trials	not serious	not serious	serious[e]	not serious	publication bias suspected[k]	56/369 (15.2%)	55/331 (16.6%)	**OR 0.84** (0.54 to 1.29)	**23 fewer per 1,000** (from 69 fewer to 38 more)	⨁⨁◯◯ Low	IMPORTANT
Acceptability profile in adults with GAD												
0									not estimable		-	IMPORTANT
Acceptability profile in adults with PD												
0									not estimable		-	IMPORTANT
Sustained reduction of anxiety symptoms in adults with mixed anxiety disorders												
0									not estimable		-	IMPORTANT
Sustained reduction of anxiety symptoms in adults with GAD												
0									not estimable		-	IMPORTANT
Sustained reduction of anxiety symptoms in adults with PD (follow-up: range 3 months to 6 months; assessed with: multiple measures of anxiety symptoms)												

Certainty assessment							№ of patients		Effect[a]		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	advice on physical activity	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
4[l]	randomized trials	serious[m]	not serious	serious[n]	not serious[g]	none	Three of four trials including follow ups reported small to moderate effects of exercise (n=92) vs control (n=85) even after the follow-up assessment (Hedges' g = 0.38 and 0.77). Conversely, one study did not find significant differences between the exercise and controls.				⨁⨁◯◯ Low	IMPORTANT
Functioning in adults with mixed anxiety disorders												
0									-	**0** (0 to 0)	-	IMPORTANT
Functioning in adults with GAD												
0									not estimable		-	IMPORTANT
Functioning in adults with PD												
0									not estimable		-	IMPORTANT

Notes. CI: confidence interval; GAD: general anxiety disorder; OR: odds ratio; PD: panic disorder; SD: standard deviation; SMD: standard mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Ramos-Sanchez et al. (2021).

c. All but one study in the review were of moderate or high risk of bias.

d. I squared = 47.9%

e. Studies included participants with excluded disorders. However, authors reported subgroup analysis indicated no differences in direction of results based on diagnosis but did not report individual diagnosis analysis results.
f. For this outcome, negative effects are reported favouring physical activity.
g. Sample size and confidence intervals indicate potential imprecision.
h. I squared = 60.72%.
i. Only a subgroup of studies reported adverse outcomes according to the review authors.
j. Vancampfort et al. (2021).
k. There was evidence of publication bias (Egger = -3.3, $p < 0.001$; Begg = -50.0, $p = 0.02$).
l. Machado et al. (2022).
m. Three of the four studies in the review were of high risk of bias.
n. Two of four studies included active control comparisons (CBT and low intensity physical exercise).

3.4. Additional evidence not mentioned in GRADE tables

An ancillary meta-analysis published outside of the review period (Vancampfort et al., 2022) reviewed data on anxiety outcomes for exercise interventions in people with anxiety and stress related disorders from a recent systematic review with meta-analysis of RCTs on the effects of exercise interventions on anxiety and stress related outcomes in anxiety and stress related disorders (Ramos-Sanchez et al., 2021).

Searches were updated for the purpose of this meta-analysis. The original meta-analysis included 13 RCTs, of which seven were excluded for this ancillary meta-analysis due to: (i) missing data for standard deviations either pre- or post- exercise or control conditions, (ii) no anxiolytic outcomes but only stress-related outcomes explored, or (iii) an active control condition.

No significant pooled interindividual differences (IIDs) were found for aerobic exercise nor resistance training demonstrating that there is currently a lack of convincing evidence to support the notion that true IIDs exist for the anxiolytic effects of exercise among adults with anxiety- and stress-related disorders. The authors thus concluded, that*: "based on the currently available evidence, it can be cautiously suggested that general recommendations, such as for example the one of the WHO can be used in clinical practice instead of highly specific, individualized aerobic exercise and strength training recommendations."*

4. From Evidence to Recommendations

4.1. Summary of findings

Table 18: Summary of findings table

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
Table 2 (Physical activity vs TAU, WL, no treatment)	Ramos-Sanchez et al. (2021)	Reduction of anxiety symptoms post treatment in adults with mixed anxiety disorders	SMD **0.425 SD lower** (0.67 lower to 0.17 lower)[b]	731 (13 RCTs)	⊕◯◯◯ Very low
	Ramos-Sanchez et al. (2021)	Reduction of anxiety symptoms post treatment in adults with GAD	SMD 0.533 SD lower (1.425 lower to 0.358 higher)[b]	20 (1 RCT)[b]	⊕◯◯◯ Very low
	Ramos-Sanchez et al. (2021)	Reduction of anxiety symptoms post treatment in adults with PD	SMD 0.919 SD lower (2.077 lower to 0.238 higher)[b]	41 (2 RCTs)	⊕◯◯◯ Very low
	Ramos-Sanchez et al. (2021)	Adverse effects in adults with mixed anxiety disorders	**0 per 1,000** (0 to 0)[c]	428 (6 RCTs)	⊕◯◯◯ Very low
	Vancampfort et al. (2021)	Acceptability profile in adults with mixed anxiety disorders	**143 per 1,000** (97 to 204) **OR 0.84** (0.54 to 1.29)	700 (16 RCTs)	⊕⊕◯◯ Low

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
	Machado et al. (2022)	Sustained reduction of anxiety symptoms in adults with PD	Effects reported based on 177 total participants from four RCTs. Three of four trials including follow ups reported small to moderate effects of exercise (n=92) vs control (n=85) even after the follow-up assessment (Hedges' g = 0.38 and 0.77). Conversely, one study did not find significant differences.		⊕⊕◯◯ Low

Notes. CI: confidence interval; GAD: generalized anxiety disorder; OR: odd ratio; RCT: randomized controlled trial; PD: panic disorder; SD: standard deviation; SMD: standardized mean difference; TAU: treatment as usual; WL: waitlist

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. For this outcome, negative effects are reported favouring physical activity.

c. No adverse effects reported in either the treatment or comparison group.

4.2 Evidence to Decision

Table 19: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations.

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	Evidence from 13 RCTs suggested a moderate, significant benefit of physical exercise on anxiety symptom reduction in **adults with mixed anxiety.** Evidence from one RCT suggested no significant difference between physical exercise and comparison on anxiety symptom reduction in **adults with GAD.** Evidence from two RCTs suggested no significant difference between physical exercise and comparison on anxiety symptom reduction in **adults with PD.** Evidence from four RCTs suggested a moderate to large, significant benefit of physical exercise on sustained reduction of anxiety symptoms in **adults with mixed anxiety disorders.**	No additional considerations.
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	Evidence from six RCTs indicated there was no significant difference in **adverse events** between physical exercise and TAU, WL, and no treatment in **adults with mixed anxiety disorders.** Evidence from 16 RCTs indicated there was no significant difference in **dropout** between physical exercise and TAU, WL, and no treatment conditions in **adults with mixed anxiety disorders.**	No additional considerations

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 overall certainty of the evidence was VERY LOW. Certainty of the evidence for **reduction of anxiety symptoms** in **adults with mixed anxiety disorders** was VERY LOW. Certainty of the evidence for reduction of anxiety symptoms in **adults with GAD** was VERY LOW. Certainty of the evidence for **adverse effects** in **adults with mixed anxiety disorders** was VERY LOW. Certainty of the evidence for **acceptability (number of dropouts)** in **adults with mixed anxiety disorders** was LOW. Certainty of the evidence for **sustained reduction of anxiety symptoms** in **adults with mixed anxiety disorders** was LOW.	No 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	A qualitative systematic review was commissioned (Gronholm et al., 2023) to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility	There is cultural variability in perception of the value of physical exercise, which may lead to variability in

Criteria, questions		Judgement	Research evidence	Additional considerations
		☐ Possibly important uncertainty or variability ☒ **Probably no important uncertainty or variability** ☐ No important uncertainty or variability	and human rights related factors in mental health care and mental health services. Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	uptake and successful implementation on this intervention in different settings.
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, considering 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	Very low-quality evidence indicated a moderately sized benefit of physical exercise vs TAU, WL, and no treatment for adults with anxiety disorders and no difference in adverse effects. **Thus, the effects favour physical** exercise**.**	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more 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. However, a recent global study described the investment case for scaling up the response to public health and economic burden of common mental disorders, including depression and anxiety disorders. Results indicated the benefit to cost ratios for anxiety disorders ranged from 3.3 to 4.0, indicating a substantial return on investment in increased economic productivity and improved health *(21)*.	Advice on physical exercise is an intervention can often be easily implemented in non-specialist and low-resource settings with limited resources.
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.	No additional considerations.

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	No additional considerations.
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? 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 based on 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)?	☐ Reduced ☐ Probably reduced ☐ Probably no impact **☒ Probably increased** ☐ Increased ☐ Varies	Evidence indicates substantial health benefits following physical exercise for adults, including : improved all-cause mortality, cardiovascular disease mortality, incident hypertension, incident site specific cancers, incident type-2 diabetes, cognitive health, sleep, and measures of adiposity (WHO, 2020)	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	• 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?	☐ Don't know	The qualitative review (Gronholm et al., 2023) also noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations. • time & travel constraints. • Accessibility, informational barriers. • Affordability - medication and treatment costs. These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials). • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities 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	The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 implementation steps for simpler decision-making and delivery.	The extent to which health worker advice to do exercise to improve anxiety will be accepted by service users in low- and middle-income countries in not known. This intervention may be less appropriate for people engaged in physical labour and instead may be more

Criteria, questions		Judgement	Research evidence	Additional considerations
			• **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** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	relevant for those with less active lifestyles.
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted several 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	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility. Mitigating steps to improve sociocultural acceptability include: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma. • Train acceptable counsellors for the local settings and target groups. Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility, and fidelity.	

Notes. GAD: generalized anxiety disorder; MBSR: mindfulness-based stress reduction; MNS: mental, neurological and substance use; PD: panic disorder; RCT: randomized controlled trial; TAU: treatment as usual; WL: waitlist

4.3. Summary of judgements

Table 20: Summary of judgements

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	- Favours no intervention	- Probably favours no intervention	- Does not favour either	✓ **Probably favours intervention**	Favours 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	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours 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

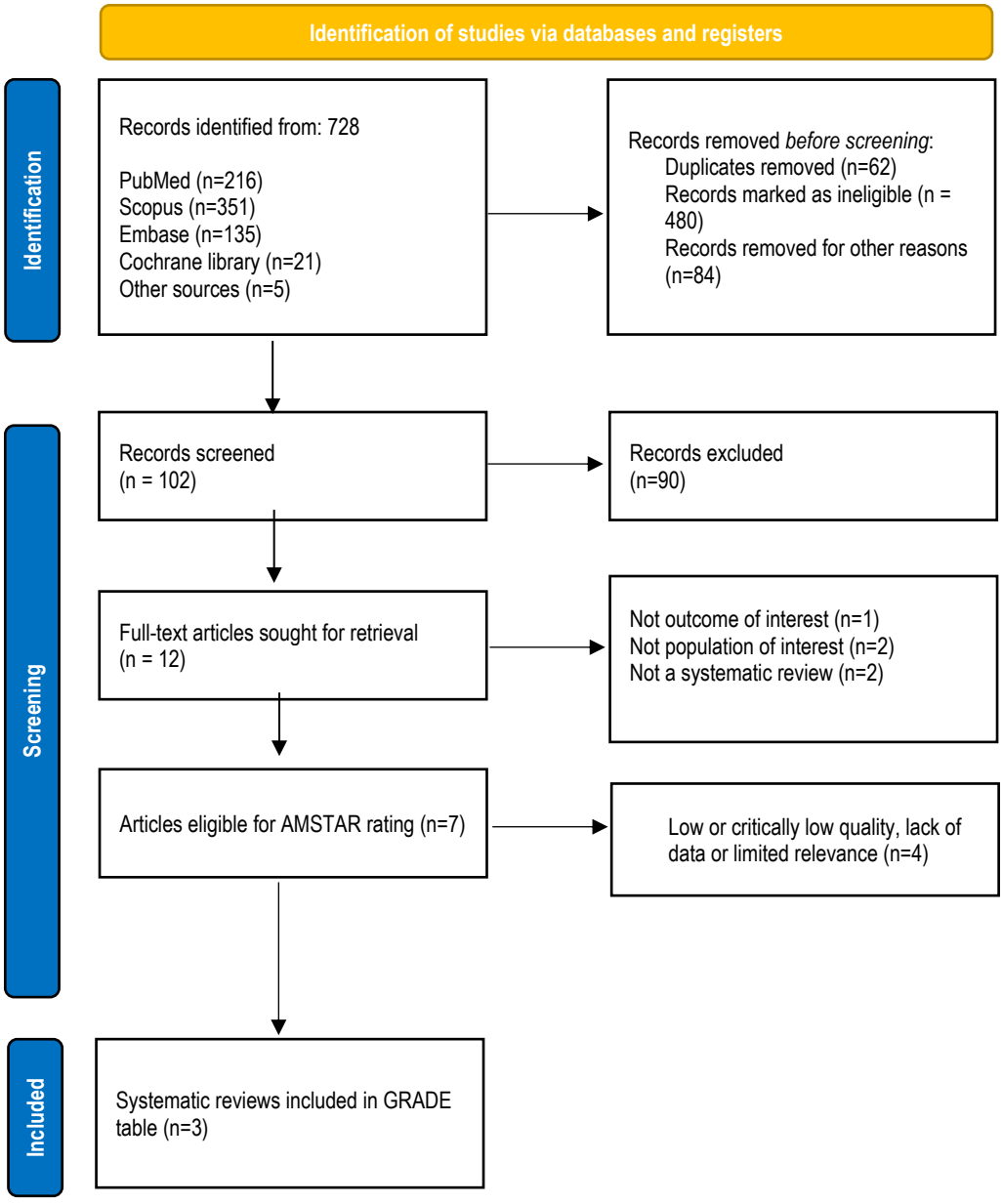
✓Indicates category selected, - Indicates category not selected.

QUESTION 6

Are benzodiazepines better (more effective/as safe as) than placebo for adults with anxiety disorders (excluding social phobia, SAD)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 21: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #6



3.1.1. Included in GRADE tables/footnotes

1. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalized anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768-77. doi:10.1016/S0140-6736(18)31793-8
2. Breilmann J, Girlanda F, Guaiana G, Barbui C, Cipriani A, Castellazzi M, et al. Benzodiazepines versus placebo for panic disorder in adults. Cochrane Database of Systematic Reviews. 2019(3). doi:10.1002/14651858.CD010677.pub2
3. Shinfuku M, Kishimoto T, Uchida H, Suzuki T, Mimura M, Kikuchi T. Effectiveness and safety of long-term benzodiazepine use in anxiety disorders: a systematic review and meta-analysis. Int Clin Psychopharmacol. 2019;34(5):211-21. doi:10.1097/YIC.0000000000000276

3.1.2. Excluded from GRADE tables/footnotes

1. Du Y, Du B, Diao Y, Yin Z, Li J, Shu Y, et al. Comparative efficacy and acceptability of antidepressants and benzodiazepines for the treatment of panic disorder: A systematic review and network meta-analysis. Asian J Psychiatr. 2021;60:102664. doi:10.1016/j.ajp.2021.102664
2. Balasubramaniam M, Joshi P, Alag P, Gupta S, Maher S, Tampi D, et al. Antidepressants for Anxiety Disorders in Late-Life: A Systematic Review. Am J Geriatr Psychiatry. 2019;27(3). doi:10.1016/j.jagp.2019.01.076
3. Gomez AF, Barthel AL, Hofmann SG. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review. Expert Opin Pharmacother. 2018;19(8):883-94. doi:10.1080/14656566.2018.1472767
4. Melani MS, Paiva JM, Silva MC, Mendlowicz MV, Figueira I, Marques-Portella C, et al. Absence of definitive scientific evidence that benzodiazepines could hinder the efficacy of exposure-based interventions in adults with anxiety or posttraumatic stress disorders: A systematic review of randomized clinical trials. Depress Anxiety. 2020;37(12):1231-42. doi:10.1002/da.23078

Table 20: Example PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 6	Benzodiazepines / placebo	Symptom reduction	Slee et al. (2019); Breilmann et al. (2019)	Slee et al. (2019) was selected for the outcome of symptom reduction because it was a high-quality review that examined effects of the intervention in adults with GAD and because it reported enough data for NMA GRADING. Breilmann et al. (2019) was selected for the outcome of symptom reduction because it was the only high-quality review identified that examined the effects of the intervention in adults with PD.
		Adverse effects	Breilmann et al. (2019); Parsaik et al. (2016)	Breilmann et al. (2019) was selected for the outcome of symptom reduction because it was the only high-quality review identified that examined the adverse effects of the intervention in adults with PD.
		Acceptability profile (dropouts)	Slee et al. (2019); Breilmann et al. (2019)	Breilmann et al. (2019) and Slee et al. (2019) were selected for the outcome of acceptability because there were the only high-quality reviews identified that examined the effects of the intervention in adults with PD and GAD, respectively.
		Sustained response	Breilmann et al. (2019); Shinfuku et al. (2019)	Breilmann et al. (2019) and Slee et al. (2019) were selected for the outcome of sustained response because they were the only high-quality reviews identified that examined the effects of the intervention in adults with PD and GAD, respectively.
		Functioning	Breilmann et al. (2019)	Breilmann et al. (2019) was selected for the outcome of functioning because it was the only high-quality review identified that examined the adverse effects of the intervention in adults with PD.

Notes. GAD: generalized anxiety disorder; NMA: Network Meta-Analysis; PD: panic disorder

3.2. Narrative description of studies that contributed to GRADE analysis

Breilmann et al. (2019) conducted a systematic review and meta-analysis to assess the efficacy and acceptability of benzodiazepines versus placebo in the treatment of panic disorder with or without agoraphobia in adults.

The review included 24 studies in the review with a total of 3599 participants, of which 2124 were randomized to benzodiazepines and 1475 to placebo. The remaining 634 participants were randomized to other active interventions in three-arm trials. The overall methodological quality of the included studies was assessed as poor.

Slee et al. (2019) conducted a systematic review and NMA of the evidence on the effectiveness of pharmacological interventions, including benzodiazepines, for adults with GAD.

In total, 89 studies were included and were published between 1 January 1998, and 31 August 2016. None of the trials deliberately restricted to incident GAD, and 73 (82%) of 89 studies used the DSM criteria, which requires a six-month duration of symptoms to complete the diagnosis. These studies ranged in duration of follow up from four to 26 weeks (median duration eight weeks), and all studies included change in HAM-A as a primary or secondary endpoint. The median baseline HAM-A score was 25 (interquartile range [IQR] 24–27). In total, 25 441 patients were enrolled in these trials. Sixty-three trials (71%) were placebo-controlled, and 45 (51%) included more than one active drug. Most of the trials were double-blind and were conducted by pharmaceutical companies as part of a clinical development programme.

Shinfuku et al. (2019) performed a systematic review and meta-analysis of the effectiveness and safety of long-term benzodiazepine use in adults with anxiety disorders. A total of eight studies were included in review. Four studies were RCTs with durations of six months, six months, 24 weeks, and 16 weeks, respectively and the other for studies were maintenance studies following RCTs lasting seven, eight, eight, and 36 months, respectively.

3.3. Grading the Evidence

Table 21.1: Benzodiazepines vs treatment as usual, waitlist, no treatment

Author(s): Brandon Gray, Biksegn Asrat and Davide Papola
Question: Are benzodiazepines better (more effective/as safe as) than placebo for adults with anxiety disorders (excluding social phobia, SAD)?
Setting: Non-specialist care settings
Reference List:
Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalized anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393(10173):768-77. doi:10.1016/S0140-6736(18)31793-8

Breilmann J, Girlanda F, Guaiana G, Barbui C, Cipriani A, Castellazzi M, et al. Benzodiazepines versus placebo for panic disorder in adults. Cochrane Database of Systematic Reviews. 2019(3). doi:10.1002/14651858.CD010677.pub2

Shinfuku M, Kishimoto T, Uchida H, Suzuki T, Mimura M, Kikuchi T. Effectiveness and safety of long-term benzodiazepine use in anxiety disorders: a systematic review and meta-analysis. Int Clin Psychopharmacol. 2019;34(5):211-21. doi:10.1097/YIC.0000000000000276

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment in adults with mixed disorders												
0									not estimable		-	CRITICAL
Reduction of anxiety symptoms post treatment in adults with GAD (assessed with HAM-A)												
8	See NMA table 2.2 below											
Reduction of panic symptoms post treatment in adults with PD (assessed with multiple measures of panic symptoms (CGI-S, CGI-I, PGI))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute (95% CI)		
7[a]	RCTs	serious[b]	very serious[c]	not serious	not serious	publication bias strongly suspected[d]	817	672	-	SMD **0.92 SD lower** (1.22 lower to 0.61 lower)	⨁◯◯◯ Very low[e]	CRITICAL
Reduction of panic attacks post treatment in adults with PD (assessed with frequency of panic attacks through patient diary)												
16[a]	RCTs	serious[b]	serious[f]	not serious	not serious	publication bias strongly suspected[d]	1268	861	-	SMD **2.12 SD lower** (3.07 lower to 1.17 lower)	⨁◯◯◯ Very low[e]	CRITICAL
Adverse events in adults with any diagnosis (follow-up: range 1 years to 22 years; assessed with mortality)												
10[g,h]	observational studies	not serious	very serious[i]	very serious[j]	not serious	none	0/0	0/0	**HR 1.60** (1.03 to 2.49)	**2 more per 1,000** (from 2 fewer to 1 more)	⨁◯◯◯ Very low[k]	CRITICAL
Adverse events in adults with GAD												
0							0/0	0/0	not estimable		-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events in adults with PD												
14[a]	randomized trials	serious[b]	not serious	not serious	not serious	publication bias strongly suspected[d]	245/1942 (12.6%)	28/1321 (2.1%)	**RR 1.58** (1.16 to 2.15)	**12 more per 1,000** (from 3 more to 24 more)	⨁⨁◯◯ Low	CRITICAL
Acceptability profile in adults with mixed anxiety disorders												
0							0/0	0/0	not estimable		-	IMPORTANT
Acceptability profile in adults with GAD (follow-up: median 8 weeks; assessed with: number of dropouts)												
8[b]	See NMA table 2.3 below											IMPORTANT
Acceptability profile in adults with PD (follow-up: range 4 weeks to 15 weeks; assessed with: number of dropouts)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute (95% CI)		
21[a]	randomized trials	serious[b]	serious[l]	not serious	not serious	publication bias strongly suspected[d]	394/2102 (18.7%)	504/1456 (34.6%)	**RR 0.50** (0.39 to 0.64)	**173 fewer per 1,000** (from 211 fewer to 125 fewer)	⨁◯◯◯ Very low	IMPORTANT

Sustained response in adults with mixed anxiety disorders (follow-up: range 4 months to 8 months; assessed with: HAM-A)

3[m,n]	observational studies	serious[o]	not serious	serious[p]	not serious	none	234	239	-	SMD **0.049 SD lower** (0.295 lower to 0.198 higher)	⨁◯◯◯ Very low[e]	IMPORTANT

Sustained response in adults with GAD

0							0/0	0/0	not estimable		-	IMPORTANT

Sustained response in adults with PD (follow-up: range 3 weeks to 15 weeks; assessed with: substantial improvement from baseline as defined by the original investigators)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	benzodiazepines	placebo	Relative (95% CI)	Absolute (95% CI)		
16[a]	randomized trials	serious[b]	serious[q]	not serious	not serious	publication bias strongly suspected[d]	1040/1536 (67.7%)	387/940 (41.2%)	**RR 1.65** (1.39 to 1.96)	**268 more per 1,000** (from 161 more to 395 more)	⨁◯◯◯ Very low	IMPORTANT
Functioning in adults with mixed anxiety disorders												
0							0/0	0/0	not estimable		-	IMPORTANT
Functioning in adults with GAD												
0							0/0	0/0	not estimable		-	IMPORTANT
Functioning in adults with PD (assessed with: multiple measures of functioning (Work and Social Disability Scale, Three-Factor Disability Scale, Social Adjustment Self-Report Questionnaire))												
5[a]	randomized trials	serious[b]	not serious	not serious	not serious	publication bias strongly suspected[d]	656	551	-	SMD **0.53 SD lower** (0.65 lower to 0.42 lower)	⨁⨁◯◯ Low[e]	IMPORTANT

Notes. CI: confidence interval; CGI: Clinical Global Impression- Improvement scale; CGI-S: Clinical Global Impression – Severity scale ; GAD: general anxiety disorder; HAM-A: Hamilton Anxiety Scale; HR: hazard ratio; NMA: Network Meta-Analysis; PD: panic disorder; PGI: Patient Global Impressions scale; SD: standard deviation; SMD: standard mean difference; RCT: randomized controlled trial.

Explanations

a. Breilmann et al. (2019).

b. All studies were rated as having an unclear risk of bias in at least three domains. In addition, 20 of the 24 included studies were rated as having a high risk of bias in at least one domain and more than half were rated as having high risk of bias in at least two domains.

c. I squared = 77.4%.

d. Authors reported probable publication bias.

e. For this outcome, negative effects are reported favouring benzodiazepines.

f. I squared = 74.97%.

g. Parsaik et al. (2016).

h. Total sample for this subgroup analysis was not reported.

i. I squared = 99%.

j. The meta-analysis was not diagnosis specific and included adults taking benzodiazepines for many causes.

k. On stratification, 10 studies reported mortality risk associated with only benzodiazepines use and pooled analysis showed 60% higher mortality among benzodiazepines users as compared to non-users (HR = 1.60, 95% CI = [1.03, 2.49])

l. 1 squared = 63%.

m. Maintenance studies after RCTs included.

n. Shinfuku et al. (2019).

o. Observed case analysis was used in one of three studies for imputing missing data.

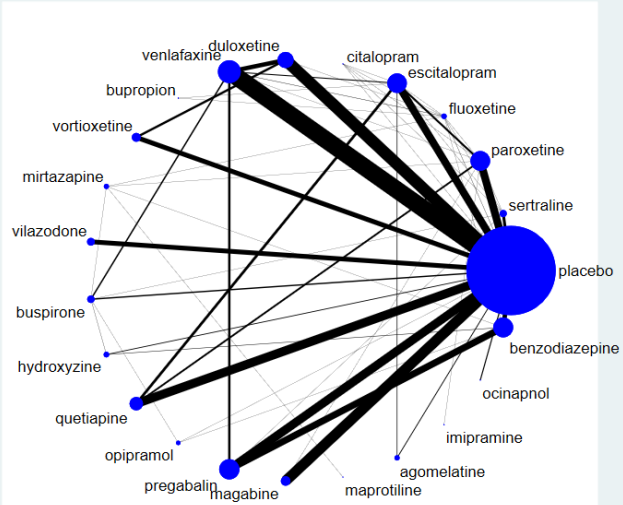
p. Studies included participants with excluded disorders and benzodiazepines appeared to be prescribed in specialist care settings.

q. I squared = 67%.

Table 21.1 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: Benzodiazepines
Comparator (reference): placebo
Outcome: reduction of anxiety symptoms
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



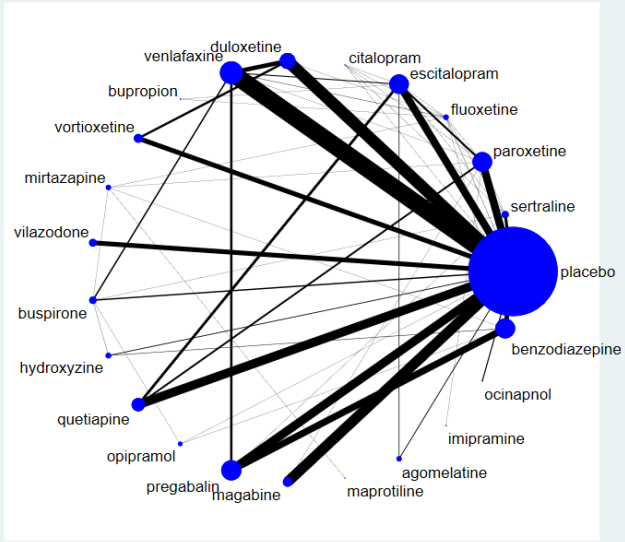
	Relative effect** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of participants (studies)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
Benzodiazepines	**-2.29 SD** (-3.19 to -1.39)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	25.4%	2992 (15 RCTs)

Notes. CI: confidence interval; CINeMA: network meta-analyses; NMA: network meta-Analysis; RCT: randomized controlled trial; SD: standard deviation
NMA table definitions
* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as mean difference.

Table 21.2 Bayesian Network Meta-Analysis Summary of Findings (NMA-SoF) table

Patient or population: adults with GAD
Interventions: Benzodiazepines
Comparator (reference): placebo
Outcome: acceptability (number of dropouts)
Setting(s): non-specialist care settings
Reference: Slee et al. (2019)

Geometry of the Network*



	Odds Ratio** (95% CI)	CINeMa ratings						Confidence rating	SUCRA	Number of participants (studies)
		Risk of bias	*Reporting bias*	*Indirectness*	*imprecision*	*Heterogeneity*	*Incoherence*			
Benzodiazepines	**1.43 SD** (1.12 to 1.86)	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	⊕⊕◯◯ Low	25.4%	2861 (15 RCTs)

Notes. CI: confidence interval; CINeMA: network meta-analyses; NMA: network meta-Analysis; RCT: randomized controlled trial; SUCRA: Surface under the cumulative ranking; SD: standard deviation
NMA table definitions

* Solid lines represent direct comparisons
** Network Metanalysis estimates are reported as risk ratio.

3.4. Additional evidence not mentioned in GRADE tables

Parsaik et al. (2016) conducted a systematic review and meta-analysis of the evidence on mortality risk associated with hypnotics or anxiolytic use that was not identified in the literature review because it was published prior to the search's timeframe and was not specific to adults with anxiety disorders.

In total, 25 studies were included in the final review. Of the 25 included studies, 24 were cohort studies (22 prospective cohorts and two retrospective cohorts), while one study was case control, wherein for mortality analysis, only cases with community-acquired pneumonia were included (Obiora et al., 2013). Studies were conducted in different countries across the world. Total sample size included in this meta-analysis was 2 350 093 (range 500 to 1 099 830) participants with 59% being females. Age of participants ranged from 18 to 102 years. Duration of follow up ranged widely from 1 to 22 years. Very low-quality evidence based on ten studies indicated that **benzodiazepines demonstrated an increased risk of mortality post treatment** (HR 1.60; 95% CI 1.03 to 2.49) compared to placebo.

Additional evidence regarding the potential for harms associated with benzodiazepines, particularly when used as a long-term treatment option, should also be considered. Firstly, Benzodiazepines have been associated with increased risk for misuse and dependence. Population-based data, though limited, appears to indicate similar rates of misuse worldwide (Votaw et al., 2019).

In a 2010 population-based survey of nearly 35 000 participants in the United States, **Benzodiazepine prescriptions were also significantly associated with increased odds of past year nonmedical use (OR = 1.94; CI 1.40 to 2.69) and developing lifetime benzodiazepine abuse or dependence (OR = 2.60; CI 1.88 to 3.60).** These results were not associated with an anxiety disorder diagnosis, severity of anxiety disorder, or co-occurring drug use (Fenton, 2010).

Evidence also indicates that **benzodiazepine**s: i) have increasingly been **associated with mortality due to drug overdos**e (Lembke et al., 2018) ii) **require months to years for individuals to taper off**, with the majority of users failing to achieve sustained discontinuation (Dell'Osso et al., 2015; Brandt & Leong, 2017) and only 13% of adults who take benzodiazepines long-term (more than four months) being able to discontinue their use within one year (Gerlach et al., 2019); and iii) **lead to re-initiation of use even after discontinuation in the majority of users**, with an estimated two in three people who have tapered off long-term benzodiazepine treatment resuming use sometime thereafter (Vosharr et al., 2006).

4. From Evidence to Recommendations

4.1. Summary of findings

Table 22: Summary of findings table

GRADE table	Source	Outcomes	Effects[b]	№ of participants (studies)	Certainty of the evidence (GRADE)
Tables 2, 2.1, 2.2 (Benzodiazepines vs TAU, WL, no treatment)[a]	Slee et al. (2019)	Reduction of anxiety symptoms post treatment in adults with GAD	MD **2.29 lower** (3.19 lower to 1.39 lower)[c]	2992 (15 RCTs)	⊕⊕◯◯ Low
	Breilmann et al. (2019)	Reduction of panic symptoms post treatment in adults with PD	SMD **0.92 SD lower** (1.22 lower to 0.61 lower)[c]	1489 (7 RCTs)	⊕◯◯◯ Very low
	Breilmann et al. (2019)	Reduction of panic attacks post treatment in adults with PD	MD **2.12 SD lower** (3.07 lower to 1.17 lower)[c]	2129 (16 RCTs)	⊕◯◯◯ Very low
	Breilmann et al. (2019)	Adverse events in adults with PD	**33 per 1000** (25 to 46) **RR 1.58** (1.16 to 2.15)	3263 (14 RCTs)	⊕⊕◯◯ Low
	Slee et al. (2019)	Acceptability profile in adults with GAD	OR **1.43** (1.12 to 1.86)	2861 (15 RCTs)	⊕⊕◯◯ Low
	Breilmann et al. (2019)	Acceptability profile in adults with PD	**173 per 1000** (135 to 222) **RR 0.50** (0.39 to 0.64)	3558 (21 RCTs)	⊕◯◯◯ Very low

GRADE table	Source	Outcomes	Effects[b]	№ of participants (studies)	Certainty of the evidence (GRADE)
	Shinfuku et al. (2019).	Sustained response in adults with mixed anxiety disorders	SMD **0.049 SD lower** (0.295 lower to 0.198 higher)	473 (3 studies)	⊕⊕◯◯ Low
	Breilmann et al. (2019)	Sustained response in adults with PD	**679 per 1000** (572 to 807) **RR 1.65** (1.39 to 1.96)	2476 (16 RCTs)	⊕◯◯◯ Very low
	Breilmann et al. (2019)	Functioning in adults with PD	SMD **0.53 SD lower** (0.65 lower to 0.42 lower)	1207 (5 RCTs)	⊕⊕◯◯ Low

Notes. CI: confidence interval; GAD: general anxiety disorder; PD: panic disorder; RR: risk ratio; SD: standard deviation; SMD: standard mean difference; RCT: randomized controlled trial.

Explanations

a. Benzodiazepines studied in the included reviews were as follows: not reported (Slee et al., 2019), alprazolam, adinazolam, clonazepam, diazepam, and midazolam (Breilman et al., 2019), and alprazolam, diazepam, lorazepam, ketazolam (Shinfuku et al., 2019).

b. Unless otherwise stated, positive effect values favour the intervention.

c. For this outcome, negative effects are reported favouring benzodiazepines.

d. No adverse effects reported in either the treatment or comparison group

4.2. Evidence to Decision

Table 23: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations.

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☒ **Small** ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	Evidence from 15 RCTs suggested a significant benefit of benzodiazepines vs placebo on **anxiety symptom reduction** in **adults with GAD.** Evidence from seven RCTs suggested a significant benefit of benzodiazepines vs placebo on **panic symptom reduction** in **adults with PD.** Evidence from 16 RCTs suggested a significant benefit of benzodiazepines vs placebo on **panic attack reduction** in **adults with PD.** Evidence from three RCTs suggested a no significant difference between benzodiazepines vs placebo on **sustained reduction of anxiety symptoms** at follow up in **adults with mixed anxiety disorders.** Evidence from five RCTs suggested a significant benefit of benzodiazepines vs placebo on **functioning** in **adults with PD.**	No additional considerations.
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☒ **Large** ☐ Moderate ☐ Small ☐ Trivial ☐ Varies ☐ Don't know	Evidence from 14 RCTs indicated there was an increased risk of **adverse events** following the use benzodiazepines vs placebo in **adults with PD.** Evidence from 14 RCTs indicated there was an increased risk of **dropout** following the use benzodiazepines vs placebo in **adults with GAD.**	Evidence from ten observational studies and RCTs in Parsaik et al. (2016) indicated there was an increased risk of mortality following the use benzodiazepines vs placebo in **adults with any diagnosis.**

Criteria, questions		Judgement	Research evidence	Additional considerations
			Evidence from 21 RCTs indicated there was a decreased risk of **dropout** following the use benzodiazepines vs placebo in **adults with PD.**	Benzodiazepines have also been associated with increased risk for misuse and dependence. Population-based data, though limited, appears to indicate similar rates of misuse worldwide (Votaw et al., 2019). In a 2010 population-based survey of nearly 35 000 participants in the United States, **Benzodiazepine prescriptions were also significantly associated with increased odds of past year nonmedical use (OR = 1.94; CI 1.40 to 2.69) and developing lifetime benzodiazepine abuse or dependence (OR = 2.60; CI 1.88 to 3.60).** These results were not associated with an anxiety disorder diagnosis, severity of anxiety disorder, or co-occurring drug use (Fenton, 2010). Evidence also indicates that **benzodiazepine**s: i) have increasingly been **associated with mortality due to drug overdos**e (Lembke et al., 2018) ii) **require months to years for individuals to taper**

Criteria, questions		Judgement	Research evidence	Additional considerations
				off, with the majority of users failing to achieve sustained discontinuation (Dell'Osso et al., 2015; Brandt & Leong, 2017) and only 13% of adults who take benzodiazepines long-term (more than four months) being able to discontinue their use within one year (Gerlach et al., 2019); and iii) **lead to re-initiation of use even after discontinuation in the majority of users**, with an estimated two in three people who have tapered off long-term benzodiazepine treatment resuming use sometime thereafter (Vosharr et al., 2006).
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 overall certainty of the evidence was LOW. Certainty of the evidence for **reduction of anxiety symptoms** in **adults with GAD** was LOW. Certainty of the evidence for **reduction of panic symptoms** in **adults with PD** was VERY LOW Certainty of the evidence for **reduction of panic attacks** in **adults with PD** was VERY LOW.	Certainty of the evidence for **adverse effects** in adults with any diagnosis from Parsaik et al.'s (2016) review was VERY LOW.

Criteria, questions		Judgement	Research evidence	Additional considerations
			Certainty of the evidence for **adverse effects** in **adults with PD** was VERY LOW. Certainty of the evidence for **acceptability (number of dropouts)** in **adults with GAD** was LOW. Certainty of the evidence for **acceptability (number of dropouts)** in **adults with PD** was VERY LOW. Certainty of the evidence for **sustained reduction of anxiety symptoms** in **adults with mixed anxiety disorders** was LOW. Certainty of the evidence for **sustained reduction of anxiety symptoms** in **adults with mixed PD** was VERY LOW. Certainty of the evidence for **functioning** in **adults with PD** was LOW.	
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**	A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services.	Regarding medications, cultural and social factors may also influence preferences for pharmacological interventions. However, no consistent direct evidence on this topic was identified.

Criteria, questions		Judgement	Research evidence	Additional considerations
		uncertainty or variability ☐ No important uncertainty or variability	Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility 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. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	
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, considering 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	Low quality evidence indicated a large benefit of benzodiazepines vs placebo for adults with GAD and PD. However, evidence also suggested an increased risk of adverse events following benzodiazepine use vs placebo in adults with GAD and PD. Additionally, evidence suggested an increased risk of dropout following benzodiazepine use vs placebo in adults with GAD but a decreased risk in adults with PD. **Thus, considering the evidence and additional considerations, the effects do not favour either the intervention or the comparison.**	Evidence for Parasaik et al.'s (2016) review also indicated an increased risk of mortality following benzodiazepine use compared to placebo.

Criteria, questions		Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more 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. However, a recent global study described the investment case for scaling up the response to public health and economic burden of common mental disorders, including depression and anxiety disorders. Results indicated the benefit to cost ratios for anxiety disorders ranged from 3.3 to 4.0, indicating a substantial return on investment in increased economic productivity and improved health Evidence also suggests benzodiazepines may be associated with unnecessary costs from medicine ingredient costs, dispensing costs, and consultation costs due to misuse and unnecessary prescribing. In a study of the United Kingdom National Health System, 67–72% of total costs related to benzodiazepines were estimated to be unnecessary with a total unnecessary cost over three years (April 2015-March 2018) of £115 588 439 to £129 870 520 and a mean yearly unnecessary cost of £38 529 480 to £43 290 173 (Davies et al., 2022). In adults with GAD, evidence also suggests long-term benzodiazepine use increases health care costs significantly. In a retrospective cohort study of 866 adults in the United States (Berger et al., 2012) also indicated that mean total healthcare costs increased by $2334 following the initiation of a long-term (>90 days) course of	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			treatment with a benzodiazepine treatment (from $4637 [SD=$9840] pre-treatment to $6971 [$17 002]; p<0.01) posttreatment; costs of accident-related encounters and other care that was possibly related to use of benzodiazepines increased by an average of $1099 ($1757 [$7656] vs $2856 [$14 836]; p = 0.03). This indicates that people with GAD who receive long-term benzodiazepine treatment have significantly higher health care costs during the 6-months following initiation compared to the 6months prior.	
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**	No direct evidence identified.	No 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?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the	No reviews examining cost effectiveness identified.	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
	• 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?	intervention or the comparison ☐ Probably favours the intervention ☐ Favours the intervention ☐ Varies **☒ No included studies**		
Health equity, equality, and non-discrimination	What would be the impact on health equity, equality and non-discrimination? 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 based on 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	*The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations. • time & travel constraints. • Accessibility, informational barriers. • Affordability - medication and treatment costs. These factors may be exacerbated for certain groups: • People with low education/literacy (e.g. written instructions, psychoeducation materials). • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			Low resource settings - affordability/cost considerations exacerbated.	
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e., the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒**Varies** ☐ Don't know	The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • **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 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** - such as e.g. mobile populations, affordability of travel to receive care, lack of private space. • **Limited resources/mental health budget.** Sustainability considerations identified were: • Training and supervision. • Integrating into routine clinical practice.	Training is required in the understanding and safe administration of all psychotropic medications. To avoid the risks of harm. This is particularly true for medications that are associated with increased risk of adverse events, such as benzodiazepines. Training of primary care practitioners would be necessary on responsible use of benzodiazepines. In many LMIC, continuous availability of psychotropic drugs in non-specialized health care is a challenge. However, benzodiazepines are associated with low acquisition costs and Diazepam (as a representative of the benzodiazepines) is included in the WHO list of essential medicines for the treatment of anxiety disorders.

Criteria, questions		Judgement	Research evidence	Additional considerations
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	The qualitative review (Gronholm et al., 2023) noted several considerations which would impact the right to health and access to healthcare. (e.g. stigma and discrimination and lack of confidentiality could affect the help-seeking among service users). • The importance of sociocultural acceptability of MNS interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility. Mitigating steps to improve sociocultural acceptability include: • To train health workers in non-judgemental care. • Integrate preventative mental health awareness messages to reduce the stigma. • Train acceptable counsellors for the local settings and target groups	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility, and fidelity	

Notes. CI: confidence interval; GAD: general anxiety disorder; LMIC: low- and middle-income; PD: panic disorder; RCT: randomized controlled trial

4.3. Summary of judgements

Table 24: Summary of judgements

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	- Favours no intervention	- Probably favours no intervention	✓ **Does not favour either**	- Probably favours intervention	- Favours 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	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours 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

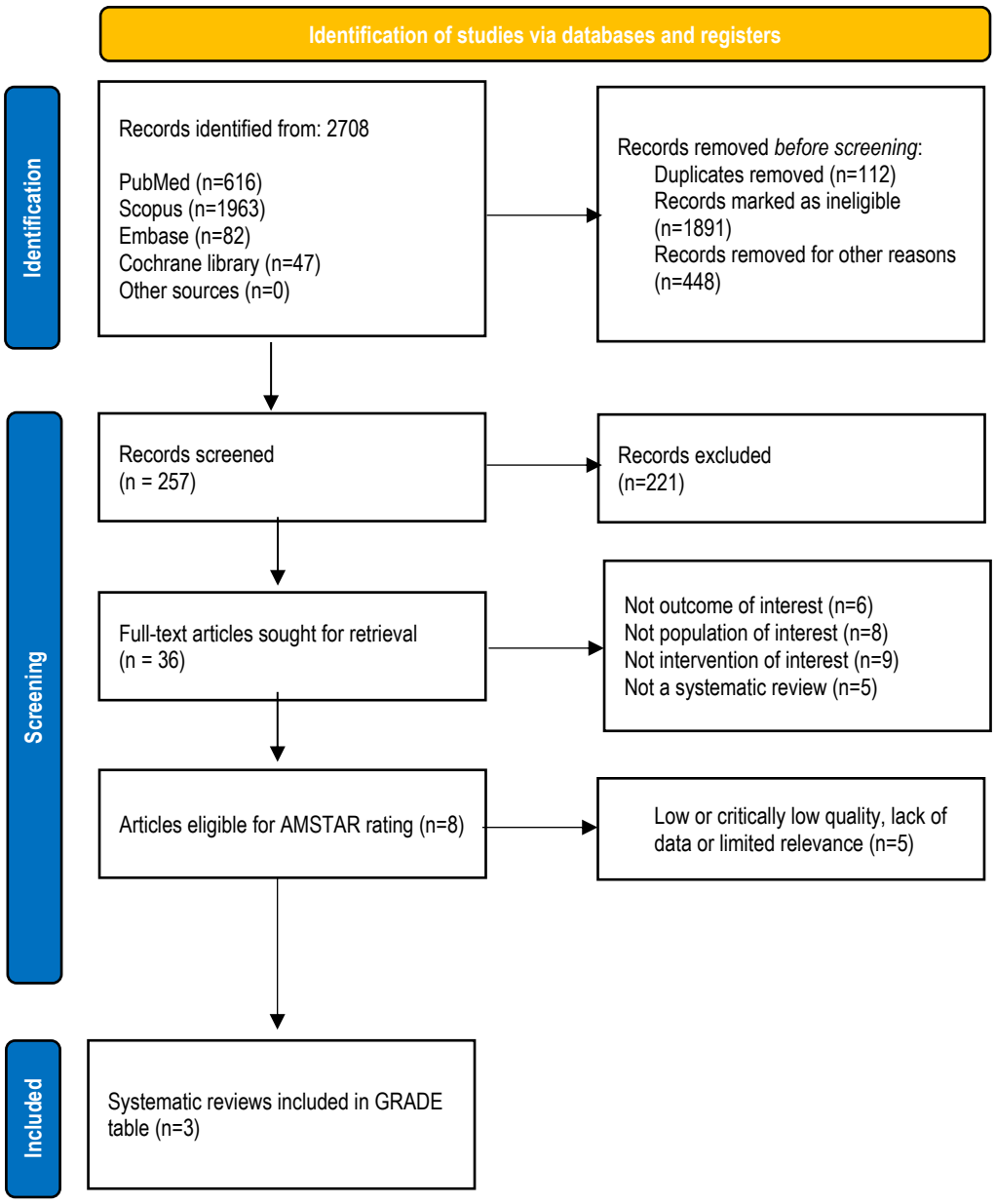
✓Indicates category selected, - Indicates category not selected.

QUESTION 7

Is collaborative care better (more effect/as safe as) than treatment as usual, waitlist, no treatment for adults with depression and anxiety (living with physical health conditions)?

3.1. List of systematic reviews and/or studies identified by the search process

Figure 7: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only for PICO Question #7



3.1.1. Included in GRADE tables/footnotes

1. Xiao L, Qi H, Zheng W, Xiang YT, Carmody TJ, Mayes TL, et al. The effectiveness of enhanced evidence-based care for depressive disorders: a meta-analysis of randomized controlled trials. Transl Psychiatry. 2021;11(1):531. doi:10.1038/s41398-021-01638-7
2. Stein B, Müller MM, Meyer LK, Söllner W. Psychiatric and Psychosomatic Consultation-Liaison Services in General Hospitals: A Systematic Review and Meta-Analysis of Effects on Symptoms of Depression and Anxiety. Psychother Psychosom. 2020;89(1):6-16. doi:10.1159/000503177
3. van der Feltz-Cornelis C, Allen SF, Holt RIG, Roberts R, Nouwen A, Sartorius N. Treatment for comorbid depressive disorder or subthreshold depression in diabetes mellitus: Systematic review and meta-analysis. Brain Behav. 2021;11(2):e01981. doi:10.1002/brb3.1981

3.1.2. Excluded from GRADE tables/footnotes

1. Hudson JL, Bower P, Kontopantelis E, Bee P, Archer J, Clarke R, et al. Impact of telephone delivered case-management on the effectiveness of collaborative care for depression and anti-depressant use: A systematic review and meta-regression. PLoS ONE. 2019;14(6):e0217948. doi:10.1371/journal.pone.0217948
2. Whitfield J, LePoire E, Stanczyk B, Ratzliff A, Cerimele JM. Remote Collaborative Care With Off-Site Behavioral Health Care Managers: A Systematic Review of Clinical Trials. Journal of the Academy of Consultation-Liaison Psychiatry. 2022;63(1):71-85. doi:10.1016/j.jaclp.2021.07.012
3. Hu J, Wu T, Damodaran S, Tabb KM, Bauer A, Huang H. The Effectiveness of Collaborative Care on Depression Outcomes for Racial/Ethnic Minority Populations in Primary Care: A Systematic Review. Psychosomatics. 2020;61(6):632-44. doi:10.1016/j.psym.2020.03.007
4. Davis B, Qian J, Ngorsuraches S, Jeminiwa R, Garza KB. The clinical impact of pharmacist services on mental health collaborative teams: A systematic review. Journal of the American Pharmacists Association : JAPhA. 2020;60(5s):S44-s53. doi:10.1016/j.japh.2020.05.006
5. Cubillos L, Bartels SM, Torrey WC, Naslund J, Uribe-Restrepo JM, Gaviola C, et al. The effectiveness and cost-effectiveness of integrating mental health services in primary care in low- and middle-income countries: systematic review. BJPsych Bull. 2021;45(1):40-52. doi:10.1192/bjb.2020.35

Table 25: Example PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
ANX 7	Collaborative Care / treatment as usual, waitlist, no treatment	Symptom reduction	Xiao et al. (2021); Stein et al. (2020); van der Feltz-Cornelis et al. (2021)	Xiao et al. (2021) was selected over Stein et al. (2020) for depression symptoms because Xiao et al (2021) included more studies (17 vs 11) and was a more recent high-quality review. Stein et al. (2020) was selected for the outcome of anxiety symptom reduction because this outcome was not reported in Xiao et al. (2021). For additional evidence on anxiety, please see 'Additional evidence not included in the GRADE table' section below. Van der Feltz-Cornelis et al. (2021) was selected for symptoms because it was the only recent high quality review reporting on a relevant outcome related to physical health outcomes (i.e. glycaemic control) following collaborative care.
		Adverse effects	No evidence	No evidence
		Acceptability profile (dropouts)	Xiao et al. (2021)	Xiao et al. (2021) was selected because it was the only recent high-quality review that reported on dropouts.
		Sustained response	No evidence	No evidence.
		Functioning	No evidence	No evidence.

3.2. Narrative description of studies that contributed to GRADE analysis

Stein et al. (2020) conducted a systematic review and meta-analysis investigating the effects of consultation-liaison services, including collaborative care, in general hospitals on depression and anxiety. Overall, 38 randomized controlled studies (N = 9994) met the inclusion criteria, reporting outcomes of depression and anxiety at the end of the intervention. Studies were grouped by type of intervention: brief interventions tailored to the patients (8), interventions based on specific treatment manuals (19), and integrated, collaborative care (11).

van der Feltz-Cornelis et al. (2021) conducted a systematic review and meta-analysis to review the effect of interventions on comorbid depressive disorder or subthreshold depression in type 1 and type 2 diabetes. The overall search resulted in 32 RCTs comprising 3,543 patients that were included in the meta-analysis. Twenty-four studies examined patients with major depressive disorder diagnoses and diabetes while Eight studies in patients with diabetes and subthreshold depressive symptoms.

Xiao et al. (2021) meta-analysis systematically examined the effectiveness of enhanced evidence-based care, including collaborative care, versus usual care for adults with depressive disorders based on cluster randomized studies or RCTs. In total, 29 RCTs with a total of 15,255 participants were included in the study. Twenty-one of these studies examined the effectiveness of Collaborative Care.

3.3. Grading the Evidence

Table 26: Collaborative care vs treatment as usual, waitlist, no treatment

Author(s): Brandon Gray, Biksegn Asrat, Maike van Niekerk and Aiysha Malik
Question: Is collaborative care better (more effect/as safe as) treatment as usual, waitlist, no treatment for adults with depression and anxiety (living with physical health conditions)?
Setting: non-specialist care settings
Reference List:
Xiao L, Qi H, Zheng W, Xiang YT, Carmody TJ, Mayes TL, et al. The effectiveness of enhanced evidence-based care for depressive disorders: a meta-analysis of randomized controlled trials. Transl Psychiatry. 2021;11(1):531. doi:10.1038/s41398-021-01638-7

Stein B, Müller MM, Meyer LK, Söllner W. Psychiatric and Psychosomatic Consultation-Liaison Services in General Hospitals: A Systematic Review and Meta-Analysis of Effects on Symptoms of Depression and Anxiety. Psychother Psychosom. 2020;89(1):6-16. doi:10.1159/000503177

van der Feltz-Cornelis C, Allen SF, Holt RIG, Roberts R, Nouwen A, Sartorius N. Treatment for comorbid depressive disorder or subthreshold depression in diabetes mellitus: Systematic review and meta-analysis. Brain Behav. 2021;11(2):e01981. doi:10.1002/brb3.1981

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	collaborative care	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of depression symptoms post treatment (assessed with multiple measures of depression symptoms)												
17[a,b]	RCTs	not serious	very serious[c]	not serious	not serious	none	9217		-	SMD **0.3 SD lower** (0.48 lower to 0.12 lower)	⊕⊕◯◯ Low[d]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	collaborative care	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
Reduction of anxiety symptoms post treatment (assessed wi multiple measures of anxiety symptoms)												
5[e]	RCTs	serious[f]	not serious	serious[g]	serious[h]	none	Data were not pooled in the study. Instead, of the five studies reporting results on anxiety, four could be used to calculate effect sizes and confidence intervals. There was a tendency for a small effect, but results were not significant (*d* ranged from -0.10 to -0.26). One of the studies yielded a tendency for an increase in depression and anxiety with a medium effect size (*d* = 0.39, 95% CI -0.29 to 1.07) that was not significant due to the small sample in this study (N = 34).				⨁◯◯◯ Very low[d]	CRITICAL
Reduction of physical health condition symptoms (assessed with glycemic control in adults with depression and diabetes)												
6[k]	RCTs	serious[l]	not serious	not serious	not serious	none	1133		-	SMD **0.207 SD higher** (0.05 higher to 0.36 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Acceptability profile (assessed with: number of dropouts)												
27[b]	RCTs	not serious	serious[i]	serious[j]	not serious	none			**RR 1.08** (0.94 to 1.23)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT
Functioning												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	collaborative care	treatment as usual, waitlist, no treatment	Relative (95% CI)	Absolute (95% CI)		
0	no evidence											

Sustained response

0	no evidence								-	**0** (0 to 0)	-	IMPORTANT

Notes. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; SD: standard deviation; SMD: standard mean difference

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. Xiao et al. (2021).

c. I squared = 82.2%.

d. For this outcome, negative effects are reported favouring collaborative care.

e. Stein et al. (2020).

f. Four of five studies were of high or moderate risk of bias.

g. Inclusion criteria for the study were not specific to adults diagnosed with depression or anxiety and living with physical health conditions. Some studies compared highly integrated collaborative care with less integrated treatment as usual (e.g. consultation only).

h. Sample size and confidence intervals indicate potential imprecision.

i. I squared = 68%.

j. Interventions included both collaborative care and other interventions defined as measurement-based care, including Collaborative Care (CC), Integrated Care (IC), and Algorithm-Guided Treatment (AGT).

k. van der Feltz-Cornelis et al. (2021).

l. All studies were rated as at high or moderate risk of bias.

3.4. Additional evidence not mentioned in GRADE tables

Muntingh et al. (2016) conduced a systematic review and meta-analysis to estimate the effect of collaborative care for adults with anxiety disorders in primary care that was not identified in the literature review because it was published prior to the search's timeframe.

Seven studies involving 2105 participants (1107 in the collaborative care condition, 998 in the control condition) were included. Of the trials, four were individually randomized controlled trials; three used cluster randomizations on the level of primary care practices; four were conducted in the USA**,** one in Germany and two in the Netherlands. Two studies exclusively included patients with PD, two studies included patients with PD and/or GAD, and three studies included multiple anxiety disorders. Comorbid depression was allowed in all studies and was reported in five studies, with prevalence rates ranging from 31 % to 64 %.

Moderate quality evidence based on seven RCTs involving 2105 participants indicated that collaborative care demonstrated a small effect on reduction of anxiety symptoms post treatment (SMD 0.35 SD higher; 95%CI 0.14 to 0.56) compared to treatment as usual, waitlist, no treatment.

Archer et al. (2012) conduced a systematic review and meta-analysis to assess the effectiveness of collaborative care on anxiety and depression (not specific to age ranges or comorbid physical conditions).

In total, 79 RCTs involving 24 308 participants diagnosed with depression (including acute, chronic, persistent, remitted, subthreshold and postnatal depression) or anxiety disorders (including: GAD, PD, PTSD, phobias, SAD, health anxiety and OCD) were included in the review.

The results of primary analyses indicated significantly greater improvement in depression outcomes for adults with depression treated with the collaborative care model in the short-term of 0 to 6 months (SMD -0.34, 95% CI -0.41 to -0.27; RR 1.32, 95% CI 1.22 to 1.43), medium-term of 7 to 12 months (SMD -0.28, 95% CI -0.41 to -0.15; RR 1.31, 95% CI 1.17 to 1.48), and long-term 13 to 24 months (SMD -0.35, 95% CI -0.46 to -0.24; RR 1.29, 95% CI 1.18 to 1.41). However, these significant benefits were not demonstrated into the very long-term of 25 months or more (RR 1.12, 95% CI 0.98 to 1.27).

The results also demonstrated significantly greater improvement in anxiety outcomes for adults with anxiety treated with the collaborative care model in the short-term of 0-6 months follow up (SMD -0.30, 95% CI -0.44 to -0.17; RR 1.50, 95% CI 1.21 to 1.87), medium-term of 7-12 months (SMD -0.33, 95% CI -0.47 to -0.19; RR 1.41, 95% CI 1.18 to 1.69), and long-term 13 to 24 months (SMD -0.20, 95% CI -0.34 to -0.06; RR 1.26, 95% CI 1.11 to 1.42). No comparisons examined the effects of the intervention on anxiety outcomes in the very long-term of 25 months or more.

Van Eck van der Sluijs et al. (2018) conduced a systematic review and meta-analysis to assess the effectiveness of collaborative care on physical outcomes in adults with comorbid physical conditions and depression or anxiety disorders. Twenty-one RCTs were included in the review including 4774 participants. Results indicated that collaborative care demonstrated a significant effect on the reduction of illness burden OR 1.64 (95%CI 1.47;1.83), d = 0.27 (95%CI 0.21;0.33) compared to care as usual.

Results also indicated that collaborative care demonstrated a significant effect on combined physical health outcomes across physical health conditions OR 1.46 (95%CI 1.28;1.67), d = 0.21 (95%CI 0.14;0.26) compared to care as usual.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 27: Summary of findings table

GRADE table	Source	Outcomes	Effects[a]	№ of participants (studies)	Certainty of the evidence (GRADE)
Table 2 (Collaborative care vs TAU, WL, and no treatment)	Xiao et al. (2021)	Reduction of depression symptoms post treatment	SMD **0.30 SD lower** (0.48 lower to 0.12 lower)	9217 (17 RCTs)	⊕⊕◯◯ Low
	Stein et al. (2020)	Reduction of anxiety symptoms post treatment[b]	Effects are based on data from 5 RCTs. Data were not pooled in the study. Instead, of the 5 studies reporting results on anxiety, 4 could be used to calculate effect sizes and confidence intervals. There was a tendency for a small effect, but results were not significant (*d* ranged from -0.10 to -0.26).[c] One of the studies yielded a tendency for an increase in depression and anxiety with a medium effect size (*d* = 0.39, 95% CI -0.29 to 1.07) that was not significant due to the small sample in this study (N = 34).		⊕◯◯◯ Very low
	van der Feltz-Cornelis et al. (2021)	Reduction of physical health condition symptoms	SMD **0.207 SD higher** (0.05 higher to 0.36 higher)	1133 (6 RCTs)	⊕⊕⊕◯ Moderate
	Xiao et al. (2021)	Acceptability profile	**1 fewer per 1,000** (1 fewer to 1 fewer) **RR 1.08** (0.94 to 1.23)	Total N not reported (27 RCTs)	⊕⊕◯◯ Low

Notes. CI: confidence interval; RR: risk ratio; RCT: randomized controlled trial; TAU: treatment as usual; SMD: standardized mean difference ; WL: waitlist

Explanations

a. Unless otherwise stated, positive effect values favour the intervention.

b. See 'Additional evidence not mentioned in the GRADE tables' above for more information on reduction of anxiety symptoms using collaborative care.

c. For this outcome, negative effects are reported favouring collaborative care.

4.2 Evidence to Decision

Table 28: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Criteria, questions		Judgement	Research evidence	Additional considerations
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a 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	Despite the impact of mhGAP and update for mhGAP-IG 2.0, feedback has indicated a need for additional guidance on conditions not currently covered in the programme. Among these are anxiety disorders, which are reported to be the most prevalent mental and substance use disorders as of 2019 *(28)*, represent the second leading cause of disability adjusted life years (DALYs) for mental and substance use disorders *(1)* and ranked among the top 25 leading causes of burden worldwide *(2)*, exert a significant social and economic burden *(3)* and are highly comorbid with other priority conditions *(4)*. What is more, these conditions may have increased significantly following the COVID-19 pandemic *(5)*. Providing strategies for managing these conditions is particularly important given that it has been estimated that almost 75% of persons with anxiety disorders globally do not receive treatment *(6)*. The development of mhGAP guidelines for anxiety disorders could support reducing the treatment gap.	No additional considerations.

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 (considering the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☒ **Small** ☐ Moderate ☐ Large ☐ Varies ☐ Don't know	Evidence from 17 RCTs suggested a small, significant benefit of collaborative care compared to TAU, WL, and no treatment on **depression symptom reduction**. Evidence from five RCTs suggested no difference between collaborative care compared to TAU, WL, and no treatment on **anxiety symptom reduction**. Evidence from six RCTs suggested a small, significant benefit of collaborative care compared to TAU, WL, and no treatment on **physical health condition symptoms**.	Evidence from seven RCTs meta-analyzed in a review not included in the GRADE tables because it was conducted prior to this profiles search timeframe (Muntingh et al. (2016)) suggested a small, significant benefit of collaborative care compared to TAU, WL, and no treatment on anxiety symptom reduction. Archer et al. (2012) conduced a systematic review and meta-analysis to assess the effectiveness of collaborative care on anxiety and depression (not specific to age ranges or comorbid physical conditions). In total, 79 RCTs involving 24 308 participants diagnosed with depression (including acute, chronic, persistent, remitted, subthreshold and postnatal depression) or anxiety disorders (including: GAD, PD, PTSD, phobias, SAD, health anxiety and OCD) were included in the review. The results of primary analyses indicated significantly greater improvement in depression outcomes for adults with depression treated with the collaborative care model in the short-term of zero to six months

Criteria, questions	Judgement	Research evidence	Additional considerations
			(SMD -0.34, 95% CI -0.41 to -0.27; RR 1.32, 95% CI 1.22 to 1.43), medium-term of 7 to 12 months (SMD -0.28, 95% CI -0.41 to -0.15; RR 1.31, 95% CI 1.17 to 1.48), and long-term 13 to 24 months (SMD -0.35, 95% CI -0.46 to -0.24; RR 1.29, 95% CI 1.18 to 1.41). However, these significant benefits were not demonstrated into the very long-term of 25 months or more (RR 1.12, 95% CI 0.98 to 1.27). The results also demonstrated significantly greater improvement in anxiety outcomes for adults with anxiety treated with the collaborative care model in the short-term of 0-6 months follow up (SMD -0.30, 95% CI -0.44 to -0.17; RR 1.50, 95% CI 1.21 to 1.87), medium-term of 7-12 months (SMD -0.33, 95% CI -0.47 to -0.19; RR 1.41, 95% CI 1.18 to 1.69), and long-term 13 to 24 months (SMD -0.20, 95% CI -0.34 to -0.06; RR 1.26, 95% CI 1.11 to 1.42). No comparisons examined the effects of the intervention on anxiety outcomes in the very long-term of 25 months or more. Van Eck van der Sluijs et al. (2018) conduced a systematic review and meta-analysis to assess the effectiveness of collaborative care

Criteria, questions		Judgement	Research evidence	Additional considerations
				on physical outcomes in adults with comorbid physical conditions and depression or anxiety disorders. Twenty-one RCTs were included in the review including 4774 participants. Results indicated that collaborative care demonstrated a significant effect on the reduction of illness burden OR 1.64 (95%CI 1.47;1.83), d = 0.27 (95%CI 0.21;0.33) compared to care as usual. Results indicated that collaborative care demonstrated a significant effect on combined physical health outcomes across physical health conditions OR 1.46 (95%CI 1.28;1.67), d = 0.21 (95%CI 0.14;0.26) compared to care as usual.
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 (considering the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	Evidence from 27 RCTs indicated there was no significant difference in **dropouts** between collaborative care and TAU, WL and no treatment.	No additional considerations.

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 overall certainty of the evidence was LOW. Certainty of the evidence for **reduction of depression symptoms** in was LOW. Certainty of the evidence for **reduction of anxiety symptoms** was VERY LOW. Certainty of the evidence for **reduction of physical health condition symptoms** was MODERATE. Certainty of the evidence for **dropouts** was LOW.	Certainty of the evidence for reduction of anxiety symptoms in Muntingh et al.'s (2016) review was MODERATE.
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**	A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values related factors in mental health care and mental health services. Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and well-being. The utility value could be limited by certain factors and barriers present in the health systems. For	The promotion of people seeking treatment's capacities and skills is a component of most brief psychological treatments that has value beyond the reduction of anxiety symptoms. There are also additional valuable aspects in teaching general health workers psychological treatments because they contribute to important interpersonal skills, such as listening, problem exploration,

Criteria, questions		Judgement	Research evidence	Additional considerations
		☐ No important uncertainty or variability	instance, low awareness, poor funding and poor political buy-in, or other social barriers. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	linking physical and psychological complaints, and involving patients in treatment decisions – making the health worker a better health worker.
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, considering 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	Low quality evidence indicated a small benefit of collaborative vs TAU, WL, and no treatment in symptom reduction and no difference in acceptability. **Thus, the effects favour collaborative care.**	No additional considerations.
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more 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	CC is more resource intensive than most usual models of care that are offered in physical health programmes *(115-117).* It is also one of the more intensive models of integrated care *(90)*. This is because CC models generally add two new team members to the medical team (a care	

Criteria, questions		Judgement	Research evidence	Additional considerations
			manager and a mental health care provider) *(118)*, and involve: i) *General training* on mental health care for providers in physical health settings. ii) *Specific training* on mental health care *skills and interventions* for providers in physical health settings. iii) *Addition of mental health care tasks* to *existing roles* of providers in physical health settings. iv) *Addition* of dedicated providers to offer mental health care (if not using existing personnel). v) *Increased coordination* between providers in physical health settings *and* mental health care providers. vi) *Strategic data management* to help improve outcomes for people receiving care. vii) *Utilization of a care manager / care coordinator (90).* In summary, CC is generally more resource intensive than most usual models of care (although there is evidence to suggest it may provide good economic value, see *cost-effectiveness* section). The resources required for CC vary widely based on how the components of the model are implemented in a setting. **Note on LMICs** Programmes in LMICs have come up with innovative ways of addressing resource costs	

Criteria, questions		Judgement	Research evidence	Additional considerations
			associated with the CC model. It is notable that some of the lowest CC costs reported have been in a study conducted in a LMIC (Chile, pre–2012) *(119)*. Since this study, Chile implemented a national depression programme in primary health care based on the CC model *(110,111)*. A report of the programme published in 2012 found the monthly cost to care for a person was US $7.90 (range US $3.30 to $13.90), demonstrating that the CC model can be implemented at a reasonable cost in a low-resource setting.[63] Another study in a LMIC similarly reported low costs and found that the total costs (i.e. health system and time costs combined) of people receiving CC for common mental disorders was significantly lower than those receiving comparator care in public facilities *(120)*.	
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 ☒ **Varies** ☐ No included studies	Evidence indicates that there is variability in the resources required to implement the CC model *(115-117)*. This largely stems from the fact that CC is a *model* of care, rather than an *intervention* in and of itself. Although there are core principles that define CC (including person-centred team care, population-based care, measurement-based treatment-to-target care, evidence-based care, and accountable care *(112)*), variations exist in the exact composition and enactment of the aforementioned principles. As a result, some settings have implemented CC at very low	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			costs and others at considerably higher costs *(115-117)*.	
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	Several reviews have summarized literature on the cost-effectiveness of CC for depression; none of these reviews focussed on anxiety as well *(115-117)*. The University of Washington also published a summary of literature on the cost-effectiveness of CC, available here (91).The aforementioned reviews reported that studies generally found CC for depression to be more effective than comparator care in increasing depression-free days (DFDs) and quality adjusted life years (QALYs), but more expensive *(115,116)*. Most studies in these reviews were conducted in the United States *(115-117)* only one study included in the reviews was conducted in a LMIC (Chile, pre–2012) *(115, 116)*. A wide range of incremental costs per QALYs were reported *(115-117)*; if one examines studies within the context in which they were conducted, results of most analyses suggest the model is cost-effective and, in some cases, even leads to overall cost reductions (refer to table below). Since the publication of these reviews, several studies have conducted economic analyses of the CC model, most of which found it to be cost-effective based on suggested thresholds *(122-129)*. However, there remains a need for	A review of the effectiveness of CC for mental health conditions (not specifically depression) reported total health costs did not differ significantly between CC and comparison care (Cohen's d = 0.05, 95% CI, -0.02 to 0.12) *(131)*. A review of the cost-effectiveness of integrating mental health services into primary care settings in LMICs concluded integrated models may increase the direct costs of primary health from increased utilization of personnel and medications, but may save costs to society (e.g. by increasing productivity) *(90)*.

Criteria, questions		Judgement	Research evidence	Additional considerations
			cost-effectiveness studies in LMICs. There are several trials in LMICs – including in South Africa, China, and India – with planned economic analyses which may help to address the current gap in knowledge *(102,108,109)*. **Note on LMICs** • **Chile (pre–2012):** The only study in the aforementioned reviews that was conducted in a LMIC reported the lowest associated costs *(119)*. It found CC to be only marginally more expensive than comparator care: approximately US $700 to $1,400 per QALY *(119)*, meeting criteria for cost-effectiveness based on suggested thresholds *(130)*. As noted above, since this study, Chile implemented a national depression programme in primary health care based on the CC model *(110,111)*. A report of the programme published in 2012 found the monthly cost to care for a person was $7.90 US (range $3.30 to $13.90), demonstrating the model could be implemented at a reasonable cost in a low-resource setting *(110)*. • **Studies in LMICs not included in the cost-effectiveness reviews:** ○ **India:** An RCT on CC for common mental disorders in India found total costs (i.e. health system and time costs combined) were significantly lower in those receiving CC than comparator care in public facilities *(120)*. ○ **Nigeria:** An RCT on CC for depression in Nigeria reported CC could be more cost-	

Criteria, questions		Judgement	Research evidence	Additional considerations
			effective than usual care enhanced by mhGAP, but that there remained uncertainty around their economic estimates (i.e. wide confidence intervals) *(103)*.	
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? 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 based on 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	**Increasing access to mental health care** Access to mental health care is limited in most parts of the world, particularly low-income, rural, and poorly resourced settings *(89,132)*. CC offers a mechanism of improving access to mental health care, by utilizing a task-sharing model to deliver evidence-based mental health care *(132)*. Importantly, evidence supports the efficacy of CC in improving outcomes for groups of people who are often underserved in health settings, including: women *(94)*, people from minority ethnic and racial backgrounds *(95)*, people with limited English proficiency *(96)*, people with low socioeconomic statuses (92,100,101), elderly people *(97)*, and people living in LMICs *(99-102,104,105,106)*. **Reducing stigma associated with mental health care** People with mental health conditions – such as depression and anxiety – often experience stigma, discrimination, and human rights	Hu et al. (2020) conducted a systematic review of the effectiveness of collaborative care on depression outcomes for racial/ethnic minority populations. In the review, five studies (one RCT and four observational) compared minority patients to white patients in collaborative care. The RCT and two of the observational studies showed more improvement in depressive symptoms in minority patients compared to white patients. One study showed no difference, and the last study showed minority patients responded better to collaborative care, although this benefit disappeared when the authors controlled for clinic. Bao et al.'s 2011 study also evaluated whether collaborative care was as effective for improving depression for white

Criteria, questions		Judgement	Research evidence	Additional considerations
			abuses *(133-135)*, which can lead to avoidance or delays in seeking mental health care *(136)*. Therefore, access to mental health care is not only limited by the scarce number of specialist mental health care providers (as outlined above), but also the stigma associated with mental health conditions. Integrating mental health care into physical disease programmes may reduce the stigma related to obtaining mental health care. Although evidence on this in LMICs is limited *(137)*, a relatively recent CC trial in China found people who received CC for depression reported significantly less perceived stigma about depression care than people who received comparator care *(99)*.	adults versus racial/ethnic minority adults. The authors found minority and white adults both experienced improvement of symptoms initially, but this improvement ceased by 18 months for minority adults while white adults continued to benefit up to the study end point (24 months).
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	Implementing the CC model is not without challenges, particularly in settings with limited resources *(93,113,114,132)*. Notwithstanding, studies have demonstrated the feasibility of providing mental health care using this model, including in LMICs where considerable numbers of people have been screened, assessed, and effectively cared for using it *(93,99-102,105,106,132,140)*. Successful implementation of CC programmes as part of routine clinical care in the United States show this model can be a feasible way of caring for people in high-income countries *(141-143)*. Although examples of widescale	Resource requirements and intervention acceptability are important aspects of intervention feasibility.

Criteria, questions		Judgement	Research evidence	Additional considerations
			real-world implementation of the CC model in LMICs remain limited, a programme in Nepal *(121,139)* and a national programme in Chile *(110,111)* that use the CC model demonstrate the potential for this model to be feasible in LMIC settings. A narrative review of CC for depression in LMIC countries argued public health programmes focussed solely on depression care may not be feasible to implement due to financial constraints in these settings, but that CC models provide a potentially cost-effective mechanism of improving depression care by integrating it into the care of other physical diseases *(93)*. For the CC model to be feasible, it is vital to engage key stakeholders in the development of the model so that (A) care pathways can be appropriately remodelled and (B) existing providers can be allocated appropriate roles and responsibilities *(0)*. The programme in rural Nepal that uses the CC model outlined above, for example, depends on a large network of stakeholders for its sustainability (including public sector institutions, nongovernmental organizations, mental health organizations, bicultural professionals, and academic medical centres) *(139)*.	

Criteria, questions		Judgement	Research evidence	Additional considerations
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? 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 groups or organization's autonomy, i.e., their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There are no systematic reviews summarizing literature on the acceptability of the CC model for depression or anxiety, although some discuss barriers and facilitators to implementing it *(113,114)*. A scope of the evidence base on CC for depression and anxiety in physical health settings in LMICs suggests service users *and* health care providers generally find it to be acceptable. Direct and indirect indicators of intervention acceptability are outlined below. **Service users** **Direct indicators of acceptability** Studies assessing service users' views of the CC model have tended to find positive results *(e.g. 107,137)*. Although some found people were initially hesitant towards taking a more active or collaborative role in their care *(106,107)*, there are reports of people ultimately viewing this favourably *(107,137)*. A core feature of the CC model being acceptable amongst service users appears to be that it facilitates the formation of therapeutic relationships between service users and health care providers, which might otherwise be absent in usual care; one paper	No additional considerations.

Criteria, questions		Judgement	Research evidence	Additional considerations
			described this as “Very Important Person” (VIP) treatment *(107)*. Still, several things have been identified as barriers to intervention acceptability, including low levels of mental health literacy; resistance towards mental health care; and stigma against mental illness. There are also context-specific considerations. Notably, a review of strategies for engaging service users and their families in CC programmes for depression and anxiety found that fewer than 10% of programmes involved service users in designing, implementing, or evaluating the programme, however those that did helped improve intervention acceptability *(98)*. Several CC programmes in LMICs elicited feedback from service users before or during programme implementation to enhance acceptability *(106,137,138)*. **Indirect indicators of acceptability** i) **Acceptance rates:** Low rates of refusal provide an indicator of intervention acceptability. RCTs and associated pilot studies on CC in LMICs have reported low refusal rates *(99-106)*, with most having around 10% or less refuse to take part *(100-106)*. ii) **Follow up rates:** High follow up rates can be seen as an indicator of intervention acceptability. The majority of RCTs and	

Criteria, questions	Judgement	Research evidence	Additional considerations
		associated pilot studies on CC in LMICs have had close to 90% of people complete final follow up assessments *(100,101,102-104)*. All cited studies followed people up for at least 6 months. iii) **Adherence rates:** High intervention adherence rates can be seen as an indicator of intervention acceptability. RCTs and associated pilot studies on CC in LMICs have reported variable intervention adherence rates. Although some have reported intervention adherence rates of over 70% *(103,106)*, others have reported lower rates of adherence *(100,101,104)*. Notably, a 2012 report on the Chilian national programme for depression care in primary care that uses a CC model found around one in three people dropped out at 6 months *(110)*. It seems low adherence in LMICs is often related to barriers in accessing care (e.g. financial barriers and competing responsibilities) *(106,107)*, rather than exclusively issues of intervention acceptability. **Health care providers** Evidence suggests providers view the CC model (or components of it) favourably *(100,103,106,138)*. In addition, those involved in offering CC for people with depression *and comorbid physical diseases* appear to find co-managing mental and physical health illnesses to be effective.	

Criteria, questions		Judgement	Research evidence	Additional considerations
			It is not uncommon, however, for providers to initially be resistant towards the CC model. A review of the enablers and barriers to implementing the CC model in high-income countries similarly found providers were often quite positive about the CC model after having experienced it, which indicates initial scepticism towards the model is not necessarily fundamental and may be overcome *(113)*. With appropriate resources, training, support, supervision, encouragement, and compensation – by enlarge – providers seem to view the CC model favourably. Acceptability also seems to increase as i) trust and rapport is built within the CC team (facilitated through co-location and regular interaction of providers), ii) observed benefits are seen in the service users, and iii) senior providers champion the service. Programmes in LMICs have implemented effective mechanisms to overcome barriers to intervention acceptability. **Leadership** Literature, albeit limited, suggests policymakers view the CC model favourably when provided information on the model and evidence of its effectiveness. In Chile, for example, promising findings from a CC RCT for depression facilitated the launch of a national programme for management of depression in primary care based on the CC model	

Criteria, questions		Judgement	Research evidence	Additional considerations
			(100,110,111). Another example of this was seen in Vietnam, where mental health policymakers were initially resistant towards the task-shifting approach to depression care (typical of the CC model) but offered increased support after hearing success studies and compelling evidence supporting this approach to care *(106)*. Policymakers in Nepal have also demonstrated favourable views of the CC model and supported its implementation in routine clinical care in a rural hospital *(121)*.	

Notes. CC: collaborative care; GAD: generalized anxiety disorder; LMIC: low- and middle-income; OCD: obsessive compulsive disorder; PD: panic disorder; RCT: randomized controlled trial; RR: risk ratio; SAD: social anxiety disorder; SMD: standard mean difference; TAU: treatment as usual; WL: waitlist

4.3. Summary of judgements

Table 29: Summary of judgements

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	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	✓ **Favours 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**	Varies		- Very low	- Low	- Moderate	- High
Cost–effectiveness	- No included studies	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	✓ **Probably favours intervention**	- Favours 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: List of PICO questions by module

Question	PICO	Comments
ANX1: In adults with anxiety disorders (excluding social anxiety disorder, specific phobias), are antidepressants (TCAs) and SSRIs) effective and safe compared to treatment as usual, waitlist, no treatment, or alternative psychological or pharmacological interventions?	**Population**: Adults with anxiety disorders (excluding SAD and specific phobias) **Interventions**: antidepressant medicines: TCAs, SSRIs **Comparison**: Head-to-head comparisons, treatment as usual, waitlist, no treatment, alternative interventions **Outcomes**: Critical – reduction of symptoms, adverse effects Important - improvement in functioning, sustained response, acceptability profile	Antidepressants are commonly available in many low- and middle-income countries. It is important for practitioners in primary healthcare and non-specialised settings to know the comparative effectiveness of alternative interventions if they exist.
ANX2: Is brief, structured psychological treatment (e.g. CBT, Problem Solving Therapy) in non-specialist care settings better (more effective/as safe as) than treatment as usual, waitlist no treatment in people with anxiety disorders (excluding SAD, specific phobias)?	**Population**: Adults with anxiety disorders (excluding SAD, specific phobias, and PTSD) **Interventions**: Brief psychological treatment in non-specialist health care settings **Comparison**: Treatment as usual **Outcomes**: Critical – reduction of symptoms, adverse effects Important - improvement in functioning, sustained response, acceptability profile	There is strong evidence for psychological interventions delivered in non-specialist settings for the treatment of GAD.
ANX3: For adults with anxiety disorders (excluding SAD, specific phobias), what is the comparative effectiveness of different formats of psychological interventions?	**Population**: Adults with anxiety disorders (excluding SAD, specific phobias)) **Interventions versus Comparisons**: a) Group vs. Individual psychological treatment b) Specialist psychological treatment vs non-specialist psychological treatment c) Unguided vs guided self-help psychological treatment d) online vs face-to-face psychological treatment **Outcomes**: *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile	Understanding which formats for intervention delivery are effective is essential to identifying adaptations and alternatives to higher cost approaches.

Question	PICO	Comments
ANX4: Are stress management techniques better (more effective/as safe as) than treatment as usual, waitlist no treatment in adults with anxiety disorders?	**Population**: Adults with anxiety disorders (excluding SAD, specific phobias) **Interventions**: Stress management techniques (e.g. relaxation training, mindfulness, yoga) **Comparison**: Treatment as usual **Outcomes**: *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile	Understanding the value of these low-cost interventions in non-specialist care settings can support implementation of cost-effective interventions.
ANX5: Is advice on physical activity better (more effective/as safe as) than treatment as usual, waitlist no treatment in adults with anxiety disorders (excluding SAD, specific phobias)?	**Population**: Adults with anxiety disorders (excluding SAD, specific phobias) **Interventions**: Advice on physical activity **Comparison**: Treatment as usual **Outcomes**: *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile	While the evidence may be limited for this question, the technical expert group agreed it is worth asking due to the low burden and risk of harm for such advice in non-specialised settings.
ANX6: Are benzodiazepines better (more effective/as safe as) than placebo for adults with anxiety disorders (excluding social phobia, SAD)?	**Population**: Adults with anxiety disorders (excluding SAD, specific phobias, and PTSD) **Interventions**: Benzodiazepines prescribed in non-specialised settings **Comparison**: Treatment as usual, wait list, no treatment **Outcomes**: *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile	Benzodiazepines should be addressed in the recommendations on anxiety disorders due to their widespread prescription in many settings and high risk for harmful outcomes (e.g. addiction).

Question	PICO	Comments
ANX7: Is collaborative care better (more effect/as safe as) treatment as usual, waitlist no treatment for adults with depression and anxiety (living with physical health conditions)?	**Population:** adults living with physical health conditions and experiencing anxiety disorders (excluding SAD, specific phobias, PTSD) or depression **Interventions:** Collaborative care **Comparison:** treatment as usual, wait list, no treatment **Outcomes**: *Critical* – reduction of symptoms, adverse effects *Important* – improvement in functioning, sustained response, acceptability profile	Mental disorders, such as depression and anxiety, are common in people with physical diseases (e.g. HIV, NCDs, TB and NTDs). These conditions are often missed, affect adherence to physical disease care, and are associated with significant suffering and disability. Collaborative care supports physical disease programmes (e.g. HIV, NCDs, TB and NTDs) to implement and monitor evidence-based care for depression and anxiety. Collaborative care can increase access to and coverage of mental health care; improve the management of common mental disorders in physical disease settings; improve adherence to physical disease care; and improve mental and physical health outcomes for people with both types of conditions

Notes. CBT: cognitive behavioural therapy; GAD: generalized anxiety disorder; HIV: human immunodeficiency virus; NCD: non-communicable disease; NTD:; SAD: social anxiety disorder; SSRI: selective serotonin reuptake inhibitor; PTSD: post-traumatic stress disorder; TB: tuberculosis; TCA: tricyclics;

APPENDIX II. Search terms used to identify systematic reviews

Question	Key words and search terms	Search strategies
ANX1: In adults with anxiety disorders, are antidepressants (TCA) and SSRI) effective and safe compared to treatment as usual, waitlist, no treatment, or alternative psychological or pharmacological interventions?	**Key word** 1. anxiety disorders (GAD and Panic disorder) 2. antidepressants (TCAs and SSRIs) Amitriptyline Amoxapine Desipramine (Norpramin) Doxepin Imipramine (Tofranil) Nortriptyline (Pamelor) Protriptyline Trimipramine Citalopram (Celexa) Escitalopram (Lexapro) Fluoxetine (Prozac) Paroxetine (Paxil, Pexeva) Sertraline (Zoloft)	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((((((((((((((((((((((((antidepressant*[tw]) OR (“tricyclic antidepressant*”[tw])) OR (“Selective serotonin reuptake inhibitor*”[tw])) OR (Amitriptyline[tw])) OR (Amoxapine[tw])) OR (Desipramine[tw])) OR (Norpramin[tw])) OR (Doxepin[tw])) OR (Imipramine[tw])) OR (Tofranil[tw])) OR (Nortriptyline[tw])) OR (Pamelor[tw])) OR (Protriptyline[tw])) OR (Trimipramine[tw])) OR (Citalopram[tw])) OR (Celexa[tw])) OR (Escitalopram[tw])) OR (Lexapro[tw])) OR (Fluoxetine[tw])) OR (Prozac[tw])) OR (Paroxetine[tw])) OR (Paxil[tw])) OR (Pexeva[tw])) OR (Sertraline[tw])) OR (Zoloft[tw])) OR ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents, Tricyclic"[Mesh] OR "Antidepressive Agents, Second-Generation"[Mesh] OR "Adrenergic Uptake Inhibitors"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "Citalopram"[Mesh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR "Iprindole"[Mesh] OR "Dibenzocycloheptenes"[Mesh]) 3. #1 AND #2 **COCHRANE LIBRARY** 1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (antidepressant* OR tricyclic NEXT antidepressant* OR Selective NEXT serotonin NEXT reuptake NEXT inhibitor* OR Amitriptyline OR Amoxapine OR Desipramine OR Norpramin OR Doxepin OR Imipramine OR Tofranil OR Nortriptyline OR Pamelor OR Protriptyline OR Trimipramine OR Citalopram OR Celexa OR

		Escitalopram OR Lexapro OR Fluoxetine OR Prozac OR Paroxetine OR Paxil OR Pexeva OR Sertraline OR Zoloft):ti,ab,kw OR MeSH descriptor: [Antidepressive Agents] explode all trees 3. #1 AND #2
ANX2: Is brief, structured psychological treatment (e.g. Cognitive Behavioural Therapy, Problem Solving Therapy) in non-specialist care settings better than treatment as usual in adults with anxiety disorders?	**Key words** 1. anxiety disorders (GAD and Panic disorder) 2. psychological interventions Psychological treatments Psychotherapy Psychological interventions Psychosocial Support/intervention/treatment Counselling Cognitive behaviour therapy Acceptance and commitment therapy Family therapy Group therapy Interpersonal therapy PSTPST Mindfulness therapy Motivational interviewing Relaxation therapy	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((((((((((((((((((“psychological treatment*”[tw]) OR (“psychological intervention*”[tw])) OR (“psychological support*”[tw])) OR (“psychosocial treatment*”[tw])) OR (“psychosocial intervention*”[tw])) OR (“psychosocial support*”[tw])) OR (counsel*[tw])) OR (“cognitive behavioural therap*”[tw])) OR (“acceptance* commitment therap*”[tw])) OR (“family therap*”[tw])) OR (“group therapy*”[tw])) OR (“interpersonal therapy*”[tw])) OR (“interpersonal psychotherap*”[tw])) OR (“problem solving therap*”[tw])) OR (“problem solving psychotherap*”[tw])) OR (“mindfulness therap*”[tw])) OR (“motivational interview*”[tw])) OR (“relaxation therap*”[tw])) OR(("Psychotherapy"[Mesh] OR "Psychotherapy, Psychodynamic"[Mesh] OR "Imagery, Psychotherapy"[Mesh] OR "Psychotherapy, Rational-Emotive"[Mesh] OR "Psychotherapy, Multiple"[Mesh] OR "Psychotherapy, Group"[Mesh] OR "Psychotherapy, Brief"[Mesh] OR "Person-Centreed Psychotherapy"[Mesh] OR "Interpersonal Psychotherapy"[Mesh] OR "Cognitive Behavioural Therapy"[Mesh]) OR "Crisis Intervention"[Mesh]) 3. #1 AND #2 **COCHRANE LIBRARY** 1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees

		2. (psychological NEXT treatment* OR psychological NEXT intervention* OR psychological NEXT support* OR psychosocial NEXT treatment* OR psychosocial NEXT intervention* OR psychosocial NEXT support* OR counsel*):ti,ab,kw OR (cognitive NEXT behavioural NEXT therap* OR acceptance NEXT commitment NEXT therap* OR family NEXT therap* OR group NEXT therapy* OR interpersonal NEXT therapy* OR interpersonal NEXT psychotherap* OR problem NEXT solving NEXT therap* OR problem NEXT solving NEXT psychotherap* OR mindfulness NEXT therap* OR motivational NEXT interview* OR relaxation NEXT therap* OR rational-emotive NEXT psychotherap*):ti,ab,kw OR MeSH descriptor: [Psychosocial Intervention] explode all trees OR MeSH descriptor: [Psychosocial Support Systems] explode all trees OR MeSH descriptor: [Psychotherapy, Brief] explode all trees OR MeSH descriptor: [Psychotherapy] explode all trees 3. #1 AND #2
ANX3: In adults and with anxiety disorders, what is the comparative effectiveness of different formats of psychological interventions?	**<u>Key words</u>** 1. anxiety disorders (GAD and Panic disorder) 2. formats of intervention 1. Individual psychological treatment 2. Face-to-face psychological treatment 3. Guided psychological treatment 4. Digital psychological treatment Group psychological treatment	**PUBMED** 1. ((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((((((((((((((((((“individual psychological treatment*”[tw]) OR (“face-to-face psychological treatment*”[tw])) OR (guided[tw])) OR (digital[tw])) OR (“group psychological treatment*”[tw])) OR (unguided[tw])) OR (“telephone therapy”[tw])) OR (“internet therapy”[tw])) OR (“online therap*”[tw])) OR (“individual psychotherap*”[tw])) OR (“group psychotherap*”[tw])) OR (“guided psychotherap*”[tw])) OR (computer-assisted therapy[tw])) OR (“guided intervention*”[tw])) OR (“digital psychotherapy”[tw])) OR (“face-to-face psychotherap*”[tw])) OR (“individual psychological intervention*”[tw])) OR (“group psychological intervention*”[tw])) OR ("Psychotherapy, Group"[Majr]) 3. #1 AND #2 **COCHRANE LIBRARY**

	Unguided self-help psychological treatment Teletherapy Internet based/online/ therapy Computer-assisted therapy	1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (individual NEXT psychological NEXT treatment* OR face-to-face NEXT psychological NEXT treatment* OR guided OR digital OR group NEXT psychological NEXT treatment* OR unguided OR telephone NEXT therapy OR internet NEXT therapy OR online NEXT therap* OR individual NEXT psychotherap* OR group NEXT psychotherap* OR computer-assisted NEXT therapy OR guided NEXT psychotherap* OR guided NEXT intervention* OR digital NEXT psychotherapy OR face-to-face NEXT psychotherap* OR individual NEXT psychological NEXT intervention* OR group NEXT psychological NEXT intervention*):ti,ab,kw 3. #1 AND #2
ANX4: Are stress management techniques better (more effective than/as safe as) than treatment as usual in adults with anxiety disorders?	**Key words** 1. anxiety disorders (GAD and Panic disorder) 2. Stress management techniques Stress management Stress therapy Relaxation therapy Mind-body therapies Meditation Relaxation Yoga Deep breathing	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((((((((((("stress management"[tw]) OR ("stress management technique*"[tw])) OR ("stress management psychotherap*"[tw])) OR ("stress management therap*"[tw])) OR (yoga[tw])) OR (massage[tw])) OR (meditation[tw])) OR (relaxation[tw])) OR ("deep breathing"[tw])) OR (breathing[tw])) OR ("Relaxation"[Mesh] OR "Relaxation Therapy"[Mesh] OR "Muscle Relaxation"[Mesh] OR "Autogenic Training"[Mesh])) OR ("stress therapy"[tw])) OR ("relaxation therapy"[tw])) OR ("Mind-Body Therapies"[Mesh]) 3. #1 AND #2 **COCHRANE LIBRARY**

		1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (stress NEXT management OR stress NEXT management NEXT technique* OR stress NEXT management NEXT psychotherap* OR stress NEXT management NEXT therap* OR yoga OR stress NEXT therapy OR relaxation NEXT therapy OR mind-body NEXT therapy OR massage OR meditation OR relaxation OR deep NEXT breathing OR breathing):ti,ab,kw OR MeSH descriptor: [Relaxation Therapy] explode all trees 3. #1 AND #2
ANX5: Is advice on physical activity better (more effective than/as safe as) than treatment as usual in adults with anxiety disorders?	**Key words** 1. anxiety disorders (GAD and Panic disorder) 2. physical activity Physical exercise Physical activity Exercise therapy	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((("physical activit*"[tw]) OR ("physical exercis*"[tw])) OR ("Exercise Therapy"[Mesh]) 3. #1 AND #2 **COCHRANE LIBRARY** 1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (physical NEXT activit* OR physical NEXT exercis* OR exercis* OR MeSH descriptor: [Exercise Therapy] explode all trees 3. #1 AND #2

ANX6: For adults with anxiety disorders, do benzodiazepines prescribed in non-specialised settings, when compared to treatment as usual, waitlist, or no treatment, result in reduction of symptoms, improved functioning/quality of life, decreased presence of disorder or adverse effects?	**Key words** 1. anxiety disorders (GAD and Panic disorder) 2. Benzodiazepines Anxiolytics Alprazolam (Xanax) chlordiazepoxide (Librium) clonazepam (Klonopin) clorazepate (Tranxene) diazepam (Valium) estazolam (Prosom) flurazepam (Dalmane) lorazepam (Ativan)	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. ((((((anxiolytic*[tw]) OR (“anxiolytic drug*”[tw])) OR (“benzodiazepine drug*”[tw])) OR (“benzodiazepine medication*”[tw])) OR (“anxiolytic medication*”[tw])) OR ((((((((((((((((benzodiazepin*[tw]) OR (alprazolam[tw])) OR (Xanax[tw])) OR (chlordiazepoxide[tw])) OR (Librium[tw])) OR (clonazepam[tw])) OR (Klonopin[tw])) OR (clorazepate[tw])) OR (Tranxene[tw])) OR (diazepam[tw])) OR (Valium[tw])) OR (estazolam[tw])) OR (Prosom[tw])) OR (flurazepam[tw])) OR (Dalmane[tw])) OR (lorazepam[tw])) OR (Ativan[tw]))) OR (("Benzodiazepines"[Mesh] OR "Chlordiazepoxide"[Mesh] OR "metaclazepam" [Supplementary Concept] OR "clonazolam" [Supplementary Concept]) OR ("Anti-Anxiety Agents"[Mesh] OR "Zolazepam"[Mesh] OR "Tranquilizing Agents"[Mesh])) 3. #1 AND #2 **COCHRANE LIBRARY** 1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (anxiolytic* OR anxiolytic NEXT drug* OR benzodiazepine NEXT drug* OR benzodiazepine NEXT medication* OR anxiolytic NEXT medication* OR benzodiazepin* OR alprazolam OR Xanax OR chlordiazepoxide OR Librium OR clonazepam OR Klonopin OR clorazepate OR Tranxene OR diazepam OR Valium OR estazolam OR Prosom OR flurazepam OR Dalmane OR lorazepam OR Ativan):ti,ab,kw OR MeSH descriptor: [Benzodiazepines] explode all trees OR MeSH descriptor: [Tranquilizing Agents] explode all trees OR MeSH descriptor: [Anti-Anxiety Agents] explode all trees 3. #1 AND #2

ANX7: Is collaborative care effective and feasible for treatment of depression and anxiety in adults (living with physical health conditions)?	**Key words** • anxiety disorders (GAD and Panic disorder) • Depression • Collaborative care Depressive disorder Major depressive disorder Depressive symptoms Affective disorders Dysthymic disorder Collaborative care Care manag*.ti,ab. Case manage*.ti,ab. Collaborat*.ti,ab. Co-ordinat*.ti,ab. Coordinat*.ti,ab. Integrat*.ti,ab. Stepped.ti,ab. Shared care*.ti,ab. Enhanced care.ti,ab. Multi-component.ti,ab. Multicomponent.ti,ab. Multi-disciplinary.ti,ab. Multidisciplinary.ti,ab. Coordinat* care Team-based care multi-professional care structured care interprofessional care	**PUBMED** 1. ((((("anxiety disorder*"[tw]) OR ("Anxiety Disorders"[Mesh])) OR ("generalised anxiety disorder"[tw])) OR ("generalized anxiety disorder"[tw])) OR ("panic disorder"[tw]) 2. (((((((((depression[tw]) OR (“depressive disorder*”[tw])) OR (“depressive symptom*”[tw])) OR (“major depressive disord*”[tw])) OR (“major depress*”[tw])) OR (“affective symptom*”[tw])) OR (“affective disorder*”[tw])) OR (dysthym*[tw])) OR (“dysthymic disorder*”[tw])) OR ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depression, Postpartum"[Mesh] OR "Dysthymic Disorder"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "Major Depressive Disorder 1" [Supplementary Concept]) 3. ((((((((((((((((((“Collaborative care”[tw]) OR (“Collaborative care manag*”[tw])) OR (“Care manag*”[tw])) OR (“Case manage*”[tw])) OR (Collaborat*[tw])) OR (Co-ordinat*[tw])) OR (Coordinat*[tw])) OR(“coordinat* care”[tw])) OR (“team-based care”[tw])) OR (“multi-professional care”[tw])) OR (“structured care”[tw])) OR (“interprofessional care”[tw])) OR (Integrat*[tw])) OR (Stepped[tw])) OR (“Shared care*”[tw])) OR (“Enhanced care”[tw])) OR (Multi-component[tw])) OR (Multicomponent[tw])) OR (Multi-disciplinary[tw])) OR (Multidisciplinary[tw]) 4. #1 OR #2 AND #3 **COCHRANE LIBRARY** 1. (anxiety NEXT disorder* OR generalised NEXT anxiety NEXT disorder OR generalized NEXT anxiety NEXT disorder OR panic NEXT disorder):ti,ab,kw OR MeSH descriptor: [Anxiety Disorders] explode all trees 2. (depression OR depressive NEXT disorder* OR depressive NEXT symptom* OR major NEXT depressive NEXT disord* OR major NEXT depress* OR affective NEXT symptom* OR affective NEXT disorder* OR dysthym* OR dysthymic NEXT disorder*):ti,ab,kw OR MeSH descriptor: [Depression] explode all trees

		3. (Collaborative NEXT care OR Collaborative NEXT care NEXT manag* OR Care NEXT manag*” OR Case NEXT manage* OR Collaborat* OR Co-ordinat* OR Coordinat* OR coordinat* NEXT care OR team-based NEXT care OR multi-professional NEXT care OR structured NEXT care OR interprofessional NEXT care OR Integrat* OR Stepped OR Shared NEXT care* OR Enhanced NEXT care OR Multi-component OR Multicomponent OR Multi-disciplinary OR Multidisciplinary):ti,ab,kw 4. #1 AND #2 AND #3