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# Psychotherapeutic treatments for depression in older adults (Protocol)

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[Intervention Protocol]

# Psychotherapeutic treatments for depression in older adults

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of psychotherapeutic interventions in the treatment of older adults with depression and whether the effects of different types of psychotherapeutic treatments vary for older adults with depression.

# BACKGROUND

## Description of the condition

Depression is the leading cause of disability worldwide and a major contributor to the global burden of disease, and is about 50% more common in women than in men (WHO 2023). It is well-recognized that depression worsens the outcome of other chronic diseases, such as the risk of cardiovascular events in individuals with coronary heart disease (Whooley 2008). A serious health condition, especially when it is recurrent and of moderate or severe intensity, depression is characterized by low mood (e.g. sadness, irritability, emptiness) or loss of pleasure, accompanied by other cognitive, behavioral, or neurovegetative symptoms that significantly affect a person's ability to function (Dhippayom 2022). Depression can cause a great deal of distress and poor functioning at work, school, and home, and can lead to suicide (Chai 2023). Furthermore, the COVID-19 pandemic has had a marked effect on depression rates: the World Health Organization (WHO) estimates that pandemic era stressors have increased rates of depression and anxiety by upwards of 25% (WHO 2022).

Major depressive disorder (MDD) is a heterogeneous condition characterized by significant and persistent low mood, driven by a combination of genetic and environmental factors (Liu 2023). Despite ongoing research, the pathophysiology of depression remains incompletely understood. The current main classificatory diagnostic systems, the International Classification of Diseases (WHO 1992), and Diagnostic and Statistical Manual of Mental Disorders (APA 2013), define the clinical diagnosis of depression through symptoms that form a syndrome and cause impairment. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* defines MDD as having at least two weeks of mild to severe persistent feelings of sadness or a lack of interest in everyday activities (APA 2013). The onset of MDD is bimodal, with most participants present in their 20s, and a second peak occurring in the 50s (Park 2019). Risk factors for depression include a combination of genetic, biological, and environmental factors (Beurel 2020; Eder 2023). Additionally, medical illness also increases the risk of depression (Harshfield 2020).

The WHO estimates that approximately 280 million people suffer from depression worldwide, and that 5.7% of adults over the age of 60 are depressed (WHO 2023). Depression is the most common and treatable mental disorder in later life, as 7% of older adults develop MDD (Blumberger 2022). Depression in older people is associated with disability, loneliness, pain, and loss (Lee 2021; Tsai 2022). A significant proportion of older people with depression describe themselves as experiencing a loss of enjoyment and a feeling of ill health rather than sadness or a feeling of low mood. In addition, late-life depression is often difficult to diagnose, as it can be confused with somatic complaints, and may even be inappropriately regarded as a normal aspect of the aging process (Nierenberg 2001). It is further complicated by comorbid physical illness and is associated with high rates of disability, mortality, and healthcare utilization.

## Description of the intervention

The first-line treatments for depression include psychological and pharmacological interventions (Kendrick 2022; NICE 2022). As outlined by the National Institute for Health and Care Excellence (NICE), antidepressants are recommended as the first-line treatment for moderate to severe episodes of depression (NICE 2022). However, people with depressive disorder respond differently to antidepressants (Kennedy 2016). A significant proportion of depressed people, ranging between one-half and two-thirds, do not reach a response threshold (Al-Harbi 2012; Trivedi 2006). Such non-response to treatment may vary from partial response to complete 'resistance' to treatment. Many individuals with depression fail to attain remission with initial antidepressant treatment (Bauer 2017). In addition to pharmacological treatments, lifestyle interventions, such as exercise programs and dietary modifications, are also employed to manage depression. These alternative therapies provide a broader context for evaluating the effectiveness and added value of psychotherapeutic treatments specifically in older adults.

The selection of treatment choice depends on multiple factors, including the severity of symptoms, the extent of functional impairment caused by the depressive episode, and patient preference. Antidepressant medications are not needed for mild depression. However, if the symptoms are moderate, it is recommended to combine cognitive behavioral therapy (CBT) with pharmacotherapy, such as antidepressants (NICE 2022).

Pharmacotherapy treatment for mental health disorders can present cardiovascular risk due to side effects of the drugs or interactions with other medications (Pina 2018). The long-term use of antidepressants is associated with a range of adverse events, including dizziness, insomnia, agitation, and flu-like symptoms (Kirsch 2018). In light of these challenges, several studies indicate the augmented benefit of incorporating psychological interventions alongside antidepressant medications (Breedvelt 2021; Thapar 2022; Verhoeven 2023). Such complementary approaches potentially enhance the efficacy of treatment, offering a more comprehensive and tailored therapeutic strategy for individuals struggling with depression.

The main psychotherapeutic approaches to treating depression in adults according to the WHO are CBT, behavioral activation (BA), problem-solving therapy (PST), interpersonal therapy (IPT), and integrative approaches such as counseling, and psychodynamic therapies (WHO 2023). These interventions, delivered by healthcare workers trained in the delivery of the intervention, include the following.

- Cognitive behavioral therapies (CBT): combine principles of both behavioral and cognitive therapy (Clark 1986) (e.g. cognitive restructuring, and skills training, such as stress management and problem-solving); numerous descriptive studies have examined the technical issues involved in adapting these therapies to the clinical diversity associated with aging (Gallagher-Thompson 2007; Laidlaw 2003; Sadler 2018; Scogin 2005). Key adaptations include an emphasis on behavioral techniques, particularly earlier in therapy, repetition of information, and the use of different sensory modalities (Grant 1995). CBT is particularly suited for older adults who are cognitively intact or have mild cognitive impairment and can actively participate in structured therapeutic sessions.
- Behavioral therapies (BT): based on the assumption that behavior is learned, and employ methods that focus on changing maladaptive behavior patterns (e.g. relaxation techniques, activity scheduling, and behavior modification) (Marks 1981). BT is particularly appropriate for older adults

who may have difficulty with cognitive tasks but can benefit from behavioral strategies to increase activity levels and modify maladaptive behaviors.

- Interpersonal therapies (IPT): IPT focuses on the intricate interplay between an individual's mood and their interpersonal relationships. By examining areas like communication patterns, grief, role transitions, and relationship conflicts, IPT offers insights into the sources of one's distress (Cuijpers 2016; Weissman 2017). Supportive counseling (SC), which is often used in conjunction with IPT, believes that by offering an environment marked by genuine understanding, empathy, and non-judgment, individuals can explore and come to understand themselves (e.g. SC and interpersonal therapy) (Esfandiari 2020). IPT is ideal for older adults whose depression is closely linked to interpersonal issues, such as grief, role transitions, or social isolation. It is also beneficial for individuals who need to explore their feelings in the context of their relationships.
- Psychodynamic therapies: focused on revealing and resolving intrapsychic or unconscious conflicts (e.g. brief psychotherapy, psychoanalytic therapy, and insight-oriented therapy) (Busch 2016; Kudler 2000). This form of therapy is suitable for older adults with long-standing emotional conflicts or unresolved past experiences that contribute to their depression.
- Third-wave CBT: includes interventions using techniques that focus on the process, rather than the content of thoughts, helping people accept their thoughts in a non-judgmental way (e.g. mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT)) (Hofmann 2010). These are particularly beneficial for older adults who may struggle with rumination or find traditional CBT challenging.
- Bibliotherapy: a self-help intervention that uses guided reading of written materials to address an individual's developmental or therapeutic needs (Songprakun 2012). With the development of technology, other mediums such as audio, video, computers, and websites have been utilized (Yuan 2018). This is suitable for individuals who can engage with reading materials and apply the concepts independently.

### Adverse effects of the intervention

Psychotherapeutic treatments have the potential to alleviate mental distress and enhance well-being for many sufferers of depression. However, the adverse effects of psychotherapeutic treatments (such as CBT, BT, IPT, etc.) are not widely discussed or reported (Parry 2016).

Most clinical trials focus on the average treatment outcome and the number of patients achieving clinically significant change, while ignoring the fact that some patients might also experience adverse or unwanted events (Berk 2009). A previous study stated that a wide range of adverse and unwanted events, such as social stigma, dependency, and novel symptoms, might occur during psychotherapeutic treatments (Hadley 1976). Others have also implied that non-response, dropout, and interpersonal difficulties may be perceived as negative effects (Dimidjian 2010; Rozental 2016).

## How the intervention might work

The etiology of depression is complex, encompassing biological, psychological, and social factors (Chai 2023). Psychotherapeutic treatment can help to relieve the symptoms of depression by helping individuals deal with negative thoughts and lower the risk of depression relapse by guiding the individual to have a better understanding of what is causing their symptoms (Angelakis 2022). The six main psychotherapeutic treatments (CBT, BT, IPT, psychodynamic therapy, third-wave CBT, and bibliotherapy) treat depression through a multipronged approach. The proposed mechanisms of actions vary with the underlying theoretical basis of individual psychological therapies.

CBT guides individuals to identify and respond to their dysfunctional thoughts and beliefs. The core of CBT lies in restructuring one's unhelpful beliefs and establishing a more appropriate association between the revised beliefs and behaviors, resulting in changes in the corresponding behavior. Behavioral therapies help the person to develop new and adaptive ways of behaving. Activity scheduling of behavioral therapies is often used for combating passivity and withdrawal in depression, assisting the depressed person in gradually re-engaging in some of their daily routines, with a focus on increasing activities that are pleasurable and associated with mastery (Uphoff 2020).

IPT operates on the belief that improving interpersonal functioning can lead to significant symptom reduction. The goals of IPT are to enable individuals with depression to make their own needed adjustments so that they can cope and reduce depressive symptoms. Through a series of targeted sessions, IPT assists the individual in understanding how their interpersonal problems contribute to their well-being, and provides strategies to improve interpersonal skills (Ravitz 2019). Individuals learn to enhance their relationships, better navigate social challenges, and alleviate depressive symptoms.

Psychodynamic therapy focuses on past experiences and an understanding of how these events might have influenced the individual and their current thoughts and behaviors (Busch 2016). The goals of psychodynamic therapy are for individuals to identify their unconscious conflicts, be aware of their feelings, and confront issues that have been unconsciously repressed, which can lead to the relief of depressive symptoms. It uses the therapeutic alliance between patient and therapist to support the development of self-awareness, helping people to recognize and modify interpersonal patterns that contribute to psychological distress (Shedler 2010).

Third-wave CBT approaches include concepts such as acceptance, mindfulness, and personal values (Hofmann 2010). Strategies such as mindful exercises and acceptance of unwanted thoughts are used to elicit changes in the thinking process and to reduce depression.

Bibliotherapy provides information and outlines approaches that readers can adopt to develop insight and awareness of negative thoughts and emotions (Jorm 2002). It also offers answers to problems and supports the individual in practicing these approaches in their daily life.

Both CBT and IPT are focused on comprehending and changing particular habits or processes. CBT focuses on how an individual thinks as thoughts influence behavior, emotions, and reactions. IPT focuses on recognizing concerns and problems in interpersonal relationships and discovering solutions to strengthen and manage them. Instead of examining the causes of the problematic patterns, both CBT and IPT focus on developing new patterns. Psychodynamic therapy is based on the notion that an individual's

unconscious mind and prior experiences influence their conduct and behavior, and involves deep and unrestricted emotional exploration of the patient. Third-wave CBT, on the other hand, focuses on how an individual relates to internal experiences rather than the content of their internal experiences. Bibliotherapy does not require intensive collaboration between clients and therapists; the role of the therapist is auxiliary, as it is primarily self-administered (Floyd 2003). These psychotherapeutic treatments can be delivered individually or in group formats. This flexibility allows therapists to cater to the unique therapeutic requirements of each patient, increasing the likelihood of successful treatment outcomes.

### Why it is important to do this review

The heightened prevalence of depression among the older population, compounded by multifaceted challenges such as diminished quality of life, impediments in daily living activities, physical comorbidities, cognitive impairment, frailty (Chu 2019), and premature death (Avasthi 2018; Zis 2017), highlight the necessity for robust evidence on efficacious treatments.

While existing systematic reviews and meta-analyses provide some evidence on psychological interventions for older adults, these reviews tend to focus on people with specific health conditions, such as dementia (Cheng 2020; Sun 2022), stroke caregivers (Panzeri 2019), or subclinical depressive symptoms (Corpas 2022). Several prior systematic reviews investigated the effects of psychotherapies across different age groups (Cuijpers 2020; Cuijpers 2023), but did not focus exclusively on depression in older people. Several reviews have reported promising results of psychological therapies for older people, particularly using CBT, problem-solving therapy, and reminiscence therapies (Cuijpers 2006; Cuijpers 2014; Wilson 2008). However, these studies did not focus on clear diagnostic populations; did not use interventions with strict protocols; and the quality of many included studies was not optimal.

High dropout rates are a common issue in clinical trials involving older adults with depression. This can be attributed to several factors, including the severity of depressive symptoms, comorbid physical health conditions, and the side effects or perceived burden of the treatments. High dropout rates can impact the validity and generalizability of study findings, indicating potential issues with the acceptability and tolerability of the psychotherapeutic interventions. Therefore, focusing on dropout rates helps assess the feasibility and practicality of these treatments in real-world settings.

In addition, depression and anxiety often co-occur, with studies indicating that many older adults with depression also experience anxiety symptoms (Gao 2023; Saade 2019; Santini 2020). This comorbidity can complicate treatment, and some psychotherapeutic interventions may inadvertently worsen anxiety, making it crucial to monitor and address this outcome.

Considering the substantial research advances and newly available evidence on the topic of psychotherapeutic treatments for depression over the past decade (Titov 2016; Wuthrich 2013), a comprehensive and up-to-date review is needed to bolster the reliability of evidence in this field. This review, using the latest Cochrane methodology, ensures a systematic and rigorous review process, with an explicit emphasis on treatments for depression in the older cohort, thereby aiming to bridge a crucial gap in the existing academic literature.

## OBJECTIVES

To assess the benefits and harms of psychotherapeutic interventions in the treatment of older adults with depression and whether the effects of different types of psychotherapeutic treatments vary for older adults with depression.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include all parallel and cluster-randomized controlled trials (RCTs). We will include trials conducted in primary, secondary, community, and inpatient settings, including nursing homes. We will include both published and unpublished studies.

We will exclude cross-over trials, as they are generally unsuitable for assessing long-term outcomes in chronic diseases, and typically focus on interventions with transient effects on stable, chronic conditions during the study period (Higgins 2022a). We will also exclude quasi-RCTs where allocation to an intervention condition is not strictly random (e.g. by resident record number or alternation) with the goal of reducing potential sources of heterogeneity.

#### Types of participants

##### *Participant characteristics*

We will include participants aged 60 years and older, regardless of gender, ethnicity, or religion. We will also consider studies that include a subset of participants aged 60 years and over, but only if the participants are randomized at the level of the subset and data for participants aged 60 years and over are reported separately.

##### *Diagnosis*

We will include participants if they have been diagnosed with: 1) MDD, according to any version of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) (APA 2013) or International Statistical Classification of Diseases and Related Health Problems (ICD) criteria (WHO 2018); or 2) depressive symptoms diagnosed via self-reported scales or questionnaires. We will include participants with all types of depression and severities.

##### *Comorbidities*

We will include participants with normal cognitive functioning or cognitive impairment of any type of severity. Studies involving participants with comorbid physical conditions or other psychological disorders will be eligible for inclusion as long as the primary focus of the study is on treating depression.

#### Types of interventions

The experimental intervention is the psychotherapeutic treatment, which will be categorized, where possible, into the following groups.

- CBT (e.g. cognitive restructuring, and skills training, such as stress management and problem-solving)
- Behavioral therapies (e.g. relaxation techniques, activity scheduling, and behavior modification)

- IPT (e.g. supportive counseling and interpersonal therapy)
- Psychodynamic therapies (e.g. brief psychotherapy, psychoanalytic therapy, and insight-oriented therapy)
- Third-wave CBTs (e.g. ACT and MBCT)
- Bibliotherapy (e.g. working through structured materials, such as books, audio, video, computer programs, and websites, independently from a clinician)

We will include both group and individual psychotherapeutic therapies, with no restrictions on frequency, intensity, or duration of the intervention. We will exclude treatments identified as:

- pharmacotherapy, exercise, reminiscence therapy, pet therapy, or music therapy;
- self-help interventions delivered without therapist involvement;
- interventions that were delivered by healthcare workers who were not described in the study as being specifically trained or following a treatment protocol.

We will include the following comparators.

- Waitlist control (received treatment only after the intervention group had completed the treatment)
- Treatment as usual or standard care (any medical care during the course of the study, including monitoring, check-ups, no treatment, or any type of pharmacological treatment)
- Different types of psychotherapeutic treatments

#### *Co-interventions*

We will allow co-interventions, such as pharmaceutical interventions, in both arms. However, when making net comparisons between groups, we will make the following distinctions:

- psychotherapeutic treatments versus waiting list or standard care;
- different psychotherapeutic treatment groups (e.g. CBT versus psychodynamic therapy, CBT versus IPT).

#### *Minimum duration of intervention*

There is no minimum duration of the intervention.

#### *Minimum duration of follow-up*

The minimum duration of follow-up will be four weeks from baseline.

### Types of outcome measures

We will include studies that meet the above inclusion criteria irrespective of whether they report on the following outcomes.

#### *Primary outcomes*

Our primary outcome will be the change in the severity of depression or depression symptoms.

- Change in depression score: change in the severity of depression or depression symptoms, measured using validated scales, following the intervention. This is treated as a continuous outcome.

We will accept psychometrically validated measures of depression, self-reported or other, along with clinical diagnosis. Commonly validated tools for depression include: the Beck Depression Inventory (BDI; Beck 1961), Zung Self-Rating Depression Scale (SDS; Zun 1965), Hamilton Depression Rating Scale (HAM-D; Hamilton 1960), Montgomery Asberg Depression Rating Scale (MADRS; Montgomery 1979), Hospital Anxiety and Depression Scale (HADS-D; Zigmond 1983), Patient Health Questionnaire-9 (PHQ-9; Kroenke 2001), and Center for Epidemiological Studies Depression Scale (CES-D; Radlof 1977).

When an included study reports on more than one measurement scale for the same outcome, we will only include validated scales. When more than one validated scale is used, priority will be given to the most commonly used scale in clinical settings, but we will include data from all validated scales.

#### *Secondary outcomes*

Where data are available, we will include the following secondary outcomes.

- Response or remission rates, or both, based on changes in depression measures, either clinician-rated or self-report or using other validated measures.
- Number of dropouts from study or treatment (all-cause dropout) within trials, where data on reasons for dropout will be collected and summarized in narrative form.
- Quality of life (QoL), measured using standardized scales, such as the 36-Item Short Form Health Survey (SF-36) (Ware 1992), the WHOQOL (WHOQOL Group 1998), or Health of the Nation Outcome Scales (HoNOS).
- Anxiety, measured as a change from baseline in severity of anxiety or anxiety symptoms at the last time point.
- Global functioning: assessed using the Global Assessment of Functioning (GAF) scale, Sheehan Disability Scale (SDS) (Sheehan 1996), or the Social Adjustment Scale-Self-report (SAS-SR) (Weissman 1976).
- Adverse effects: we will define adverse effects as reported in the individual studies.
- Self-harm and suicide-related events, measured as the number of participants experiencing self-harm and suicide-related events (suicide ideation, suicide attempts, and completed suicide).

#### Timing of outcome assessment

If the data allow, we will extract post-intervention outcomes (i.e. at the end of the treatment period and follow-up period) at the time points reported in the studies and group them into short-term (up to three months), medium-term (three to six months), and long-term (more than six months). If a study reports multiple time points within one of the prespecified time periods, we will select the latest time point.

We will report outcomes at the first assessment post-intervention in the Abstract and summary of findings table.

#### Hierarchy of outcome measures

We will analyze depression symptoms (assessed using continuous measures) and MDD diagnosis (assessed using a dichotomous measure or rate recovered) separately, with depressive symptoms considered the primary outcome. If a study uses more than one

instrument to assess depression symptoms, we will prioritize these in the following order: clinician-rated scale, informant-rated scale, and self-rated scale, given concerns about the reliability of self-reported symptoms of depression. If several outcome measures on the same scale are available (e.g. multiple subscales of the HAM-D), we will prioritize the outcome measure most frequently used across studies (namely, availability across studies). If multiple outcome measures of the same type have equivalent availability across studies, we will choose the one that best addresses the aims of the review.

#### Minimally important difference (MID)

If possible, we will compare the pooled estimates with the MID values for continuous outcomes to aid interpretation. We will use published MIDs when available. When multiple MID estimates are available for an outcome, we will use the smallest validated MID.

## Search methods for identification of studies

### Electronic searches

We will search the following databases and trial registers using relevant keywords, subject headings (controlled vocabularies), and search syntax, appropriate to each resource (Appendix 1), placing no restrictions on language of publication:

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years);
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- Ovid MEDLINE (1946 to date);
- PsycINFO (Ovid) (all available years);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/; all available years);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; all available years).

We will not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (Cochrane 2023).

### Searching other resources

We will check the reference lists of all included studies, relevant books, and any relevant systematic reviews that we identify for additional references to studies. We will also conduct internet searches for relevant grey literature sources such as reports, dissertations, theses, databases, and databases of conference abstracts. In addition, we will contact experts in the field for ongoing and unpublished trials.

## Data collection and analysis

### Selection of studies

Two review authors (LA and ES) will independently assess the relevance of each title and abstract produced by the search strategy, categorizing each as relevant, not relevant, or uncertain. We will retrieve the full-text reports of studies deemed relevant or uncertain. The same two review authors (blind to each other's decision) will read the full texts using preset criteria and a recording sheet to identify studies for inclusion in the review. In cases of disagreement, open discussion will take place between all review authors and a decision will be reached by consensus. We will record the study selection process in sufficient detail to produce a PRISMA flow diagram (Page 2021). We will list all articles excluded after a full-text assessment in a 'Characteristics of excluded studies' table along with the reasons for their exclusion (Page 2021). We will use the latest version of Covidence software for study selection (Covidence).

To screen non-English language papers for eligibility, we will start with Google Translate. If needed, we will seek translators in our university networks or Cochrane Engage to assist with assessing the eligibility of studies, and if eligible, to assist with data extraction by native speakers.

#### *Dealing with duplicates and companion publications*

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximize the information yield by collating all available data, and we will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study. We will also list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

### Data extraction and management

Two review authors (LA and ES) will use a piloted data extraction form based on the Cochrane Effective Practice and Organisation of Care (EPOC) data extraction form, to extract data regarding participants, interventions and their comparators, methodological details, and treatment effects, including dropouts and possible biases. Any disagreements will be discussed with a third review author (MSL). Additionally, we will contact study authors for any unpublished data if necessary.

We will extract information related to inclusion/exclusion criteria, number screened, number suitable, total number started, method of randomization, allocation concealment, number in each arm, intention-to-treat numbers, the number completed in each arm, number and reasons for dropout, age, sex, health status, recruitment source, baseline scores and standard deviation (SD) of all rating scales used (including QoL), diagnosis and criteria used, length of the trial and any follow-up period, therapy type and model used, length of sessions and frequency, setting of therapy, group or individual therapy, compliance to therapy, therapists' background/qualifications, supervision, single/multicenter, country where the trial was conducted, and study funding sources.

We will follow the Template for Intervention Description and Replication (TIDieR) checklist to extract details of interventions and comparisons for each eligible study (Hoffmann 2014; Hoffmann 2017). For trials using pharmacotherapy, we will record the name of the medication, dosage, frequency, side effects, and compliance. Where data are unclear or missing, we will contact trialists for the additional information. We will report these data in 'Characteristics of included studies' tables, summary of findings tables, and the main text.

### Assessment of risk of bias in included studies

Two review authors (LA and ES) will independently assess risk of bias in each included study using Cochrane's RoB 2 tool (Higgins 2022b), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Any disagreements will be discussed with a third review author (MSL). If information is unclear or missing, we will contact the corresponding authors of primary studies to request the required data. We will assess the following criteria.

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in the measurement of the outcome
- Bias in the selection of the reported result

For the scope of this review, we will assess the effect of the assignment to the intervention (intention-to-treat effect) for our primary outcome. We will perform an evaluation using the RoB 2 tool for the following outcomes.

- Change in depression score: change in the severity of depression or depression symptoms, measured using validated scales, following the intervention (medium term).
- Response or remission rates, or both: based on changes in depression measures, either clinician-rated or self-reported, or using other validated measures (long term).
- Number of dropouts from study or treatment (all-cause dropout) within trials, where data on reasons for dropout will be collected and summarized in narrative form (medium term).
- QoL: measured using standardized scales, such as the SF-36, WHOQOL, or HoNOS (medium term).
- Anxiety: measured as a change from baseline in severity of anxiety or anxiety symptoms at the last time point (medium term).
- Global functioning: assessed using the GAF scale, SDS, or SAS-SR (long term).
- Adverse effects: we will define adverse effects as reported in the individual studies (long term).

Answers to signaling questions and supporting information will collectively lead to a domain-level judgment of either low risk of bias, some concerns, or high risk of bias. These domain-level judgments will inform an overall risk of bias judgment for a single result in the form of (a) low risk, if all domains are judged as being low risk; (b) some concerns, if one or more domains are judged as being of some concerns; and (c) high risk, if one or more domains are judged as being high risk, or if four domains are judged as being of some concerns. We will provide a quote from the study report together with a justification for our judgment in the risk of bias table. We will summarize the risk of bias judgments across different studies for each of the domains listed. We will aim to source trial registries, protocols, and analysis plans to assess selective reporting. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

We will assess the risk of bias of a specific result of cluster-randomized trials using the domain 'Bias arising from the timing of identification and recruitment of participants' of the Cochrane RoB 2 tool (Higgins 2024), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome. We will construct summary assessments of the risk of bias for each important outcome (across domains), within and across studies (Higgins 2022b).

### Measures of treatment effect

We will analyze continuous outcomes by calculating the mean difference (MD) and 95% confidence intervals (CIs) between groups if studies used the same outcome measure for comparison. When available, we will use the mean change from baseline to endpoint. If the mean change is not available, we will use the mean endpoint score. If studies used different outcome measures to assess the same outcome, we will pool the standardized mean difference (SMD) and 95% CIs. We will analyze dichotomous data as risk ratios (RR) with 95% CIs.

### Unit of analysis issues

Where included trials have more than two comparator groups, if possible we will compare the psychotherapeutic treatment with the inactive control group. We will next prioritize comparisons between different types of psychotherapeutic treatments (e.g. CBT versus psychodynamic therapy).

If more than one comparison from the same study is eligible for inclusion in the same meta-analysis, we will combine the intervention groups to create a single pair-wise comparison to avoid possible bias caused by overlapping samples with multiple comparisons to one control group.

We will attempt to re-analyze cluster-RCTs that did not appropriately adjust for clustering of participants in their analyses. The variance of intervention effects will be inflated by a design effect. Calculation of a design effect involves the estimation of an intracluster correlation coefficient (ICC), as specified in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c). We will obtain estimates of ICCs by contacting study authors, or by imputing ICC values, using either estimates from other included studies that report ICCs, or external estimates from empirical research. We plan to examine the impact of clustering by performing sensitivity analyses.

### Dealing with missing data

We will contact study authors to request missing data as needed. If data remain unavailable, we will attempt to estimate the missing data using the available information from the study, such as CIs, following the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023). Where possible, we will attempt to impute missing data. Where this is not possible, we will report the study narratively and discuss its impact on the overall assessment of results.

For studies in which the SD of the outcome is not available at follow-up, we will standardize by the mean of the pooled baseline SD from studies that reported this information for that scale.

### Assessment of heterogeneity

We will take into account a visual examination of the variability in point estimates and the overlap in CIs. We will use the $I^2$ statistic to quantify heterogeneity among studies in each analysis. We will use the rough guide to interpretation of the $I^2$ described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will avoid the use of absolute cutoff values, but interpret $I^2$ in relation to (a) the size and direction of effects, and (b) the strength of evidence for heterogeneity (e.g. P value from the $Chi^2$ test, or CI for $I^2$).

### Assessment of reporting biases

We will handle different forms of reporting bias, especially publication bias and outcome reporting bias, following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c). If we are able to include more than 10 studies in the analysis, we will create and examine a funnel plot to explore possible small-study biases for the primary outcome of interest. We will also use Egger's test to assess asymmetry (Egger 1997).

### Data synthesis

We will include all eligible trials in the primary analysis. If there is sufficient similarity among studies, and data availability allows for meaningful comparisons between intervention and control groups, we will conduct meta-analyses. Unless good evidence shows homogeneous effects across studies of different methodological quality, we will pool data primarily using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects, and will present a CI. If there are outcomes that could be reported as time-to-event data, we will analyze them as hazard ratios.

If meta-analysis is not possible (e.g. due to insufficient data), we will provide a narrative synthesis of the evidence including the summary statistics of intervention effect estimates, the combination of P values, and vote counting, based on the direction of effects (McKenzie 2023).

### Subgroup analysis and investigation of heterogeneity

Where possible, we will conduct the following subgroup analyses for depressive symptoms at end of intervention.

- Baseline depression severity: this may impact the outcome measurements across intervention groups. We plan to test for differences between older adults with MDD and subthreshold depressive symptoms at baseline.
- Length of study/number of sessions: the duration and number of sessions may impact the effectiveness and acceptability of psychotherapeutic interventions.
- Age (under 75 versus over 75): age may impact the effect size and acceptability of interventions. We plan to test for differences in outcomes between participants under 75 and those over 75 years old.
- Types of psychotherapeutic therapies: different therapies may have a different effect size and acceptability to participants. We will test for differences between different types of psychotherapeutic therapy.
- Types of comparators: different controls may yield differing effect sizes, therefore we will examine the effect of any psychotherapeutic therapy compared to each distinct comparator type.

We will use the formal test for subgroup interactions in RevMan, acknowledging its limitations due to its observational nature and low power to detect differences with fewer than 10 studies per category (Higgins 2022c; RevMan 2024).

### Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes.

- Excluding studies at high risk of bias
- Parallel RCTs without cluster-RCTs
- Studies without imputed data
- Excluding studies comparing bibliotherapy

### Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in summary of findings tables according to the GRADE approach (Schünemann 2022), which takes into account issues related to internal validity (overall risk of bias, inconsistency, imprecision, publication bias), and external validity (directness of results). The certainty of the evidence can be downgraded by one or two levels for each of these considerations. We will follow the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022), employing GRADEpro GDT software (GRADEpro GDT).

The summary of findings table will provide key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We will justify all decisions to downgrade the certainty of the evidence by using informative footnotes.

We will report the following outcomes and comparisons in the summary of findings tables, measured at end of intervention and short-term follow-up (where sufficient data are available), and will present standardized effect size estimates and 95% CIs.

#### *Outcomes*

- Change in depression score: change in the severity of depression or depression symptoms, measured using validated scales, following the intervention (medium term).
- Response or remission rates, or both: based on changes in depression measures, either clinician-rated or self-reported, or using other validated measures (long term).

- Number of dropouts from study or treatment (all-cause dropout) within trials, where data on reasons for dropout will be collected and summarized in narrative form (medium term).
- QoL: measured using standardized scales, such as the SF-36, WHOQOL, or HoNOS (medium term).
- Anxiety: measured as a change from baseline in severity of anxiety or anxiety symptoms at the last time point (medium term).
- Global functioning: assessed using the GAF scale, SDS, or SAS-SR (long term).
- Adverse effects: we will define adverse effects as reported in the individual studies (long term).

***Comparators***

- Waitlist control
- Treatment as usual or standard care
- Different types of psychotherapeutic treatments

Two review authors (LA and ES), will independently assess the certainty of evidence, with any disagreements to be resolved by discussion or by involving a third review author (MSL). All judgments will be justified, documented, and incorporated into the reporting of results for each outcome.

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- Sign-off Editor (final editorial decision): Adib Essali, Community Mental Health, Counties Manukau Health, Manukau, New Zealand;
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# APPENDICES

## Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1. Depression/

2. Depressive Disorder/

3. Depressive Disorder, Major/

4. Mental disorders/

5. (depression or depressive or depressed or MDD or TRD or affective disorder* or affective symptom or mental).mp.

6. 1 OR 2 OR 3 OR 4 OR 5

7. Aged/

8. Aging/

9. (older or elderly or ageing or aging or aged or geriatric* or senior* or old age or late* life or elder* care).tw,kf.

10. 7 OR 8 OR 9

11. Randomized controlled trial.pt.

12. Controlled clinical trial.pt

13. Random $.ti,ab,ot.

14. Randomization/

15. Single-blind method or /double-blind method/ or random allocation/

16. (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or crossover or cross over))).ti,ab,kf.

17. (randomized or randomised or randomly).mp.

18. Trial.ti,ot.

19. Clinical trials as topic/

20. OR/11-19

21. 6 AND 10

22. 20 AND 21

23. exp animals/ not humans.sh.

24. (22 NOT 23)

# CONTRIBUTIONS OF AUTHORS

Ang L, Lee MS, Cao L, and Yao L conceived and designed the review.

All authors contributed to the development of the protocol.

Ang L and Cao L drafted and revised the protocol.

All authors revised the protocol critically for important intellectual content and approved the final version.

Details of the contributions of authors are as follows.

- Ang L: conceptualization, methodology, project administration, writing—original draft, writing—review and editing
- Lee MS: conceptualization, funding acquisition, investigation, methodology, project administration, supervision
- Song E: methodology, writing—review and editing

- Lee HW: methodology, writing—review and editing
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- Papola D: methodology, writing—review and editing

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Lin Ang: no known conflict of interest to declare.

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Authors will not be involved in the risk of bias assessment or GRADE assessment of data from their own study.

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