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Which psychotherapy is effective in panic disorder? And which delivery formats are supported by the evidence? Study protocol for two systematic reviews and network meta-analyses

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ABSTRACT

Introduction Panic disorder is among the most prevalent anxiety diseases. Although psychotherapy is recommended as first-line treatment for panic disorder, little is known about the relative efficacy of different types of psychotherapies. Moreover, there is little evidence concerning the effectiveness of different formats of major psychotherapeutic types, such as cognitive–behavioural therapy (CBT). In this protocol, we present an overarching project consisting of two systematic reviews and network meta-analyses (NMA) to shed light on which psychotherapy (NMA-1), and specifically, which CBT delivery format (NMA-2) should be considered most effective for adults suffering from panic disorder with or without agoraphobia.

Methods and analyses Starting from a common pool of data, we will conduct two systematic reviews and NMA of randomised controlled trials examining panic disorder. A comprehensive search will be performed in electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Register of Controlled Trials—CENTRAL from database inception to 1 January 2021 to identify relevant studies. A systematic approach to searching, screening, reviewing and data extraction will be applied. Titles, abstract and—whenever necessary—full texts will be examined independently by at least two reviewers. The quality of the included studies will be assessed using the revised Cochrane risk of bias tool V.2. The primary efficacy outcome will be anxiety symptoms at study endpoint. The primary acceptability outcome will be all-cause discontinuation, as measured by the proportion of patients who had discontinued treatment for any reason at endpoint. Data will be pooled using a random-effects model. Pairwise and NMA will be conducted.

Ethics and dissemination No ethical approval is necessary for these two studies, as there will be no collection of primary data. The results will be disseminated through peer-reviewed publications and presentations at national and international conferences and meetings.

Strengths and limitations of this study

- ► Network meta-analyses compare, in the context of a systematic review, multiple treatments using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator.
- ► We will comprehensively assess the efficacy and acceptability of all available psychotherapies for panic disorder with or without agoraphobia in adults at the end of the acute treatment, and subsequently, the comparative efficacy and acceptability of different types of cognitive–behavioural therapy delivery formats, for the same population.
- ► These studies will inform policy and clinical decision making. Such information can be particularly relevant in resource-limited settings, carrying practice-changing potential.
- ► Dissertations and trials on maintenance and relapse prevention will not be considered.

INTRODUCTION

Background and rationale

A panic attack is a spontaneous and unexpected abrupt surge of intense fear or discomfort with a rapid onset and that reaches a peak within 10 min. The main characteristic of panic disorder is the recurrence of panic attacks. In order to be diagnosed with panic disorder, according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V),[1] at least one episode must be followed by 1 month (or more) of persistent concern about having additional attacks, worry about the implications of the attack (or its consequences), or a significant change in behaviour related to the attacks. Panic disorder is a common disorder that presents across the spectrum of severity, with

very large numbers of people suffering from considerable functional impairment and decrease in quality of life as a result. Indeed, the life-time prevalence of panic disorder ranges between 1.1% and 3.7%.[2] In primary care settings, panic symptoms have been reported to have a prevalence of around 10%.[3]

In around a quarter of patients, panic disorder is accompanied by agoraphobia (avoidance of situations where escape would be difficult when panic attacks occur).[2] Agoraphobia is anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help may not be available in the event of having a panic attack. The prognosis of panic disorder in worsened by the coexistence of agoraphobia.[2] There are several risk factors that predict the development of agoraphobia in people suffering from panic disorder, among them female gender, more severe dizziness during panic attacks, dependent personality traits and social anxiety disorder.[4]

In recent decades, a large number of trials have been conducted and the effects of psychological treatments on panic examined. These studies have clearly shown that psychological treatments have beneficial effects, in terms of symptom reductions and increased well-being.[5] In particular, there is abundance of evidence on the effectiveness of cognitive–behavioural therapy (CBT) to treat panic disorder.[6–8] Dozens of randomised controlled trials (RCTs) have examined different CBT treatment formats in the last decades. As an alternative to the classical individual face-to-face format, CBT for panic disorder can be administered by telephone, in a digital-assisted modality, to groups of people or as self-help therapy in which patients work through a standardised protocol independently. The protocol can be in book format or available on the internet. Self-help therapy can either be guided (ie, involving a professional therapist) or unguided (ie, providing no professional guidance to the patient using the materials).[9]

Because of this huge body of knowledge, it is important that the results of these studies are summarised and integrated in meta-analytical studies. This has been done during the previous 20 years, as the evidence base grew over time.[6 10–12] Although meta-analyses are seen as representing the pinnacle of a hierarchy of evidence used to inform clinical practice, the trustworthiness of their output is not to be taken for granted, and specific methodological tools exist to challenge their results.[13] As for many other research areas, some doubts on the reporting quality of meta-analyses on anxiety treatment have been put forward as well.[14]

Thanks to the advent of network meta-analyses (NMA), it is now possible to compare, in the context of a systematic review, multiple treatments (ie, three or more) using both direct comparisons of interventions within RCTs and indirect comparisons across trials.[15] A systematic review and NMA on the psychological treatment of panic disorder[7] was published in the Cochrane Library; although exhaustive and methodologically sound, this NMA did not take into account all available psychotherapies, did not consider delivery methods other than face-to-face sessions and did not consider drug therapy with antidepressants and/or benzodiazepines as comparators. Furthermore, its search was last updated at the beginning of 2015. As the matter of psychotherapy for mental health problems is dynamic and controversial[16 17] and the number of trials is constantly increasing, it is important to keep a good, up-to-date overview of the field. Furthermore, there is evidence warning about the relatively short time on which a systematic reviews directly relevant to clinical practice can be considered outdated.[18]

Against this background, we will conduct two fully updated and state-of-the-art systematic reviews and NMA addressing both efficacy and acceptability of psychotherapies delivered in any treatment format for adults suffering from panic disorder with or without agoraphobia, and the efficacy and acceptability of different types of CBT delivery formats for adults suffering from the aforementioned condition.

Aim and objectives

The overall aims of these systematic reviews and NMA are:

1. To evaluate the effectiveness and acceptability of different types of psychotherapies for adults suffering from panic disorder with or without agoraphobia (NMA-1).
2. To evaluate the efficacy and acceptability of different types of CBT delivery formats for adults suffering from panic disorder with or without agoraphobia (NMA-2).

The PICO format for the two research questions is displayed in table 1.

Table 1 PICO format for the two research questions

NMA-1: psychotherapies for panic disorder	NMA-2: CBT delivery formats for panic disorder
P=adults suffering from panic disorder with or without agoraphobia	P=adults suffering from panic disorder with or without agoraphobia
I-C=any psychotherapy; inactive/active comparators	I-C=CBT delivered in any format; inactive comparators
O=1) anxiety symptoms reduction (efficacy); 2) all-cause treatment discontinuation (effectiveness)	O=(1) anxiety symptoms reduction (efficacy); (2) all-cause treatment discontinuation (effectiveness)

CBT, cognitive–behavioural therapy; NMA, network meta-analyses.

METHODS

The project started on 1 March 2020 and it is expected to be completed by 31 August 2021. The protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols checklist[19 20] (online supplemental file online).

Types of studies

We will include RCTs on psychotherapies for panic disorder with or without agoraphobia. We will include RCTs that tested combination therapies of psychotherapy and drug, as long these combinations were balanced within the same trial (eg, arm A: alprazolam +CBT; arm B: alprazolam +waiting list). We will include RCTs comparing psychotherapy against drug treatment (irrespective of drug class and dosage) or psychotherapy against drug treatment and/or placebo pill or a type of psychotherapy against another type of psychotherapy. Trials designed as maintenance treatment or relapse prevention will be excluded. We will set no limits in term of duration of treatment, number of sessions and minimal number of participants.

Types of participants

We will include RCTs in which participants are aged 18 or older, of both sexes, with a primary diagnosis of panic disorder with or without agoraphobia according to any standardised diagnostic criteria, such as the DSM or International Classification of Diseases . Patients must be in the acute phase of their disorder at the time of enrolment in the RCT. We will include RCT that enrolled exclusively participants diagnosed with panic disorder with or without agoraphobia. Where trials include participants suffering from an array of anxiety disorders, the data will be included if data on participants with a diagnosis of panic disorder with or without agoraphobia can be extracted separately. We will also consider including trials in which participants have a secondary diagnosis of comorbid general psychiatric (eg, major depression) or organic disorder. All research settings, such as outpatient clinics, inpatient services, community clinics, will be included.

Types of interventions

In NMA-1, we will consider any kind of psychotherapy. We define psychotherapy as the informed and intentional application of clinical methods derived from established psychological principles to assist participants with their behaviours, cognitions and emotions in directions that the participants deem desirable (modified from Campbell *et al*[21]). Therapies can be delivered by any therapist (psychologist, psychiatrist, nurse, social worker, etc, but also lay health counsellors and paraprofessionals) as long as they were trained to deliver the therapy, or as self-help. As for standard CBT protocols, we expect most of the interventions to last from 4[22] to 12 sessions,[23] delivered on a weekly basis, although we will consider psychotherapy interventions of any length. In line with the meta-analysis from Pompoli *et al*,[7] we will consider the nodes for the psychotherapies displayed in table 2, leaving open the possibility to add further intervention nodes if other types of psychotherapy will be detected during the screening phase.

Different treatment formats will be allowed, including individual or group face to face, telephone, guided self-help (through the internet or not) and couple therapy. We will also include self-guided interventions without any professional support (remote/unguided self-help) or digital-assisted therapies (table 3).

Starting from the same pool of data considered for NMA-1, in the second project (NMA-2) we will specifically focus only on those trials that evaluated CBT, comparing the efficacy and effectiveness of the different treatment delivery formats. We defined CBT as a therapy in which cognitive restructuring was one of the core components.[24–26] Cognitive restructuring is aimed at evaluating, challenging and modifying a patient's dysfunctional beliefs. In NMA-2, we will focus on CBT only (not considering all of the other types of psychotherapy) because the homogeneity of the intervention is essential to inform on the efficacy of the different treatment modalities. Furthermore, being CBT the most recommended and studied form of psychotherapy for panic disorder,[27] information regarding its efficacy when administered in different treatment modalities will probably have the best impact on policy and clinical decision making.

In NMA-2, the intervention nodes will be those displayed in table 3.

Types of controls

In the first NMA (NMA-1), we will consider the nodes for the control groups as for Pompoli *et al*,[7] plus a node for antidepressant medications, a node for benzodiazepine medications and a node for placebo pill. For the second NMA (NMA-2), we will not consider antidepressants and benzodiazepine. Control groups and their definitions are displayed in table 4.

Types of outcome measures

The primary efficacy outcome will be anxiety symptoms at study endpoint.

The standardised mean difference (SMD) will be used as a measure of effect size in efficacy outcome. We will consider scale endpoint data as first choice, since we expect no baseline imbalances resulting from the trials randomisation process. As an alternative, we will consider mean change scores in anxiety symptoms from baseline to post-treatment. It has been shown that combining endpoint and change data in meta-analysis is generally valid.[28] We will select one outcome measure for each study using the following algorithm[7]: scales specific for panic disorder (Panic Disorder Severity Scale >Panic and Agoraphobia Scale > Anxiety Sensitivity Index-Revised >Anxiety Sensitivity Index > Agoraphobic Cognitions Questionnaire>Body Sensations Questionnaire > other); global symptoms scales (Clinical Global

Table 2 Experimental interventions and their definitions

Experimental interventions	Definition
Psychoeducation (PE)	An intervention in which patients are only provided information about their disease.
Supportive psychotherapy (SP)	An intervention with or without a psychoeducational component, intended as sessions in which patients were administered an active, although non-specific, psychological treatment.
Physiological therapies (PT)	An intervention that uses some kind of physical training (eg, breathing retraining, progressive muscle relaxation, applied relaxation) in order to reduce the physiological manifestations of anxiety.
Behaviour therapy (BT)	An intervention with or without physiological components, aiming at patients' habituation or extinction to anxiety provoking situations and sensations through some kind of exposure (eg, interoceptive, in vivo).
Cognitive therapy (CT)	An intervention with or without physiological components and behavioural experiments, aiming at the modification of maladaptive thoughts through some kind of cognitive restructuring.
Cognitive–behavioural therapy (CBT)	An intervention, with or without physiological components, containing both cognitive and behavioural therapy elements.
Third-wave CBT (3W)	An intervention including acceptance and commitment therapy, mindfulness-based therapy, and other so-called 'third-wave' therapies administered with or without other CBT components (eg, exposure, cognitive restructuring, breathing retraining, muscle relaxation).
Psychodynamic therapies (PD)	Focused on revealing and resolving intrapsychic or unconscious conflicts.

Impression Severity Scale >Clinical Global Impression-Improvement Scale>10Global Assessment Scale> Global Assessment of Functioning>other); scales specific for agoraphobia only (Fear Questionnaire-Agoraphobia Subscale >Fear Questionnaire- Global>Mobile Inventory for Agoraphobia-Avoidance-Alone>Mobility Inventory -Avoidance-Accompanied > other); scales specific for panic attacks (panic frequency >panic severity >other) (table 5).

Global Assessment Scale Clinical Global Impression-Improvement scale>GAS > GAF>other); scales specific for agoraphobia only (FQ-ag >FQ-global>MI AAL>MIAAC>other); scales specific for panic attacks (panic frequency>panic severity>other) (table 5).

The primary acceptability outcome will be all-cause discontinuation, as measured by the proportion of patients who had discontinued treatment for any reason at endpoint.

All outcomes will refer to acute phase treatment (study endpoint), which normally last 2–6 months.

Where different symptom severity rating scales were used for the purpose of pooling results, we will choose the single best available outcome measure according to a hierarchy based on psychometric properties and frequency of use.

Search strategy

Four bibliographical databases will be searched (MEDLINE, Embase, PsycINFO and the Cochrane Register of Controlled Trials-CENTRAL) from database inception to 1 January 2021, to identify RCTs examining the effects of psychotherapy for panic disorder with or without agoraphobia, compared with any other intervention or control condition. No language or geographical restrictions will be applied. In the search strings, we will combine index terms and text words indicative of panic disorder with or without agoraphobia and psychotherapies, with filters for RCTs. We will also add the references of trials through other sources, such as other meta-analyses, and contact with other researchers. The full search strategy is provided in online supplementary file. A PRISMA flow chart[29] will be used to present the search strategy used in these NMA.

Study selection and data extraction

Selection of trials

All records from all sources will be entered into Endnote, and duplicates will be removed. All resulting records will be checked by two independent researchers (DP and EK). If one of the researchers will indicate that a record possibly contained a study meeting the inclusion criteria, the full text of that paper will be retrieved. The full texts of the papers will be read by the same researchers for final inclusion. Any disagreements will be resolved by a third review author (CB or PC).

When multiple publications come from the same data set, we will use all relevant data.

Table 3 Treatment delivery formats and their definitions

Treatment delivery formats	Definition
Individual format	The psychotherapy is delivered by the therapist in a face-to-face individual setting.
Group format	The psychotherapy is delivered by the therapist in a face-to-face group setting.
Guided self-help	A psychotherapy in which a professional therapist is involved in the treatment process, offering guidance to the patient using the self-help materials (administered through the internet or other media, such as a book).
Unguided self-help	A psychotherapy in which no professional guidance is provided to the patient using the self-help materials (internet based or not).
Digital assisted	A psychotherapy format that uses technology to deliver some aspects of psychotherapy or behavioural treatment directly to patients via interaction with smartphone applications, computer programmes, or delivered via the Internet.
Telephone	A psychotherapy format that uses the telephone to deliver psychotherapy or behavioural treatment directly to patients.

Data extraction

Four independent reviewers (DP, PC, EK and MS) will extract the data from the original reports using standardised data extraction forms, characteristics of the participants (recruitment methods, type of diagnosis, target group), of the therapies (format and number of sessions of the therapies, for type of therapy), for studies including pharmacotherapy we will rate the type and for studies including a control group we will rate the type of control group. We will also report where the study was conducted and in which year it was published. We will also rate other characteristics of the included studies: source of patient recruitment, diagnosis (panic disorder without agoraphobia only, panic disorder with or without agoraphobia, agoraphobic patients only), age group, mean age, the percentage of women participating, percentage of agoraphobic participants in the trial, comorbidity (mental or general disorders), intervention format, number of sessions of the intervention, presence/absence of pharmacotherapy coadministration, type of control condition, country where the RCT was carried out, year of publication, baseline scores on anxiety rating scales.

Any disagreements will be resolved by consulting a fifth review author (CB).

Table 4 Control conditions and their definitions

Control group	Definition
No treatment/-reatment as usual (NT/TAU)* †	Participants receive assessment only with or without simple provision of informational material or minimal therapist contact or both, and they know that they will not receive the active treatment in question after the trial. The participants in this condition are usually allowed to seek treatment as available in the community; when such additive treatments are substantive, we will include such trials only if it is balanced between the two arms to be compared.
Waiting list (WL)* †	Participants receive assessment, with or without simple provision of informational material or minimal therapist contact or both and they know that they will receive the active treatment in question after the waiting phase.
Attention or psychological placebo (APP)* †	Participants receive a face-to-face inactive intervention that can be perceived both as ineffective or effective.
Placebo (PL)*†	Placebo pill.
Antidepressant (AD)*	Antidepressant medications.
Benzodiazepine (BZP)*	Benzodiazepine medications.

*Control conditions for the NMA-1.
†Control conditions for the NMA-2.
NMA, network meta-analyses.

Risk of bias assessment

We will assess the risk of bias (RoB) in included studies using the Cochrane's second version of 'RoB' tool for randomised trials (RoB V.2).[30] We will assess RoB for each study that contributes to the primary outcomes at post intervention. Two review authors (DP and EK) will independently use the RoB V.2 signalling questions to form judgments of material RoB for the following five domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of outcome and (5) bias in selection of the reported outcome.

We will not consider the following items in the domain number 2 ('bias due to deviations from intended interventions'): 2.1–2.2 in the subsection named 'effect of assignments to intervention' and 2.1–2.2 in the subsection

Table 5 Hierarchy of symptom severity measurement scales

Hierarchy	Symptom severity rating scales	Abbreviation
1	Panic Disorder Severity Scale	PDSS
2	Panic and Agoraphobia Scale	PAS
3	Anxiety Sensitivity Index-Revised	ASI-R
4	Anxiety Sensitivity Index	ASI
5	Agoraphobic Cognitions Questionnaire	ACQ
6	Body Sensations Questionnaire	BSQ
7	Other scales specifically focused on panic disorder	
8	Clinical Global Impression Severity Scale	CGI-S
9	Clinical Global Impression-Improvement Scale	CGI-I
10	Global Assessment Scale	GAS
11	Global Assessment of Functioning	GAF
12	Other global symptoms scales	
13	Fear Questionnaire-Agoraphobia Subscale	FQ-agoraphobia
14	Fear Questionnaire-Global	FQ global
15	Mobile Inventory for Agoraphobia-Avoidance-Alone	MI-AAL
16	Mobility Inventory-Avoidance-Accompanied	MIAAC
17	Other scales specifically focused on agoraphobia	
18	Panic frequency	
19	Panic severity	
20	Other scales specific for panic attacks only	

named 'effect of adhering to intervention'. These particular biases were referred to as 'performance biases' in the original Cochrane tool for assessing RoB in RCTs.[31] Since 'blinding of participants and personnel to treatment allocation' is not possible in psychotherapy trials, we will not assess the aforementioned items to avoid all the trials resulting to be at 'high RoB' by default. Thus, domain 2 will be limited to the evaluation of the type of statistical analysis that was carried out ('intention-to-treat (ITT)', 'modified ITT', 'per protocol', 'as treated'). On the other hand, to better understand the methodological validity of the included RCTs and to enable an examination of research gaps, we will consider in the 'RoB' assessment three additional items, consistently with two recent Cochrane Reviews on psychotherapy[32 33]: (1) Evaluating therapist qualifications: to check whether the professionals involved in the study were adequately trained and supervised to deliver the interventions; (2) Intervention implementation fidelity: adherence to intervention's manual, which should lead to greater consistency among therapists and clearer distinction from control conditions and (3) Therapist allegiance: to state whether the professionals that delivered the interventions had beliefs and investment in benefit for the active arm of intervention over control arm/s.

RoB V.2 allows for a judgement of overall RoB for each included study: low RoB; some concern of bias; or high RoB. We will assign a rating of 'low RoB' to studies considered at low RoB for all five domains for the specific result. We will assign a rating of 'some concern of bias' to studies we judge to be at high RoB in at least one domain for the result in question. We will assign a rating of 'high RoB' to studies where there is a high RoB in at least one domain for a result or we judge the study to have some concerns for multiple domains in a way that substantially lowers confidence in the result.[30]

Any disagreements will be resolved by a third review author (CB or PC). We will present completed 'RoB' tables and justifications for each judgement in the published review.

Assessment of the strength of the body of evidence

To assess the overall strength of evidence, we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for NMA through the CINeMA application (http://cinema.ispm.ch/).[34 35] As in pairwise meta-analyses, we will apply the GRADE system to direct evidence (ie, data with head-to-head comparisons). When only indirect evidence will be available, we will use the NMA estimate and evaluate the shortest indirect pathway with the largest number of trials. The GRADE approach classifies evidence as high, moderate, low or very low quality based on considerations of RoB, consistency, directness, precision and publication bias.[36]

Missing data

When relevant outcomes are not reported, we will ask trial authors to supply the data. In the absence of data from authors, we will employ validated statistical methods to impute missing outcomes, with due consideration of the possible bias of these procedures, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[37] and with www.missingdata.org.uk. When SDs are not reported and not supplied by authors on request, we will calculate them based on other measures reported in the study, for example, SEs, t-statistics or P values, according to Altman.[38] If this is not possible, we will use the correlation coefficients of other studies included in the analysis to calculate the SDs, or substitute them with a mean of those reported in other trials in the review, provided that they employed the same rating scale.[37 39]

Statistical analysis

For each of the two projects, we will perform standard pairwise meta-analyses with a random-effects model for every comparison with at least two studies. We will use the random-effects approach, as we expect considerable heterogeneity. If a sufficient number of clinically similar studies is available, we will perform, for each outcome, a NMA with a random-effects model in a frequentist framework, using the STATA 16.1 "Special Edition" (SE) mvmeta package. For the continuous outcomes (efficacy), we will pool the mean differences between treatment arms at endpoint if all trials measured the outcome using the same rating scale, otherwise we will pool SMDs.

We will test for publication bias using Egger test[40] of the intercept to quantify the bias captured by the funnel plot and to test whether it is statistically significant.

For the dichotomous outcome (acceptability), we will calculate ORs with a 95% CI for each study and then pool these.

Transitivity is a basic and fundamental assumption to perform an NMA. This assumption is met when effect modifiers are equally distributed across the comparisons. All studies included will be similar in terms of characteristics of participants, study design and outcomes, therefore, we expect that the assumption of transitivity will be met, and that all treatments included in the network can be considered 'exchangeable' (as if all of them were part of a large, multiarm trial). Transitivity is a logical construct, whose statistical counterpart is indicated as coherence, which evaluates the statistical disagreement between direct and indirect evidence of a treatment comparison.[41] We will evaluate this assumption by different means. We will extract key study characteristics judged to be potential effect modifiers, namely: number of participants included, percentage of agoraphobic participants, baseline panic frequency and number of sessions of the intervention. We will compare their distribution across comparisons in the network. Along with this qualitative evaluation of transitivity from a clinical and methodological viewpoint, we will also assess this assumption statistically.

We will statistically evaluate the presence of incoherence by comparing direct and indirect evidence within each closed loop[42] and comparing the goodness of fit for an NMA model that assumes consistency with a model that allow for inconsistency in 'design by treatment interaction model' framework[43–45] by using the Stata commands mvmeta[15] and ifplot[46] and the Stata network suite.[15] If there is evidence of inconsistency, we will investigate this further using a node-splitting[47] approach between comparisons.

We will calculate a treatment hierarchy by means of surface under the cumulative ranking curve and mean ranks.[48] Studies that compare two or more formats of similar psychotherapeutic interventions will be included in meta-analysis by combining group arms into a single group[37] only if the trial includes a control condition, otherwise the RCT will be excluded as it cannot contribute to the network.

We will calculate dichotomous data on a strict ITT basis, considering the total number of randomised patients as denominator. Where participants had been excluded from the trial before the endpoint, we will assume that they experienced a negative outcome by the end of the trial. For continuous variables, we will apply a loose ITT analysis, whereby all the participants with at least one post-baseline measurement were represented by their last observations carried forward . For RCTs that implemented a per protocol analysis we will consider completers data, with due consideration of potential biases, including number and timings of drop-outs in each arm.

For pairwise meta-analyses, we will assess heterogeneity by visual inspection of forest plots, and using the I^2 statistics, following the interpretation suggested by the Cochrane handbook[37]: 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity. For the NMA, common heterogeneity across all comparisons[49] will be assumed and estimated in each network. Heterogeneity of the network will be evaluated by the common τ^2, by comparing it with its empirical distributions.[50] To verify the transitivity assumption according to which effect modifiers are similarly distributed across comparisons in the network, we will compile a table of important trial and patient characteristics and visually inspect the similarity of factors we consider likely to modify treatment effect, for each comparison. We will also assess the inclusion and exclusion criteria of every trial in the network to ensure that patients, trial protocols, etc are similar. Furthermore, in addition to the description of study characteristics in the aforementioned table, we will deepen the characterisation of every intervention by producing a detailed adjunctive table where we will describe each intervention and give information on the reference intervention manuals/important theoretical articles. An example is reported in online supplementary file. Such a synoptic summary will ease the identification of

transitivity-threatening differences between interventions considered for the same node.

Sensitivity analyses

- A sensitivity analysis will be conducted to explore the effects of the RCTs missing data imputation techniques on outcomes. In the analysis, we will exclude the trials which data were imputed according to the strategies described in the above paragraph 'missing data'.
- A second sensitivity analysis will be conducted in case of high statistical heterogeneity (I^2 >75%) to explore the putative effects of the study quality assessed through the RoB V.2 on heterogeneity. In the analysis, we will exclude the trials judged to be at 'high RoB'.

Patient and public involvement

Patients and the public were not involved in the design of this review protocol.

ETHICS AND DISSEMINATION

These two systematic reviews and network meta-analyses will be published separately in peer-reviewed journals. The results of these investigations will be disseminated electronically and in print, as well presented as abstracts and/or personal communications during national and international conferences. Since no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

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Contributors DP and CB conceived the study. DP drafted the protocol manuscript. CB, PC, TAF, EK, MS, GO, MP, CG, CDG and AP assisted in the protocol design and revision. GO, CB, TAF, CDG and DP designed the statistical analysis; PC, TAF and CB are the guarantors. All authors read and approved the final version of the manuscript.

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