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Pharmacological and psychological interventions for depression in people with tuberculosis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Pharmacological and psychological interventions for depression in people with tuberculosis

Rocio Nava-Ruelas[1], Alexander Jarde[1], Helen Elsey[1], Kamran Siddiqi[1,2], Olamide Todowede[1], Gerardo Zavala[1], Najma Siddiqi[1,2]

[1]Department of Health Sciences, University of York, York, UK. [2]Hull York Medical School, University of York, York, UK

Contact address: Rocio Nava-Ruelas, rdnr500@york.ac.uk, rocionavarls@gmail.com.

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ABSTRACT

Objectives

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

To assess the effectiveness of pharmacological and psychological interventions for the treatment of depression in people with tuberculosis (TB). This review will assess the impact of these interventions on depression,TB-related outcomes, and health-related quality of life.

BACKGROUND

Description of the condition

Major depressive disorder, or depression, represents a debilitating mental disorder, characterised by low mood (e.g. sadness, irritability, emptiness) or loss of pleasure, accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the person's ability to function.

The *Diagnostic and Statistical Manual* (DSM-5) describes depression as experiencing at least five of the following symptoms listed below in the presence of depressed mood, or loss of interest or pleasure, for at least two weeks, every day or nearly every day (APA 2013):

- Sadness (or irritability in children)
- Loss of interest or pleasure in usual activities
- Changes in appetite (increased or decreased) or weight change
- Disturbed sleep (insomnia or hypersomnia)
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of guilt, self-blame
- Decreased ability to concentrate or make decisions
- Thinking about or planning suicide or suicidal behaviour.

These symptoms refer to adult populations only.

Tuberculosis (TB) is broadly defined as an infectious disease caused by Mycobacterium tuberculosis. It can affect any organ in the body, but its classification, based on the anatomical site of disease, divides TB into pulmonary and extrapulmonary infections. Pulmonary TB affects the lungs, lung parenchyma, or tracheobronchial tree; extrapulmonary TB affects organs other than the lungs, such as lymph nodes, pleura, abdomen, skin, joints, bones, meninges, or genitourinary tract (WHO 2020). TB can also be classified according to the drug-susceptibility of the strain, on active or latent status of the infection, and on HIV status (WHO 2020).

The recommended standard for the diagnosis of TB is the use of molecular or biomarker-based techniques, which can also detect drug-resistant TB strains (WHO 2020). However, the diagnosis of TB can also be made using smear microscopy, or based on clinical symptoms, such as persistent cough and haemoptysis. A notified case is when TB is diagnosed in a patient and is reported within the national surveillance system, and then on to the World Health Organization (WHO). Currently, around 55% of pulmonary TB cases notified to the TB programme management authorities are confirmed using molecular or bacteriological techniques, with the remainder based on the assessment of symptoms by a clinician (WHO 2019).

TB infection is a curable disease, with established treatment regimes. The prognosis of the condition can depend on whether the strain is drug-susceptible or drug-resistant. Treatment for drug-resistant forms of TB (DR-TB) can be more burdensome for the person with TB, with longer regimes and a higher risk of treatment attrition or adverse effects (Cohen 2018). Treatment success, defined as the sum of treatment completion and cure, is influenced by successful adherence to treatment, and is also mediated by age, nutritional status, alcohol consumption, smoking, and gender (Chaves Torres 2019 WHO 2020). Comorbidities may also negatively influence treatment outcomes for TB (Samuels 2018). Most of the current evidence focuses on the correlation between HIV seropositivity and TB WHO 2019, but increasingly, research is addressing other physical (Tegegne 2018), and mental health comorbidities (Ruiz-Grosso 2020), and the influence of these on TB outcomes.

Depression is a common comorbidity in people with TB. Based on data from the World Health Survey, collected between 2002 and 2004, it is estimated that the prevalence of depression in people with TB is 23.7% versus 6.7% in people without TB (Koyanagi 2017). Depression, combined with TB, has a negative impact on health outcomes and quality of life for people living with TB (Lee 2020). Depression in people with TB is associated with increased death and loss to follow-up during TB treatment (Ruiz-Grosso 2020). Studies have consistently found that depression has a negative effect on adherence to treatment. Due to heterogeneity of definitions and measurement, a consistent effect size or risk has not been found across studies (Ruiz-Grosso 2020).

The aetiology of depression in TB is unclear, but the following reasons can increase the risk (Doherty 2013;Sweetland 2017):

- treatment of the illness (i.e. substance-induced depression);
- direct result of the illness (i.e. organic depression);
- psychological response of coping with the illness, the associated stigma, or both, or;
- it might co-occur with the illness due to chance.

Description of the intervention

Depression can be effectively treated by pharmacological or psychological interventions, or both, depending on the severity of symptoms. For example, clinical practice guidelines for treating depression focus on people with treatment-resistant disease, the use of pharmacological interventions (Gabriel 2020), perinatal depression (Fedock 2018), depression in the elderly (Kok 2017), and other specific populations (Cheung 2018). Guidelines vary across countries, reflecting each country's health services and approaches to the treatment of depression (Rathod 2017).

Pharmacological interventions for depression refer to the use of antidepressants; the most common types are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs (Allida 2020; Pollok 2018)). There is no consensus on the most effective dose for each type of antidepressant for the severity of depression; instead, guidelines recommend starting with the lowest dose, to minimize the risk of adverse effects and treatment attrition, and either increasing the dose if symptoms of depression do not improve after four to six weeks, or consider the use of a different antidepressant (NICE 2009).

Psychological interventions refer to any type of group or individual therapy used to treat mental health conditions, such as depression, anxiety, or psychosis. Examples of psychological interventions for depression are behavioural therapy (e.g. behavioural activation), interpersonal therapy, cognitive behavioural therapy (including third-wave cognitive behavioural therapies, such as behavioural activation), psychodynamic therapies (e.g. group therapy or psychoanalytic therapy), and other types of psychological therapies (e.g. family therapy (Shinohara 2013; Thabrew 2018)).

All interventions must have a psychological component – talking, listening, support, advice – and be delivered by somebody with recognised training in, and supervision of, therapies. National guidelines can influence the definition and scope of psychological therapies for depression; in the UK, guidelines recommend six to eight sessions, delivered over 9 to 12 weeks for low-intensity psychosocial interventions, aimed at people with mild to moderate depression (NICE 2009). For high-intensity psychosocial interventions, guidelines recommend 16 to 20 sessions, delivered over three to four months. Recommendations on the length of sessions are based on the analysis of published evidence, and can range from 45 to 55 minutes for all types of psychological therapies discussed in this protocol (NICE 2009).

How the intervention might work

Pharmacological interventions

Pharmacological interventions for depression are the prescription of antidepressants. TCAS and SSRIs can improve mood by affecting intra-synaptic levels of monoamines, such as noradrenaline, 5-hydroxytryptamine, and dopamine (NICE 2009). MAOIs work by blocking the monoamine oxidase enzyme, which breaks down different types of neurotransmitters in the brain, such as norepinephrine, serotonin, dopamine, and tyramine, resulting in increased levels of these neurotransmitters in the brain (Sub Laban 2020). In a systematic review including placebo-controlled and head-to-head trials, the use of different antidepressants (i.e. agomelatine, amitriptyline, escitalopram, citalopram, clomipramine, duloxetine, mirtazapine, paroxetine, venlafaxine, vortioxetine, fluoxetine, fluvoxamine, reboxetine, trazodone, and sertraline) for the treatment of major depression was more effective than placebo for all the antidepressants included in the meta-analysis (Cipriani 2018).

Pharmacological treatment of depression can improve the body's immune response, which in turn, could protect against TB (Zhang 2019); it can also help to improve health-related domains that affect a person's quality of life, such as sleep, mobility, and self-care (Koyanagi 2017). Treating depression in people with TB may also reduce the non-adherence associated with stigma, and other negative perceptions that develop at the onset of TB infection (Pachi 2013).

Psychological interventions

Psychological interventions are broadly categorised into four different theoretical or philosophical schools: cognitive, behavioural, psychodynamic, and humanistic. Compared to no intervention, psychological interventions can improve depressive symptoms. Long-term (50 or more sessions, or sessions delivered over the course of one year) and short-term psychotherapy (less than 20 sessions), cognitive behavioural therapy, cognitive therapy, interpersonal therapy, or psychodynamic therapy, can reduce symptoms of depression in the short term (e.g. decreased number of depressive symptoms or total remission (Berg 2010)). In long term effects, there is less conclusive evidence on the sustained improvement of depressive symptoms, with the exception of long term psychotherapy, in which the effects are sustained for the duration of the intervention (Berg 2010). Compared to the use of antidepressants alone, the combined use of psychological and pharma

Psychological interventions can improve the beneficial effect of each type of treatment for people who are resistant to antidepressants (Ijaz 2018). A Cochrane Review on the effect of psychological therapies for treatment-resistant depression, defined in the review as an absence of response to depression treatment using TCAs for more than six weeks, concluded that the use of psychological therapies improved self-reported depressive symptoms when used alongside antidepressants (Ijaz 2018). There is inconclusive evidence as to which type of psychological intervention is the most effective, or which components of a psychological intervention (e.g. therapeutic alliance) might be linked to their effectiveness, given the variability of definitions used across settings (Shinohara 2013). However, it is argued that factors relating to the person with depression and the therapist, and therapist competence can affect the effectiveness of psychological treatments for depression (Shinohara 2013).

Why it is important to do this review

The treatment of depression in people with health conditions, such as HIV (Eshun-Wilson 2018), stroke (Allida 2020), diabetes (Baumeister 2012), chronic obstructive pulmonary disease (Pollok 2018), and chronic conditions lasting longer than three months (Thabrew 2018), has improved depression scores, and other health-related outcomes, such as mobility. The quality of evidence for these reviews ranges from moderate to low and further studies are needed to asses the effects on other health outcomes, such as glycaemic control, dropouts, and mortality, amongst others. However, these reviews conclude that psychological and pharmacological interventions have reduced the severity of depression and improved self-described depressive symptoms in people with different chronic conditions more than no intervention or placebo.

Despite the evidence on the increased risk of depression in people with TB, and its association with poorer TB and mental health outcomes, there is a dearth of evidence on how to effectively address this comorbidity. Little is known about the effectiveness of pharmacological and psychological interventions for treating depression in people with TB, and their impact on TB-related and mental health outcomes. There are no systematic reviews that explore the use of antidepressants, with or without psychological interventions, to treat depression in people with TB, and their effect on TB-related health outcomes.

This review will help to determine whether treating depression in people with TB is effective for improving mental and physical health outcomes, by summarising the existing evidence on pharmacological and psychological interventions. It can also help to assess the effect of treating depression in other outcomes of interest, such as health-related quality of life.

OBJECTIVES

To assess the effectiveness of pharmacological and psychological interventions for the treatment of depression in people with tuberculosis (TB). This review will assess the impact of these interventions on depression,TB-related outcomes, and health-related quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials (RCTs), crossover trials, and cluster-randomized trials (cRCT) that evaluate interventions to treat depression in people with tuberculosis (TB).

Types of participants

People with depression and TB.

- **Diagnostic criteria (TB)**. We will include adults aged 18 years and over, living with all forms of TB. For the purposes of this review, we will define a diagnosis of TB as any person who presents signs or symptoms suggestive of TB, or has a confirmed laboratory or clinical diagnosis of TB. We will include people with latent, drug-susceptible, or drug-resistant TB, from all countries, and from all clinical settings, such as community-based care, primary care, secondary care, and TB programmes.
- **Diagnostic criteria (depression).** We will include participants with a diagnosis of depression co-occurring with tuberculosis. The categories of depression diagnosis included in this review will be a mild, moderate, or severe depressive disorder, either as a single or recurrent episode. Depression should be diagnosed using the criteria from the World Health Organization International Classification of Diseases (ICD) for mental and behavioural disorders (e.g. ICD-10: F32, F33, F34.1 (WHO 2004)), the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM; Revisions DSM-IIIR, DSM-IV, DSM-5 (APA 2013)), a combination, or measures based on these.

Types of interventions

Psychological or pharmacological interventions for clinical depression in people with TB

- **Psychological interventions** refer to any type of group or individual therapy used to treat depression. We will consider psychological therapies if they involve direct person-professional interaction, face-to-face interaction, interventions in which face-to-face therapy was augmented by telephone or internet-based support, or interventions delivered entirely online (e.g. through web pages or e-mail), or through mobile applications (i.e. applications (apps)), via computer or mobile device. Examples of eligible psychological interventions are: behaviour therapy (e.g. behaviour modification), cognitive behavioural therapy (including third wave cognitive behavioural therapies, such as behavioural activation), psychodynamic therapies (e.g. group therapy, interpersonal therapy, or psychoanalytic therapy), and other types of psychological therapy (e.g. family therapy). All interventions must have a psychological component – talking, listening, support, advice – and be delivered by somebody with recognised training in, and supervision of, therapies, and must be directed at helping people develop their social problem-solving skills.
- **Pharmacological interventions** refer to the use of any type of antidepressant (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and other antidepressant medications) commonly used to treat depression.
- **Psychological and pharmacological interventions** (e.g. combined treatment).

Comparator intervention

For pharmacological interventions with or without psychological interventions, comparator interventions will include placebo, no intervention, or routine or usual care. For psychological interventions, comparators will include no intervention, or routine or usual care.

Types of outcome measures

Primary outcomes

1. **Treatment effectiveness**: defined as improvement in or recovery from depression, when compared to a pre-intervention baseline assessment, or as defined in the study, measured at study end. We will define this as changes in depression scores (i.e. continuous outcomes), measured using the Patient Health Questionnaire, Hamilton Depression Rating Scale, the Montgomery Åsberg Depression Rating Scale, the Beck Depression Inventory, the Hospital Anxiety and Depression Scale, the General Health Questionnaire, Generalised Anxiety Disorder test, the Hamilton Anxiety Scale, the Beck Anxiety Inventory, the Hospital Anxiety and Depression Scale, or any other scale validated for the measurement of depression, provided that measures are taken with the same scale at baseline and end of treatment.
2. **Adverse events (for all forms of TB)**:
   a. Self-reported adverse events: defined as any adverse effects expressed by the participant, related to interventions for treating depression, TB, or both.
   b. Diagnosed adverse events: defined as adverse events diagnosed using blood tests, audiometry, vision tests, or electrocardiogram (ECG). Examples of these are toxicities, audiological complaints, hearing loss, and QT prolongation.

Secondary outcomes

1. **Effect on TB**: defined as changes in TB-related outcomes (i.e. dichotomous outcomes (WHO 2020)):
   a. Cure: a person who initially had a positive diagnosis of TB, and has a negative sputum smear test in the last month of treatment, or at least on one previous occasion.
   b. TB treatment failure: a person with a positive sputum test after five months or more of treatment.
   c. Treatment completed: a person who completed the anti-TB pharmacological treatment, without evidence of failure, with no record of negative sputum or culture test at the end of treatment, due to either unavailability of the test or results.
   d. Loss to follow-up: a person with a confirmed diagnosis of TB who did not start treatment, or whose treatment was interrupted for at least two consecutive months.
   e. Relapse: a person who has been previously treated for TB, has been declared cured or completed treatment, and is now diagnosed with a recurrent episode of TB (either by re-infection or by true relapse).
   f. Mortality: death by any cause during the intervention or the anti-TB treatment.
2. **Changes in health-related quality of life**: outcomes measured using composite scales, such as the Short Form Health Survey (36- or 12-item version), Quality of Life Scale, or any other

scale validated for the measurement of health-related quality of life, provided that measures are taken with the same scale at baseline and end of treatment. We will consider this a continuous outcome.

Search methods for identification of studies

Electronic searches

An information specialist with the Cochrane Common Mental Disorders (CCMD) Group will search the following bibliographic databases, using relevant subject headings, keywords, and search syntax appropriate to each resource.

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR; all available years)
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue)
- MEDLINE Ovid (1946 onwards; Appendix 1)
- Embase Ovid (1974 onwards)
- PsycINFO Ovid (all years)
- Web of Science Social Science Citation Index (SSCI; all years)
- Scopus (all years)

We will not apply any restriction on date, language, or publication status to the searches.

We will search ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; all years) to identify ongoing or unpublished trials.

Searching other resources

Grey literature

We will search the following sources of grey literature (primarily for dissertations and theses).

- Open Grey (www.opengrey.eu/)
- ProQuest Dissertations & Theses Global (www.proquest.com/products-services/pqdtglobal.html)
- DART-Europe E-theses Portal (www.dart-europe.eu/)
- EThOS – the British Libraries e-theses online service (ethos.bl.uk/)
- Networked Digital Library of Theses and Dissertations (NDLTD; search.ndltd.org)
- Open Access Theses and Dissertations (oatd.org)

Correspondence

We will contact experts from the field of tuberculosis and mental health research to identify relevant studies. We will also contact relevant organisations, including the WHO, Centers for Disease Control and Prevention, Tuberculosis Trials Consortium, International Union Against Tuberculosis and Lung Disease (IUATLD), and the Stop TB Partnership, to identify unpublished or ongoing trials.

Reference lists

We will check the reference lists of all relevant study reports and reviews retrieved by the searches. We will also conduct a forward citation search on the Web of Science and Google Scholar, to identify additional research.

Data collection and analysis

Selection of studies

Two review authors (RNR, GZ) will independently screen titles and abstracts during the first screening stage, and the selected full texts during the second screening stage. For studies excluded during the full-text screening stage, they will record a reason for exclusion. We will resolve any discrepancies through recourse to a third review author (NS). If there is insufficient information to make a decision, we will add the article to those 'awaiting assessment', and contact study authors for clarification. We will present a PRISMA flowchart of study selection at the end of the review (Liberati 2009).

Data extraction and management

For studies that fulfil inclusion criteria, two review authors (RNR, OT) will independently extract key study, participant, and intervention characteristics, and outcomes using a standard pre-piloted data extraction form. Any disagreements will be resolved by discussion or, if required, by a third author (AJ). Data extracted will be the following:

- General information: authors of study or report, year of publication, citation
- Study design: year of study, study duration, recruiting and sampling procedures, trial design, sequence generation, unit of analysis, funding sources and author affiliations
- Participants information: population description, sample size, TB diagnosis information, depression diagnosis information, other comorbidities, age, gender, country, socioeconomic status (if available)
- Intervention: description of intervention, frequency, length and dose of intervention, length of follow-up, mode of delivery of intervention, description of co-intervention (if applicable):
  * For pharmacological interventions: class of drug used, dose, frequency, duration
  * For psychological interventions: description of the intervention, provider or mode of delivery of the intervention, theoretical approach or content of the intervention (or both), intensity (length, frequency, and duration of sessions
- Comparison interventions: description of comparator or control groups, data on routine or usual care, and no intervention comparators
- Outcomes (Higgins 2019b):
  * In RCTs:
    - ☐ For dichotomous (binary) data (e.g. mortality), for each intervention group, we will extract the number of events and participants randomised to that group. If these numbers are not available, we will extract the reported effect estimate (odds ratio (OR) or risk ratio) with its uncertainty measure (95% confidence interval (CI), standard error, or exact P value).
    - ☐ For numerical or continuous outcomes (e.g. depression scores), we will extract the mean value, standard deviation, and number of participants in each group. If these numbers are not available, we will extract the reported effect estimate (difference in means) with its uncertainty measure (95% CI). If a study reports the same outcome using different depression scores (e.g.

improvement in Patient Health Questionnaire and Beck Depression Inventory), we will extract both.

* In cluster-RCTs:
  - ☐ For studies that take into account the cluster design in their analyses (e.g. multi-level analysis), we will extract the effect estimate (e.g. OR for dichotomous data) and its confidence interval.
  - ☐ For studies that do not report our outcomes of interest, analysed taking into account the cluster design, we will extract the outcome data for the total number of participants (e.g. the number or proportion of participants with events, or means and standard deviations for continuous data), the average (mean) size of each cluster, and if available, an estimate of the intracluster (or intraclass) correlation coefficient (ICC).
* In cross-over trials:
  - ☐ For studies using a cross-over design, we will only use data from the first active treatment phase to minimize risk of carry-over effects.

- Adverse events: if reported, we will extract these verbatim from the study report
- Study or author's conclusions

We will pool data from multiple reports of the same study during the data extraction phase; we will identify these studies through trial registration numbers, and specific details of the intervention, such as type of intervention, country, setting, date, and duration. We will keep a log of missing or unreported data. and include this information in the 'Characteristics of included studies' table. If data are reported with insufficient detail, or in a format that is unusable, we will contact the study authors for further information.

Management of time points

We plan to summarise and categorise post-treatment outcomes, and outcomes at each reported follow-up point as follows: at the end of treatment (zero to four weeks after treatment), short-term (up to three months post-treatment), medium-term (six months post-treatment), and long-term (longer than 12 months post-treatment).

Assessment of risk of bias in included studies

Two review authors (RNR, AJ) will independently assess the risk of bias of each included study. We will resolve disagreements by consensus, or by consultation with a third review author (KS).

We will assess risk of bias using version 2 of the Cochrane tool for assessment of risk of bias (RoB 2 (Higgins 2019c)). We will assess the following domains for risk of bias:

- Randomisation process (i.e. whether the allocation sequence was random, adequately concealed, or if there are baseline differences between intervention groups that would suggest a problem with the randomisation process);
- Blinding (i.e. whether participants were aware of their assigned intervention during the trial, or whether carers and people delivering the interventions were aware of participants' assigned intervention during the trial);
- Effect of assignment to intervention (i.e. deviations from the intended intervention arose because of the experimental context, as these do not reflect usual practice, and if so, whether they were unbalanced between groups and likely to have affected the outcome);
- Missing outcome data (i.e. whether data for this outcome were available for all, or nearly all, participants randomised);
- Outcome measurement (i.e. the method of measuring the outcome was inappropriate);
- Other potential sources of bias (i.e. whether the study is apparently free of other problems that could lead to a high risk of bias, such as baseline imbalances, evidence of carry-over in cross-over trials, comparability of groups in cluster trials).

We will judge risk of bias criteria as low risk, high risk, or unclear risk, and evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019c). We will present a risk of bias graph and a risk of bias summary figure. We will assess the impact of individual bias domains on study results at the end point and study levels.

Measures of treatment effect

We will express dichotomous data as odds ratios (OR) or risk ratios (RR), with 95% confidence intervals (CI). We will express continuous data as mean differences (MD) with 95% CIs (Higgins 2019b). If the same outcome of interest is measured using different instruments (i.e. depression scales) across studies, we will address this by using the standardised mean difference (SMD), as long as the difference lies in the instrument used to measure the outcome, and not in the population (Higgins 2019b). If data allow, we will separate severe depression data from mild and moderate depression data.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome (Deeks 2019).

For studies with more than two interventions (multiple-arm studies), consisting either different types of interventions or different doses of medication, we will avoid any possible bias caused by multiple comparisons with one control group by combining the groups to create a single pair-wise comparison.

Dealing with missing data

We will deal with missing data in line with the *Cochrane Handbook for Systematic Review of Interventions* (Deeks 2019), which outlines the following:

- We will collect and document information on missing data. Whenever possible, we will contact the original study authors to obtain relevant missing data. We will document all correspondence with authors, and report which authors responded, and what methods they (might) have used for imputing data (such as multiple imputations).
- When we can assume that data are 'missing at random' (due to available information), we will only analyse the available data. Otherwise, we will assume that data are 'not missing at random'. This might be due to the study design itself, when participants drop out as a response to the intervention. In this case, we will assume that participants who drop out after randomisation have a negative outcome; we will conduct our analyses according to the principle of intention-to-treat (ITT).

- We will conduct sensitivity analyses to assess the impact caused by missing data.
- We will thoroughly discuss the potential impact of missing data on the findings in the full review.

Assessment of heterogeneity

We will interpret assessment of heterogeneity, using the I^2 statistic, as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). In the event of substantial clinical, methodological, or statistical heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis. We will identify heterogeneity by using a standard Chi^2 test or I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis.

When we find heterogeneity, we will attempt to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will use funnel plots to assess bias in reporting of effects when 10 or more studies report on the same outcome of interest, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2019).

Data synthesis

We will combine data in a meta-analysis if the study designs, interventions, and participant characteristics are sufficiently similar. To aid this assessment, we will consider statistical heterogeneity – which is a consequence of clinical or methodological diversity, or both – of 75% or higher, as quantified by the I^2 statistic, as substantial.

We will use a random-effects model for the meta-analyses, using the generic inverse-variance method (DerSimonian 1986). For cluster-RCTs that reported outcomes without considering the cluster design, we will approximate such an analysis by inflating their standard error before pooling the results with the remaining studies (Higgins 2019a).

When studies report the same primary outcome using different measurement scales, we will choose the one that is most prevalent in the pool of studies.

Subgroup analysis and investigation of heterogeneity

We will carry out the following subgroup analyses, based on the characteristics of the population or intervention that might influence the primary outcomes:

- type of TB (i.e. drug-susceptible, drug-resistant, or extensively drug-resistant);
- age and gender;
- intervention duration (less than three months versus three months or more);
- length of follow-up (less than three months versus three months or more; this is likely to influence the detection of outcomes);
- risk of bias (low risk of bias versus uncertain or high risk of bias);
- presence of other comorbidities (if applicable, specify which).

We agree that the effectiveness of an intervention can vary depending on the severity of depression. If data allow, we will separate severe depression data from mild and moderate depression data.

Sensitivity analysis

If we include two or more studies in a meta-analysis, we will conduct a sensitivity analysis to explore the influence on effect sizes of the following:

- Effect of trial size. We will exclude trials with a sample size smaller than 50.
- Effect of choosing the most prevalent measurement scale outcome when studies report the same outcome using different scales. When multiple instruments are used in the same study to report the same primary outcome, we will re-do the meta-analysis using the measurement of the less prevalent one in the pool of studies (as we choose the one that is most prevalent in the pool of studies for the main analyses).

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table in line with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019). We will create it using the GradePRO GDT software (GRADEpro GDT 2015). We will present data on absolute and relative effects with 95% CI, risk for treatment and for usual care, the number of participants and studies for each outcome, and the quality assessment of the evidence, using the GRADE approach for each outcome. For each outcome, we will analyse the factors that can limit the quality of evidence according to the GRADE handbook: limitation in study design or execution, inconsistency of results, indirectness of evidence, imprecision, and publication bias (GRADE Handbook). We will explain the reasons for downgrading the certainty of the evidence in the footnotes.

We will show the results for outcomes of the following comparisons:

- Psychological intervention versus no intervention or usual care
- Pharmacological intervention versus placebo, no intervention or usual care
- Psychological and pharmacological intervention versus placebo, no intervention or usual care

We will report on these outcomes in the summary of findings table, reporting on depression and TB outcomes as appropriate:

- treatment effectiveness for depression,
- adverse events for all forms of TB, self-reported and diagnosed,
- TB treatment success (cured),
- TB treatment failure,
- TB treatment completion,
- loss to follow-up, and
- changes in health-related quality of life.

We will fully describe these in the table, including information on thresholds and values for outcomes that are assessed using scales, such as depression scores.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table in line with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019). We will create it using the GradePRO GDT software (GRADEpro GDT 2015). We will present data on absolute and relative effects with 95% CI, risk for treatment and for usual care, the number of participants and studies for each outcome, and the quality assessment of the evidence, using the GRADE approach for each outcome. For each outcome, we will analyse the factors that can limit the quality of evidence according to the GRADE handbook: limitation in study design or execution, inconsistency of results, indirectness of evidence, imprecision, and publication bias (GRADE Handbook). We will explain the reasons for downgrading the certainty of the evidence in the footnotes.

We will show the results for outcomes of the following comparisons:

- Psychological intervention versus no intervention or usual care
- Pharmacological intervention versus placebo, no intervention or usual care
- Psychological and pharmacological intervention versus placebo, no intervention or usual care

We will report on these outcomes in the summary of findings table, reporting on depression and TB outcomes as appropriate:

- treatment effectiveness for depression,
- adverse events for all forms of TB, self-reported and diagnosed,
- TB treatment success (cured),
- TB treatment failure,
- TB treatment completion,
- loss to follow-up, and
- changes in health-related quality of life.

We will fully describe these in the table, including information on thresholds and values for outcomes that are assessed using scales, such as depression scores.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table in line with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019). We will create it using the GradePRO GDT software (GRADEpro GDT 2015). We will present data on absolute and relative effects with 95% CI, risk for treatment and for usual care, the number of participants and studies for each outcome, and the quality assessment of the evidence, using the GRADE approach for each outcome. For each outcome, we will analyse the factors that can limit the quality of evidence according to the GRADE handbook: limitation in study design or execution, inconsistency of results, indirectness of evidence, imprecision, and publication bias (GRADE Handbook). We will explain the reasons for downgrading the certainty of the evidence in the footnotes.

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We will fully describe these in the table, including information on thresholds and values for outcomes that are assessed using scales, such as depression scores.

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APPENDICES

Appendix 1. MEDLINE search

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 onwards>
Search Strategy:
---
1 Mycobacterium tuberculosis/
2 exp Tuberculosis/
3 Tuberculosis, Multidrug-Resistant/
4 Tuberculin Test/
5 (tubercul* or TB or MTB or Koch* disease).ti,ab,kf.
6 or/1-5
7 Depression/
8 exp Depressive Disorder/
9 Mood Disorders/
10 (depression? or depressive? or dysthymi* or MDD or mood? or affective disorder? or affective symptom?).ti,ab,kf.
11 depressed.ti,ab,kf.
12 (mental* or psych*).ti,kf.
13 ((mental* or psychological*) adj (distress* or trauma*)).ab.
14 or/7-13
15 (6 and 14)
16 controlled clinical trial.pt.
17 randomized controlled trial.pt.
18 clinical trials as topic/
19 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.
20 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf.
21 placebo.ab,ti,kf.
22 trial.ti.
23 (control* adj3 group*).ab.
24 (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw.
25 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf.
26 double-blind method/ or random allocation/ or single-blind method/
27 or/16-26
28 exp animals/ not humans.sh.
29 27 not 28
30 (15 and 29) (126 hits retrieved as of 25-Sept-2020)
****

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

Drafting of protocol: RNR, AJ, OT, GZ, HE, KS, NS
Search strategy: RNR

DECLARATIONS OF INTEREST

RNR: none known
AJ: none known
HE: none known
KS: none known
OT: none known
GZ: none known
NS: none known

SOURCES OF SUPPORT

Internal sources

- University of York, UK

  RNR is completing her doctoral studies at the University of York

External sources

- Consejo Nacional de Ciencia y Tecnología (CONACyT), Mexico

  RNR holds a CONACyT studentship that supports her doctoral studies at the University of York