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Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized evidence

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ABSTRACT

Introduction

There is rising awareness that we need multi-disciplinary approaches integrating psychological treatments for schizophrenia, but a comprehensive evidence base on their relative efficacy is lacking. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs) to rank psychological treatments for schizophrenia according to their efficacy, acceptability and tolerability.

Methods and analysis

We will include all RCTs comparing a psychological treatment aimed at positive symptoms of schizophrenia with another psychological intervention or with a no treatment condition (waiting list, treatment as usual). We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. prodromal or first episode patients). Primary outcome will be the change in positive symptoms on a published rating scale. Secondary outcomes will be acceptability (dropout), change in overall and negative symptoms of schizophrenia, response, relapse, adherence, depression, quality of life, functioning and adverse events. Published and unpublished studies will be sought through database searches, trial registries and websites. Study selection and data extraction will be conducted by at least two independent reviewers. We will conduct random-effects NMA to synthesize all evidence for each outcome and obtain a comprehensive ranking of all treatments. NMA will be conducted in Stata and R within a frequentist framework. The risk of bias in studies will be evaluated using the Cochrane Risk of Bias tool and the credibility of the evidence will be evaluated using an adaptation of the GRADE framework to NMA, recommended by the Cochrane guidance. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination

No ethical issues are foreseen. Results from this study will be published in peer-reviewed journals and presented at relevant conferences.

PROSPERO registration number: CRD42017067795

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will conduct a random-effects network meta-analysis to synthesize all available published or unpublished randomized controlled trials for each pre-specified outcome, and obtain a comprehensive ranking of all treatments.
- This will be the first network meta-analysis on psychological treatments for schizophrenia; the findings from this study have the potential to inform and influence clinical decision-making and guideline development.
- The risk of heterogeneity and inconsistency is high, given the different psychological interventions that will be included: however, we try to control variability by carefully framing the inclusion criteria about population and interventions, and we will evaluate consistency employing local as well as global methods.
- The limitations of primary studies will be addressed with the Cochrane risk of bias tool and the quality of evidence for network estimates will be assessed with an appropriate

adaptation of the GRADE framework; these approaches are considered the gold standard for critical appraisal of evidence quality.

INTRODUCTION

Schizophrenia is a debilitating, and often life-long disorder that ranks among the top 20 causes of disability according to the World Health Report (1). Although pharmacological interventions have been the mainstay of treatment for schizophrenia, antipsychotics have a number of limitations (limited response, high incidence of disabling side effects, poor adherence to treatment) (2) and are problematic in many situations (such as medical comorbidities, tolerability problems and pregnancy). Besides, there has been growing recognition of the importance of psychological processes in psychosis, both as contributors to onset and persistence, and in terms of the negative psychological impact of a diagnosis of schizophrenia on the individual's well-being, psychosocial functioning and life opportunities. Psychological interventions for psychosis and schizophrenia have been developed to address these aspects, and, in accordance with guidelines from the National Institute for Health and Care Excellence in the United Kingdom (3) and the Schizophrenia Patient Outcomes Research Team in the United States (4), psychological treatments are widely regarded as a necessary intervention for schizophrenia.

A broad range of interventions that can be defined as "psychological" have been studied in the treatment of schizophrenia. These interventions can be provided at different stages of the illness and address different aspects, like social and cognitive functioning, adherence to medication and symptoms of schizophrenia. Table 1 presents the panorama of existing systematic reviews of randomized controlled trials that have been conducted on the topic. These reviews have mainly included studies comparing the intervention under examination with so called no treatment conditions (waiting-list, treatment as usual (TAU)) (5, 6). Other reviews included also active comparisons with other psychological treatments (7–9). An attempt to provide information on active comparisons was made by Turner and colleagues, who performed separate meta-analysis when there were at least five eligible randomized controlled trials comparing one intervention to another psychological intervention (10). However, all the available reviews applied pairwise meta-analysis as a method, being able to pool results only when a comparison of two treatments was considered in existing studies. The comparative efficacy and tolerability of the existing interventions has not been checked yet; as a result, it is still currently unclear which are the most efficacious, the most acceptable and the best tolerable psychological treatments for schizophrenia.

To overcome this gap in the current knowledge, a network meta-analysis would be necessary to consider both direct and indirect comparisons, and produce hierarchies of the effects of the various psychological treatments in the various efficacy and tolerability outcomes. Such hierarchies are essential for guidelines, which should ideally be able to indicate which treatment is likely to be the best, the second best and so on for a given outcome. Only the method of network meta-analysis can provide such hierarchies by combining all the randomised evidence. Our aim is to produce such a network meta-analysis of all psychological interventions for schizophrenia in multiple outcomes. We focus here on the interventions primarily aimed at treating positive symptoms in the acute phase of the illness.

Intervention	Existing reviews	RCT*	Comparator
Acceptance and commitment therapy	Ongoing Cochrane review (11)	-	TAU, pharmacological intervention, another psychosocial intervention
Adherence interventions	Gray 2016 (12)	6	TAU, didactic health education
Active comparisons (Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling)	Turner 2014 (10)	48	Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling, Family intervention, Art therapy, Body psychotherapy, Occupational therapy, Problem-solving therapy
Art therapy	Ruddy 2005 (6)	2	Standard care
Assertive community treatment	Marshall 1998 (13)	20**	TAU, hospital-based rehabilitation, case management
Befriending	-		
Bibliotherapy	-		
Body oriented psychological therapy	-		
Case management	Dieterich 2017 (14)	40**	Assertive Community Treatment, Assertive Outreach model, Case Management model, standard community care
Cognitive behavioural therapy	Zimmermann 2005 (positive symptoms) (9)	15	Waiting-list, TAU or another therapeutic treatment
	Jones 2012 (7)	20	Active (Psychoeducation, Family Intervention, Supportive Psychotherapy, Supportive Counselling, Cognitive Remediation) and nonactive control treatments (Recreation and support, social activities, befriending, non-specific counselling)
	Jauhar 2013 (15)	52	Waiting list, TAU or an intervention designed to control for the non-specific effects of psychotherapy (recreation and support, group support, befriending, supportive counselling/therapy, social activity therapy and goal-focused supportive contact) or active treatments (cognitive remediation, psychoeducation)
	Van der Gaag 2014 (individually tailored) (16)	18	Any control condition was accepted
	Hazell 2016 (low intensity) (17)	8	TAU, supportive psychotherapy
	Kennedy 2016 (auditory hallucinations) (18)	2	Non-specialized therapy (focused on supportive interactions and social integration)
Cognitive remediation	Cella 2016 (19)	45	TAU, active control (e.g. computer games) another active treatment (e.g. CBT)
Dance therapy	Ren 2013 (20)	1	Standard care plus supportive counselling
Family interventions	Pitschel-Walz 2001 (21)	25	TAU, patient intervention, other family interventions
	Pharoah 2006 (22)	25	TAU, discussion groups, psychoeducation, supportive psychotherapy, psychosocial support
Group psychotherapeutic treatments	Orfanos 2015 (23)	34	TAU, other groups (active discussion group, support group, counselling group, occupational therapy group or problem-solving discussion group)

Integrated psychological Therapy (IPT)	Roder 2006 (24)	16	TAU, placebo-attention condition, other active treatments
Psychological and psychosocial interventions for negative symptoms in psychosis	Lutgens 2017 (8)	95	TAU, active comparator (including psychoeducation, supportive therapy, cognitive remediation)
Metacognitive training	Eichner 2016 (25)	12	TAU, Wait list control, Supportive Therapy, Newspaper discussion group, CogPack (=Cognitive remediation)
Mindfulness	Aust 2017 (26)	11**	Active control intervention (e.g. Befriending, Progressive Muscle Relaxation), TAU
Music therapy	Geretsegger 2017 (27)	18	Placebo defined as an alternative therapy designed to control for effects of the therapist's attention; TAU or no treatment
Psychodynamic therapy	Malmberg 2012 (28)	4	Reality-adaptive, supportive psychotherapy, Hospital comparison, Ataraxic drugs, electro convulsive therapy, Milieu therapy, individual vs. group
Psychoeducation	Pekkala 2006 (29)	10	TAU, supportive psychotherapy, behavioral intervention, leisure-time group
Social skills training	Almerie 2015 (30)	13	TAU, structured activities, discussion group, interaction group, no treatment control
Supportive therapy	Buckley 2015 (31)	24	Standard care, any other treatment (biological, psychological or social) such as medication, problem-solving therapy, psychoeducation, social skills training, CBT, family therapy or psychodynamic psychotherapy
Systemic therapy	Pinquart 2016 (5)	7	No treatment

Table 1. Existing reviews about psychological treatments for schizophrenia.
RCT: randomized controlled trial; TAU: treatment as usual.
*number of RCTs on schizophrenic patients; **RCTs about patients with severe mental illness including schizophrenia

Objectives

To estimate relative treatment effects and obtain a hierarchy for the psychological treatments in patients with schizophrenia, in terms of:

1. Efficacy on positive symptoms
2. Acceptability
3. Other efficacy measures, such as overall symptoms, negative symptoms, response, relapse, adherence, depression, quality of life, functioning
4. Tolerability.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Methods for this systematic review have been developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions (32, 33). This systematic review and NMA is registered in the PROSPERO database (registration number: CRD42017067795); the record in PROSPERO will be updated with any amendment made to the protocol.

Types of studies

We will include all randomised trials (RCTs) in which participants with schizophrenia received a psychological intervention as defined below (see *Types of interventions*). Studies whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week) will be excluded. We will accept open and blinded RCTs; this choice is particularly relevant in trials on psychological interventions, in which in best case only the assessor of outcome can be blind, but not the therapist. Open RCTs will be excluded in a sensitivity analysis. We will include both trials in which psychological interventions were compared with a control condition and trials in which they were compared with another intervention. There will be no language restriction in order to avoid the problem of 'language bias' (34). As an exception, we will exclude studies conducted in mainland China (while studies conducted in Taiwan and Hong Kong will not be excluded) to avoid a systematic bias, since many of these studies do not use appropriate randomisation procedures and often do not report their methods (35, 36). In the case of cross-over studies we will use only the first cross-over phase in order to avoid the problem of carry-over effects which are very likely in schizophrenia and with psychological treatments. We will exclude cluster randomized trials.

Types of participants

Our aim is to collect information on the efficacy of psychological treatments on patients with positive symptoms. In order to select this population, we operationalized the inclusion criteria as follows. We will include adults, however defined by study authors, with a diagnosis of schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders); there is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (37). We will include trials irrespective of the diagnostic criteria used. Here we will follow the strategy of the Cochrane Schizophrenia Group (38) to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-V, because these criteria are not meticulously used in clinical routine either. This decision should increase generalizability and representativeness.

Studies including participants with other diagnoses part of the psychosis spectrum will be included only if participants with a diagnosis of schizophrenia, schizophreniform or schizoaffective disorders were more than 80% of the participants considered. We will include studies recruiting patients with positive symptoms, either delusions, hallucinations or both, or acute phase of illness, however defined by inclusion criteria of the trial.

We will exclude studies focused on specific subpopulations of patients, such as (1) studies recruiting patients with predominant negative symptoms, (2) studies on patients with comorbid psychiatric disorders including substance abuse, (3) studies recruiting patients with concomitant medical illnesses, (4) trials enrolling stable patients (relapse prevention studies), (5) studies on first episode patients, (6) trials on patients who show prodromal signs of psychosis (also defined as "at risk for psychosis").

Types of interventions

Any psychological intervention that occurs through interaction between therapist and patient, either face-to-face individually or in group, with the primary aim to reduce positive symptoms. Interventions with an explicit primary aim different from positive symptoms (e.g. functioning, cognition, adherence to medication, knowledge of the illness) will be excluded. Psychological

treatments will be compared to each other and to any non-pharmacological control condition considered in the included studies. Comparators will include the so called "treatment as usual", waiting list and inactive treatments. "Non-active" comparators have been associated with a nocebo effect, therefore their effect on the network will be analysed in a sensitivity analysis (39). Patients also receiving treatment as usual, including pharmacological interventions will be included. If psychological treatments that we do not include among the interventions (e.g. psychoeducation, supportive therapy) are used as control condition in the studies, they will be included as nodes in order to strengthen the network, but will not be part of our decision set.

Outcome measures

Outcomes will be measured at study endpoint, as defined in each study.

Primary outcome

Change in positive symptoms of schizophrenia, examined accordingly to the respective subscale of the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) or the Scales for Assessment of Positive Symptoms (SAPS) or any other published scale.

As not all studies will have used the same scale, we will extract data according to the following hierarchy: mean change of the PANSS positive symptoms subscale from baseline to endpoint, if not available mean change of the BPRS positive symptoms subscale, or if again not available the mean values at endpoint of the PANSS/BPRS positive symptoms subscale. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal, because it has been shown that non-validated schizophrenia scales exaggerate differences (40).

Secondary outcomes

1. Acceptability, defined as the percentage of patients leaving the study early ('dropout') for any reason. All-cause discontinuation due to any reason combines efficacy, tolerability, and other factors and can therefore be considered as a measure of 'acceptability of treatment' (38) or of overall "effectiveness";
2. Change in overall symptoms, measured by rating scales such as the PANSS or the BPRS, or any other published scale (e.g. the Manchester Scale) for the assessment of overall schizophrenic symptomatology. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal;
3. Change in negative symptoms, measured by the respective subscale of the PANSS, or the "Scales for Assessment of Negative Symptoms" (SANS) or any other published scale;
4. Response, measured by the percentage of responders defined by reduction on the PANSS, BPRS or CGI scores, accepting the criteria used by study authors;
5. Percentage of patients with relapse, by definitions operationalized by rating scales, and, if not available, number of rehospitalisations due to psychopathology. We will not include data from studies that used non-operationalized relapse criteria (e.g. "clinical judgement");
6. Adherence, measured by any published rating scale (e.g. "Adherence Therapy Patients Satisfaction Questionnaire", "Adherence Rating Scale");
7. Depression, measured by the Calgary Depression Scale for Schizophrenia, the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Scale or other published symptom scales;

8. Quality of life, measured by any published rating scale (e.g. “Heinrichs quality of life scale”, Quality of Life Scale (QOLS);
9. Functioning, measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale, or any other published rating scale.
10. Tolerability, measured as the percentage of patients experiencing adverse events. Adverse events associated with psychological treatments are not covered as comprehensively as in trials on pharmacological treatments (41). However, there is a raising awareness of the importance of considering possible harms associated with psychological interventions (42). Therefore we will collect any available information in clinical studies about this outcome, using a classification proposed by Linden and colleagues (42): a) emergence of new symptoms; b) deterioration of existing symptoms; c) lack of improvement or deterioration of illness; d) prolongation of treatment; e) patient’s non-compliance; f) strains in the patient-therapist relationship; g) very good patient-therapist relationship, therapy dependency; h) strains or changes in family relations; i) strains or changes in work relations; l) any change in the life circumstances of the patient; m) stigmatization. Suicide attempts and any other possible adverse event related to psychological treatment will also be considered.
11. Mortality. Psychosocial treatments may actually reduce or, by contrast, increase overall mortality, in particular connected to suicidality. To test this, we will examine this outcome in terms of a) death for any reason, b) death due to natural causes and c) due to suicide.

Search strategy

Electronic searches

The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PUBMED. The search terms that will be used for PubMed are provided as Supplement material. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP)
2. BIOSIS
3. Cochrane Collaboration Controlled Trials Register
4. ClinicalTrials.gov.

Reference lists and other sources

References of all selected studies will be inspected for other published reports and citations of unpublished studies. We will also inspect previous reviews conducted on psychological treatments for schizophrenia to check if some studies meet our inclusion criteria as well. In addition, we will contact the first author of each included study published in the last 30 years for missing information about their studies.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Citavi; duplicates will be excluded. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently inspect title and abstracts identified in the literature searches, and exclude those not pertinent. Disagreement will be resolved by discussion, and where doubt

still remains, we will acquire the full article for further inspection and the article will proceed to the next stage;

2. Once the full articles are obtained, two reviewers will independently assess them for eligibility. Disagreements will be resolved by discussion, and, if needed, a third senior author will be involved. When required, further information will be obtained from study authors.

Data extraction

Two authors will independently extract data from all selected trials. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient we will contact the study authors.

The following data will be collected from each included study:

- Study citation, year(s) of study, registration number to trials registries, year of publication, location, setting, number of centers, sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Methodology, including study design (type of RCT), number of arms, risk of bias (see below);
- Characteristics of study participants, including gender, age, details on diagnosis, number randomized to each arm, sociodemographic characteristics, whether psychological treatments naïve at baseline, or with previous experience with the experimental intervention);
- Characteristics of intervention, including number and frequency of sessions, therapy setting, expertise of therapist, researcher allegiance at study arm level;
- Outcome measures, including information on whether an Intention to Treat (ITT) approach has been used and how it was defined.

The two reviewers will independently input data into an Access database especially created for this study. The software will automatically detect any inconsistencies, and they will be resolved by discussion.

Measurement of treatment effect

Relative treatment effects

- Continuous outcomes: For continuous outcomes we will use the standardized mean difference (SMD), because we expect that the studies use different rating scales of overall schizophrenia symptomatology.
- Dichotomous outcomes: The effect size for dichotomous outcomes will be the risk ratio (RR) and its 95% confidence intervals (CIs).

Relative treatment ranking

We will estimate the probability for each intervention to be ranked at each possible place, given the relative effect sizes as estimated in NMA. As described in Salanti et al (43) we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options.

Dealing with missing outcome data and missing statistics

For continuous outcomes we will extract data for all randomized patients if possible, and we will give preference to data based on mixed-effect models of repeated measurements of multiple imputations over last-observation-carried-forward data.

We will use published standard deviations (SDs), where available. When standard errors instead of SDs are presented, the former will be converted to SDs (44). If both are missing we will estimate SDs from p-values or confidence intervals, as described in Section 7.7.3 of the Cochrane Handbook for Systematic Reviews (45). If none of these options is viable we will contact the original authors. When no information can be obtained we will derive SDs from those of the other studies using a validated imputation technique (44).

For dichotomous outcomes, everyone allocated to the intervention will be counted whether they completed the follow up or not. If the authors applied such a strategy, we will use their results. If the original authors presented only the results of the per-protocol or completer population, we will assume that those participants lost to follow-up would not have changed in a given outcome. In terms of efficacy this means that they would be conservatively considered to have not responded to treatment or control. In terms of tolerability it would mean that participants would not have developed a side-effect.

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool (45, 46). The following domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants: was knowledge of the allocated treatment adequately prevented during the study? Given the peculiarity of the included studies, in which the therapist cannot be blind, we will consider under this item only if a way was found to keep patients unaware of the treatment they were receiving (even if we expect this will not be likely);
4. Blinding of outcome assessors: were outcome evaluated by blind raters? Were adequate measures taken to prevent them to discover treatment allocation during the study?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective reporting: are reports of the study free from suggestion of selective outcome reporting?
7. Researcher's allegiance: do the researchers involved have a vested interest for the psychological treatment under investigation? We will additionally consider this point as possible source of bias, since it has been claimed to be relevant in trials on psychological interventions (47, 48, 49).

A description of what was reported about the same domains in each study will be provided, and a judgement on the risk of bias will be made for each one of them, based on the following three categories: 'high risk of bias', 'low risk of bias' and 'unclear risk of bias' where information are not sufficient to make a judgement. Two independent review authors will assess the risk of bias in selected studies. Any disagreement will be resolved through discussion. Where necessary, the authors of the studies will be contacted for further information. Studies will be classified as having low risk of bias if none of the domains above was rated as high risk of bias and three or less were rated as unclear risk; moderate if one was rated as high risk of bias or none was rated as high risk of bias but four or more were rated as unclear risk, and all other cases will be assumed to pertain to high risk of bias (50). We will not include studies in the data analyses whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week). Effects of high risk of bias in the other domains will be analyzed by sensitivity analyses.

Data analysis

Characteristics of the included studies

We will produce descriptive statistics and study population characteristics across all eligible trials, describing the types of comparisons and other clinical or methodological variables, such as age, duration of illness, co-medication, country, duration of study and number of session.

Two-step procedure

In a first step we will perform series of conventional pair-wise meta-analyses by combining studies that compared the same interventions, including the comparison between active treatments and the different control arms. In subgroups with very few RCTs available or if the requirements of network meta-analysis are not met it can be that network meta-analysis will not be appropriate and in this case, conventional pairwise meta-analysis will be the most straightforward approach. As heterogeneity is likely, a random effects model will be used. In a second step we will then perform a network meta-analysis within a frequentist framework.

Assessment of heterogeneity

The heterogeneity (variability in relative treatment effects within the same treatment comparison) will be measured with the tau-squared (the variance of the random effects distribution). The heterogeneity variance will be assumed common across the various treatment comparisons (grouped by comparison type) and the empirical distributions will be used to characterize the amount of heterogeneity as low, moderate or high using the first and third quantiles (51–53). Potential reasons for heterogeneity will be explored by subgroup analysis (see below).

Assessment of the transitivity assumption

Joint analysis of treatments can be misleading if the network is substantially intransitive. We assume that patients who fulfill the inclusion criteria outlined in criteria for considering studies for this review section are equally likely to be randomised to any of the interventions that we plan to compare. We will need to investigate the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons (54). We have maximized the chances of transitivity in our network with regard to clinical variables by limiting our samples to participants with schizophrenia and excluding specific subgroups like first episode patients or patients with prevalent negative symptoms. Other clinical or methodological variables that may influence the efficacy of psychological interventions include administration mode and frequency of the treatment (like number of sessions and experience of the therapist), baseline severity (see below, “Investigation of heterogeneity and inconsistency”), and blinding, which will also be assessed in sensitivity analyses. We will investigate if these variables are similarly distributed across studies grouped by comparison. The comparability of studies comparing the intervention with treatment as usual or waiting list conditions with those that provide head-to-head evidence will be examined carefully.

Network meta-analysis

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and can therefore provide estimates with maximum power and increased precision (55). If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers (refer Assessment of transitivity assumption section), we will conduct a random-effects NMA to synthesize all evidence for each outcome, and obtain a comprehensive ranking of all treatments. We will assume a single heterogeneity parameter for each network. We will present the summary SMDs or RRs for all pairwise comparisons in a league table. We will also estimate the prediction intervals to

assess how much the common heterogeneity affects the relative effect with respect to the extra uncertainty anticipated in a future study. To rank the various treatments for each outcome, we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks.

Assessment of inconsistency

The strategical and conceptual evaluation of transitivity will be supplemented with a statistical evaluation of consistency, the agreement between direct and indirect evidence. We will employ local as well as global methods to evaluate consistency (56). Local methods detect 'hot spots' of inconsistency, evidence loops that are inconsistent or comparisons for which direct and indirect evidence disagree. We will employ a method that separates direct evidence from indirect evidence provided by the entire network and then evaluate the agreement of these two pieces of evidence (57). We will also evaluate consistency in the entire network by calculating the design-by-treatment interaction test and I-squared for network heterogeneity, inconsistency, and for both (58). Tests for inconsistency are known to have low power, and empirical evidence has suggested that 10% of evidence loops published in the medical literature are expected to be inconsistent (60). Therefore, interpretation of the statistical inference about inconsistency will be carried out with caution and possible sources of inconsistency will be explored even in the absence of evidence for inconsistency.

Investigation of heterogeneity and inconsistency

We expect small amounts of heterogeneity and inconsistency to be present given the variety of study settings we plan to include. The following potential effect modifiers of the primary outcome will be explored by subgroup analyses:

a) Number of sessions
b) Study duration
c) Setting: individual vs group
d) Expertise of the therapist
e) Baseline severity (PANSS or BPRS score at baseline)
f) High versus low and middle income countries.

Sensitivity analyses

We will explore the following sensitivity analyses by excluding:

a) studies in which the outcome assessor was not blind (open studies)
b) studies that presented only completer analyses
c) studies characterized as pertaining to high risk of bias
d) studies with high risk of bias in researchers' allegiance
e) studies focused on treatment resistant patients (study defined)
f) studies with a non-active comparison group.

Publication bias

We will first examine funnel plots of pairwise MAs if there are 10 or more studies included. We will also explore the association between study size and effect size with a comparison-adjusted funnel plot that has been adapted to network meta-analysis (59).

Evaluating the quality of the evidence

The quality of evidence contributing to each network estimate will be evaluated using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework specifically developed for network meta-analysis (56). We will characterize the credibility of a body of evidence based on the study limitations, imprecision, heterogeneity/inconsistency, indirectness, and publication bias.

Statistical software

The analysis and presentation of results will be performed using the Stata packages network and network_graphs, the R package netmeta.

ETHICS AND DISSEMINATION

This review does not require ethical approval. Findings will be published in peer reviewed scientific journals, granting open access, and the database will be made publicly available (in agreement with European Research Council Guidelines on Implementation of Open Access to Scientific Publications and Research Data (http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/oa-pilot/h2020-hi-erc-oa-guide_en.pdf).

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Authors' contributions: IB and SL designed this study, drafted and critically revised the protocol. IB will screen search results for inclusion, conduct data extraction and data analysis, and draft the final manuscript. SL will assist with data extraction and analysis, and revise the final manuscript. CR and SW will screen search results for inclusion and conduct data extraction. GS provided substantial methodological advice in planning the study, and will assist with data analysis. CB and TF contributed with clinical and methodological input in planning the study. All authors contributed to and have approved the final manuscript.

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Search terms for Pubmed

("Schizophrenia"[Mesh] OR "Paranoid Disorders"[Mesh] OR schizo*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract]) AND ("Psychotherapy"[Mesh] or "Behavior Therapy"[Mesh] or "Cognitive Therapy"[Mesh] or "Complementary Therapies"[Mesh] or "Psychoanalysis"[Mesh] or "Counseling"[Mesh] or "Hypnosis"[Mesh] or "Association"[Mesh] or "Association Learning"[Mesh] OR abreaction[Title/Abstract] OR "acceptance[Title/Abstract] AND commitment therapy"[Title/Abstract] OR "acting out"[Title/Abstract] OR adlerian[Title/Abstract] OR "analytical psychotherapy"[Title/Abstract] OR "analytical psychotherapies"[Title/Abstract] OR "anger control"[Title/Abstract] OR "anger management"[Title/Abstract] OR "animal therapy"[Title/Abstract] OR "animal therapies"[Title/Abstract] OR "art therapy"[Title/Abstract] OR "art therapies"[Title/Abstract] OR "assertive training"[Title/Abstract] OR "assertiveness training"[Title/Abstract] OR "attention training technique"[Title/Abstract] OR "autogenic training"[Title/Abstract] OR autosuggestion[Title/Abstract] OR "aversion therapy"[Title/Abstract] OR "aversion therapies"[Title/Abstract] OR "balint group"[Title/Abstract] OR befriending[Title/Abstract] OR "behavior contracting"[Title/Abstract] OR "behavior modification"[Title/Abstract] OR "behavior regulation"[Title/Abstract] OR "behavior therapy"[Title/Abstract] OR "behavior therapies"[Title/Abstract] OR "behaviour contracting"[Title/Abstract] OR "behaviour modification"[Title/Abstract] OR "behaviour regulation"[Title/Abstract] OR "behaviour therapy"[Title/Abstract] OR "behaviour therapies"[Title/Abstract] OR bibliotherapy[Title/Abstract] OR bibliotherapies[Title/Abstract] OR biofeedback[Title/Abstract] OR "body psychotherapy"[Title/Abstract] OR "body psychotherapies"[Title/Abstract] OR "brief psychotherapy"[Title/Abstract] OR "brief psychotherapies"[Title/Abstract] OR "caregiver support"[Title/Abstract] OR cbt[Title/Abstract] OR "client centre"[Title/Abstract] OR "client center"[Title/Abstract] OR "cognitive behavior"[Title/Abstract] OR "cognitive behaviorial"[Title/Abstract] OR "cognitive intervention"[Title/Abstract] OR "cognitive interventions"[Title/Abstract] OR "cognitive rehabilitation"[Title/Abstract] OR "cognitive remediation"[Title/Abstract] OR "cognitive technique"[Title/Abstract] OR "cognitive techniques"[Title/Abstract] OR "cognitive therapy"[Title/Abstract] OR "cognitive therapies"[Title/Abstract] OR "cognitive treatment"[Title/Abstract] OR "cognitive treatments"[Title/Abstract] OR "color therapy"[Title/Abstract] OR "color therapies"[Title/Abstract] OR "colour therapy"[Title/Abstract] OR "colour therapies"[Title/Abstract] OR "compassionate mind training"[Title/Abstract] OR "conjoint therapy"[Title/Abstract] OR "conjoint therapies"[Title/Abstract] OR "contingency management"[Title/Abstract] OR "conversational therapy"[Title/Abstract] OR "conversational therapies"[Title/Abstract] OR "conversion therapy"[Title/Abstract] OR "conversion therapies"[Title/Abstract] OR "coping skills"[Title/Abstract] OR counseling[Title/Abstract] OR counselling[Title/Abstract] OR countertransference[Title/Abstract] OR "couples therapy"[Title/Abstract] OR "couples therapies"[Title/Abstract] OR "covert sensitization"[Title/Abstract] OR "covert sensitisation"[Title/Abstract] OR "crisis intervention"[Title/Abstract] OR "dance therapy"[Title/Abstract] OR "dance therapies"[Title/Abstract] OR dialectic[Title/Abstract] OR dialectical[Title/Abstract] OR "dream analysis"[Title/Abstract] OR eclectic[Title/Abstract] OR "emotion focused"[Title/Abstract] OR "emotionally focused"[Title/Abstract] OR "emotional freedom technique"[Title/Abstract] OR "encounter group therapy"[Title/Abstract] OR "encounter group therapies"[Title/Abstract] OR "existential therapy"[Title/Abstract] OR "existential therapies"[Title/Abstract] OR "experiential

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 (title)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16-17
Sponsor	5b	Provide name for the review funder and/or sponsor	16-17
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	16-17
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9, 11, 12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12, 13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized controlled trials

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Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction

There is rising awareness that we need multi-disciplinary approaches integrating psychological treatments for schizophrenia, but a comprehensive evidence base on their relative efficacy is lacking. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs) to rank psychological treatments for schizophrenia according to their efficacy, acceptability and tolerability.

Methods and analysis

We will include all RCTs comparing a psychological treatment aimed at positive symptoms of schizophrenia with another psychological intervention or with a no treatment condition (waiting list, treatment as usual). We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. first episode patients, or patients with psychiatric comorbidities). Primary outcome will be the change in positive symptoms on a published rating scale. Secondary outcomes will be acceptability (dropout), change in overall and negative symptoms of schizophrenia, response, relapse, adherence, depression, quality of life, functioning and adverse events. Published and unpublished studies will be sought through database searches, trial registries and websites. Study selection and data extraction will be conducted by at least two independent reviewers. We will conduct random-effects NMA to synthesize all evidence for each outcome and obtain a comprehensive ranking of all treatments. NMA will be conducted in Stata and R within a frequentist framework. The risk of bias in studies will be evaluated using the Cochrane Risk of Bias tool and the credibility of the evidence will be evaluated using an adaptation of the GRADE framework to NMA, recommended by the Cochrane guidance. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination

No ethical issues are foreseen. Results from this study will be published in peer-reviewed journals and presented at relevant conferences.

PROSPERO registration number: CRD42017067795

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will conduct a random-effects network meta-analysis to synthesize all available published or unpublished randomized controlled trials for each pre-specified outcome, and obtain a comprehensive ranking of all treatments.
- This will be the first network meta-analysis on psychological treatments for schizophrenia; the findings from this study have the potential to inform and influence clinical decision-making and guideline development.
- The risk of heterogeneity and inconsistency is high, given the different psychological interventions that will be included: however, we try to control variability by carefully framing the inclusion criteria about population and interventions, and we will evaluate consistency employing local as well as global methods.

- The limitations of primary studies will be addressed with the Cochrane risk of bias tool and the quality of evidence for network estimates will be assessed with an appropriate adaptation of the GRADE framework; these approaches are considered the gold standard for critical appraisal of evidence quality.

INTRODUCTION

Schizophrenia is a debilitating, and often life-long disorder that ranks among the top 20 causes of disability according to the World Health Report (1). Although pharmacological interventions have been the mainstay of treatment for schizophrenia, antipsychotics have a number of limitations (limited response, high incidence of disabling side effects, poor adherence to treatment) (2) and are problematic in many situations (such as medical comorbidities, tolerability problems and pregnancy). Besides, there has been growing recognition of the importance of psychological processes in psychosis, both as contributors to onset and persistence, and in terms of the negative psychological impact of a diagnosis of schizophrenia on the individual's well-being, psychosocial functioning and life opportunities. Psychological interventions for psychosis and schizophrenia have been developed to address these aspects, and, in accordance with guidelines from the National Institute for Health and Care Excellence in the United Kingdom (3) and the Schizophrenia Patient Outcomes Research Team in the United States (4), psychological treatments are widely regarded as a necessary intervention for schizophrenia.

A broad range of interventions that can be defined as "psychological" have been studied in the treatment of schizophrenia. These interventions can be provided at different stages of the illness and address different aspects, like social and cognitive functioning, adherence to medication and symptoms of schizophrenia. Table 1 presents the panorama of existing systematic reviews of randomized controlled trials that have been conducted on the topic. These reviews have mainly included studies comparing the intervention under examination with so called no treatment conditions (waiting-list, treatment as usual (TAU)) (5, 6). Other reviews included also active comparisons with other psychological treatments (7–9). An attempt to provide information on active comparisons was made by Turner and colleagues, who performed separate meta-analysis when there were at least five eligible randomized controlled trials comparing one intervention to another psychological intervention (10). However, all the available reviews applied pairwise meta-analysis as a method, being able to pool results only when a comparison of two treatments was considered in existing studies. The comparative efficacy and tolerability of the existing interventions has not been checked yet; as a result, it is still currently unclear which are the most efficacious, the most acceptable and the best tolerable psychological treatments for schizophrenia.

To overcome this gap in the current knowledge, a network meta-analysis would be necessary to consider both direct and indirect comparisons, and produce hierarchies of the effects of the various psychological treatments in the various efficacy and tolerability outcomes. Such hierarchies are essential for guidelines, which should ideally be able to indicate which treatment is likely to be the best, the second best and so on for a given outcome. Only the method of network meta-analysis can provide such hierarchies by combining all the randomised evidence. Our aim is to produce such a network meta-analysis of all psychological interventions for schizophrenia in multiple outcomes. We focus here on the interventions primarily aimed at treating positive symptoms in the acute phase of the illness.

Intervention	Existing reviews	RCT*	Comparator
Acceptance and commitment therapy	Ongoing Cochrane review (11)	-	TAU, pharmacological intervention, another psychosocial intervention
Adherence interventions	Gray 2016 (12)	6	TAU, didactic health education
Active comparisons (Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling)	Turner 2014 (10)	48	Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling, Family intervention, Art therapy, Body psychotherapy, Occupational therapy, Problem-solving therapy
Art therapy	Ruddy 2005 (6)	2	Standard care
Assertive community treatment	Marshall 1998 (13)	20**	TAU, hospital-based rehabilitation, case management
Befriending	-		
Bibliotherapy	-		
Body oriented psychological therapy	-		
Case management	Dieterich 2017 (14)	40**	Assertive Community Treatment, Assertive Outreach model, Case Management model, standard community care
Cognitive behavioural therapy	Zimmermann 2005 (positive symptoms) (9)	15	Waiting-list, TAU or another therapeutic treatment
	Jones 2012 (7)	20	Active (Psychoeducation, Family Intervention, Supportive Psychotherapy, Supportive Counselling, Cognitive Remediation) and nonactive control treatments (Recreation and support, social activities, befriending, non-specific counselling)
	Jauhar 2013 (15)	52	Waiting list, TAU or an intervention designed to control for the non-specific effects of psychotherapy (recreation and support, group support, befriending, supportive counselling/therapy, social activity therapy and goal-focused supportive contact) or active treatments (cognitive remediation, psychoeducation)
	Van der Gaag 2014 (individually tailored) (16)	18	Any control condition was accepted
	Hazell 2016 (low intensity) (17)	8	TAU, supportive psychotherapy
	Kennedy 2016 (auditory hallucinations) (18)	2	Non-specialized therapy (focused on supportive interactions and social integration)
Cognitive remediation	Cella 2016 (19)	45	TAU, active control (e.g. computer games) another active treatment (e.g. CBT)
Dance therapy	Ren 2013 (20)	1	Standard care plus supportive counselling
Family interventions	Pitschel-Walz 2001 (21)	25	TAU, patient intervention, other family interventions
	Pharoah 2006 (22)	25	TAU, discussion groups, psychoeducation, supportive psychotherapy, psychosocial support
Group psychotherapeutic treatments	Orfanos 2015 (23)	34	TAU, other groups (active discussion group, support group, counselling group, occupational

			therapy group or problem-solving discussion group)
Integrated psychological Therapy (IPT)	Roder 2006 (24)	16	TAU, placebo-attention condition, other active treatments
Psychological and psychosocial interventions for negative symptoms in psychosis	Lutgens 2017 (8)	95	TAU, active comparator (including psychoeducation, supportive therapy, cognitive remediation)
Metacognitive training	Eichner 2016 (25)	12	TAU, Wait list control, Supportive Therapy, Newspaper discussion group, CogPack (=Cognitive remediation)
Mindfulness	Aust 2017 (26)	11**	Active control intervention (e.g. Befriending, Progressive Muscle Relaxation), TAU
Music therapy	Geretsegger 2017 (27)	18	Placebo defined as an alternative therapy designed to control for effects of the therapist's attention; TAU or no treatment
Psychodynamic therapy	Malmberg 2012 (28)	4	Reality-adaptive, supportive psychotherapy, Hospital comparison, Ataraxic drugs, electro convulsive therapy, Milieu therapy, individual vs. group
Psychoeducation	Pekkala 2006 (29)	10	TAU, supportive psychotherapy, behavioral intervention, leisure-time group
Social skills training	Almerie 2015 (30)	13	TAU, structured activities, discussion group, interaction group, no treatment control
Supportive therapy	Buckley 2015 (31)	24	Standard care, any other treatment (biological, psychological or social) such as medication, problem-solving therapy, psychoeducation, social skills training, CBT, family therapy or psychodynamic psychotherapy
Systemic therapy	Pinquart 2016 (5)	7	No treatment

Table 1. Existing reviews about psychological treatments for schizophrenia.
RCT: randomized controlled trial; TAU: treatment as usual.
*number of RCTs on schizophrenic patients; **RCTs about patients with severe mental illness including schizophrenia

Objectives

To estimate relative treatment effects and obtain a hierarchy for the psychological treatments in patients with schizophrenia, in terms of:

1. Efficacy on positive symptoms
2. Acceptability
3. Other efficacy measures, such as overall symptoms, negative symptoms, response, relapse, adherence, depression, quality of life, functioning
4. Tolerability.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Methods for this systematic review have been developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions (32, 33). This systematic review and NMA is registered in the PROSPERO database

(registration number: CRD42017067795); the record in PROSPERO will be updated with any amendment made to the protocol.

Types of studies

We will include all randomised trials (RCTs) in which participants with schizophrenia received a psychological intervention as defined below (see *Types of interventions*). Studies whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week) will be excluded. We will accept open and blinded RCTs; this choice is particularly relevant in trials on psychological interventions, in which in best case only the assessor of outcome can be blind, but not the therapist. Open RCTs will be excluded in a sensitivity analysis. We will include both trials in which psychological interventions were compared with a control condition and trials in which they were compared with another intervention. There will be no language restriction in order to avoid the problem of 'language bias' (34). In case we retrieve references in languages in which we are not fluent, study authors will be contacted to check inclusion criteria and eventually ask for study data. As an exception, we will not search Chinese databases, since serious concerns have been raised on the trustworthiness of Chinese trials found in these databases (35, 36). Chinese studies found in Western databases will be considered for inclusion. In the case of cross-over studies we will use only the first cross-over phase in order to avoid the problem of carry-over effects which are very likely in schizophrenia and with psychological treatments. We will exclude cluster randomized trials.

Types of participants

Our aim is to collect information on the efficacy of psychological treatments on patients with positive symptoms. In order to select this population, we operationalized the inclusion criteria as follows. We will include adults, however defined by study authors, with a diagnosis of schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders); there is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (37). We will include trials irrespective of the diagnostic criteria used. Here we will follow the strategy of the Cochrane Schizophrenia Group (38) to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-V, because these criteria are not meticulously used in clinical routine either. This decision should increase generalizability and representativeness.

Studies including participants with other diagnoses part of the psychosis spectrum will be included only if participants with a diagnosis of schizophrenia, schizophreniform or schizoaffective disorders were more than 80% of the participants considered. We will include studies recruiting patients with positive symptoms, either delusions, hallucinations or both, or in the phase of acute exacerbation of positive symptoms, however defined by inclusion criteria of the trial.

We will exclude studies focused on specific subpopulations of patients, such as (1) studies recruiting patients in which negative symptoms are predominant, according to authors' definition, (2) studies on patients with comorbid psychiatric disorders including substance abuse, (3) studies recruiting patients with concomitant medical illnesses, (4) trials enrolling stable patients (relapse prevention studies), (5) studies on first episode patients, (6) trials on patients who show prodromal signs of psychosis (also defined as "at risk for psychosis").

Types of interventions

Any psychological intervention that occurs through interaction between therapist and patient, either face-to-face individually or in group, with the primary aim to reduce positive symptoms. Interventions with an explicit primary aim different from positive symptoms (e.g. functioning, cognition, adherence to medication, knowledge of the illness) will be excluded. The identified treatments will be classified after identification of eligible studies. Psychological treatments will be compared to each other and to any non-pharmacological control condition considered in the included studies. Comparators will include the so called "treatment as usual", waiting list and inactive treatments. The effect of "non-active" comparators will be analysed in a sensitivity analysis (39). Patients also receiving treatment as usual, including pharmacological interventions, will be included. If psychological treatments that we do not include among the interventions (e.g. psychoeducation, supportive therapy) are used as control condition in the studies, they will be included as nodes in order to strengthen the network, but will not be part of our decision set.

Outcome measures

Outcomes will be measured at study endpoint, as defined in each study.

Primary outcome

Change in positive symptoms of schizophrenia, examined accordingly to the respective subscale of the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) or the Scales for Assessment of Positive Symptoms (SAPS) or any other published scale.

As not all studies will have used the same scale, we will extract data according to the following hierarchy: mean change of the PANSS positive symptoms subscale from baseline to endpoint, if not available mean change of the BPRS positive symptoms subscale, or if again not available the mean values at endpoint of the PANSS/BPRS positive symptoms subscale. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal, because it has been shown that non-validated schizophrenia scales exaggerate differences (40).

Secondary outcomes

Given the focus on treatments for positive symptoms, the results of this review will be informative for the treatment of positive symptoms. They will also describe how these interventions can have an effect on a number of other outcomes. With this aim, the following secondary outcomes will be assessed:

1. Acceptability, defined as the percentage of patients leaving the study early ('dropout') for any reason. All-cause discontinuation due to any reason combines efficacy, tolerability, and other factors and can therefore be considered as a measure of 'acceptability of treatment' (38) or of overall "effectiveness";
2. Change in overall symptoms, measured by rating scales such as the PANSS or the BPRS, or any other published scale (e.g. the Manchester Scale) for the assessment of overall schizophrenic symptomatology. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal;
3. Change in negative symptoms, measured by the respective subscale of the PANSS, or the "Scales for Assessment of Negative Symptoms" (SANS) or any other published scale;

4. Response, measured by the percentage of responders defined by reduction on the PANSS, BPRS or CGI scores, accepting the criteria used by study authors;
5. Percentage of patients with relapse, by definitions operationalized by rating scales, and, if not available, number of rehospitalisations due to psychopathology. We will not include data from studies that used non-operationalized relapse criteria (e.g. "clinical judgement");
6. Adherence, measured by any published rating scale (e.g. "Adherence Therapy Patients Satisfaction Questionnaire", "Adherence Rating Scale");
7. Depression, measured by the Calgary Depression Scale for Schizophrenia, the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Scale or other published symptom scales;
8. Quality of life, measured by any published rating scale (e.g. "Heinrichs quality of life scale", Quality of Life Scale (QOLS);
9. Functioning, measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale, or any other published rating scale.
10. Tolerability, measured as the percentage of patients experiencing adverse events. Adverse events associated with psychological treatments are not covered as comprehensively as in trials on pharmacological treatments (41). However, there is a raising awareness of the importance of considering possible harms associated with psychological interventions (42). Therefore we will collect any available information in clinical studies about this outcome, using a classification proposed by Linden and colleagues (42): a) emergence of new symptoms; b) deterioration of existing symptoms; c) lack of improvement or deterioration of illness; d) prolongation of treatment; e) patient's non-compliance; f) strains in the patient-therapist relationship; g) very good patient-therapist relationship, therapy dependency; h) strains or changes in family relations; i) strains or changes in work relations; l) any change in the life circumstances of the patient; m) stigmatization. Suicide attempts and any other possible adverse event related to psychological treatment will also be considered.
11. Mortality. Psychosocial treatments may actually reduce or, by contrast, increase overall mortality, in particular connected to suicidality. To test this, we will examine this outcome in terms of a) death for any reason, b) death due to natural causes and c) due to suicide.

Search strategy

Electronic searches

The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PUBMED. The search terms that will be used for PubMed are provided as Supplement material. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP)
2. BIOSIS
3. Cochrane Collaboration Controlled Trials Register
4. ClinicalTrials.gov.

Reference lists and other sources

References of all selected studies will be inspected for other published reports and citations of unpublished studies. We will also inspect previous reviews conducted on psychological treatments for schizophrenia to check if some studies meet our inclusion criteria as well. In addition, we will contact the first author of each included study published in the last 30 years for missing information about their studies.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Citavi; duplicates will be excluded. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently inspect title and abstracts identified in the literature searches, and exclude those not pertinent. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection and the article will proceed to the next stage;
2. Once the full articles are obtained, two reviewers will independently assess them for eligibility. Disagreements will be resolved by discussion, and, if needed, a third senior author will be involved. When required, further information will be obtained from study authors.

Data extraction

Two authors will independently extract data from all selected trials. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient we will contact the study authors.

The following data will be collected from each included study:

- Study citation, year(s) of study, registration number to trials registries, year of publication, location, setting, number of centers, sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Methodology, including study design (type of RCT), number of arms, risk of bias (see below);
- Characteristics of study participants, including gender, age, details on diagnosis, number randomized to each arm, sociodemographic characteristics, whether psychological treatments naïve at baseline, or with previous experience with the experimental intervention);
- Characteristics of intervention, including number and frequency of sessions, therapy setting, expertise of therapist, researcher allegiance at study arm level;
- Outcome measures, including information on whether an Intention to Treat (ITT) approach has been used and how it was defined.

The two reviewers will independently input data into an Access database especially created for this study. The software will automatically detect any inconsistencies, and they will be resolved by discussion.

Measurement of treatment effect

Relative treatment effects

- Continuous outcomes: For continuous outcomes we will use the standardized mean difference (SMD), because we expect that the studies use different rating scales of overall schizophrenia symptomatology.
- Dichotomous outcomes: The effect size for dichotomous outcomes will be the risk ratio (RR) and its 95% confidence intervals (CIs).

Relative treatment ranking

We will estimate the probability for each intervention to be ranked at each possible place, given the relative effect sizes as estimated in NMA. As described in Salanti et al (43) we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options.

Dealing with missing outcome data and missing statistics

For continuous outcomes we will extract data for all randomized patients if possible, and we will give preference to data based on mixed-effect models of repeated measurements of multiple imputations over last-observation-carried-forward data.

We will use published standard deviations (SDs), where available. When standard errors instead of SDs are presented, the former will be converted to SDs (44). If both are missing we will estimate SDs from p-values or confidence intervals, as described in Section 7.7.3 of the Cochrane Handbook for Systematic Reviews (45). If none of these options is viable we will contact the original authors. When no information can be obtained we will derive SDs from those of the other studies using a validated imputation technique (44).

For dichotomous outcomes, everyone allocated to the intervention will be counted whether they completed the follow up or not. If the authors applied such a strategy, we will use their results. If the original authors presented only the results of the per-protocol or completer population, we will assume that those participants lost to follow-up would not have changed in a given outcome. In terms of efficacy this means that they would be conservatively considered to have not responded to treatment or control. In terms of tolerability it would mean that participants would not have developed a side-effect.

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool (45, 46). The following domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants: was knowledge of the allocated treatment adequately prevented during the study? Given the peculiarity of the included studies, in which the therapist cannot be blind, we will consider under this item only if a way was found to keep patients unaware of the treatment they were receiving (even if we expect this will not be likely);
4. Blinding of outcome assessors: were outcome evaluated by blind raters? Were adequate measures taken to prevent them to discover treatment allocation during the study?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective reporting: are reports of the study free from suggestion of selective outcome reporting?
7. Researcher's allegiance: do the researchers involved have a vested interest for the psychological treatment under investigation? We will additionally consider this point as possible source of bias, since it has been claimed to be relevant in trials on psychological interventions (47, 48, 49). An evaluation of high risk of bias will be given, for example, when the authors are founders of the therapy or have written a manual for that therapy.

A description of what was reported about the same domains in each study will be provided, and a judgement on the risk of bias will be made for each one of them, based on the following three categories: 'high risk of bias', 'low risk of bias' and 'unclear risk of bias' where information are not sufficient to make a judgement. Two independent review authors will assess the risk of bias in selected studies. Any disagreement will be resolved through discussion. Where necessary, the authors of the studies will be contacted for further information. Studies will be classified as having low risk of bias if none of the domains above was rated as high risk of bias and three or less were rated as unclear risk; moderate if one was rated as high risk of bias or none was rated as high risk of bias but four or more were rated as unclear risk, and all other cases will be assumed to pertain to high risk of bias (50). We will not include studies in the data analyses whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week). Effects of high risk of bias in the other domains will be analyzed by sensitivity analyses.

Data analysis

Characteristics of the included studies

We will produce descriptive statistics and study population characteristics across all eligible trials, describing the types of comparisons and other clinical or methodological variables, such as age, duration of illness, co-medication, country, duration of study and number of session.

Two-step procedure

In a first step we will perform series of conventional pair-wise meta-analyses by combining studies that compared the same interventions, including the comparison between active treatments and the different control arms. In subgroups with very few RCTs available or if the requirements of network meta-analysis are not met it can be that network meta-analysis will not be appropriate and in this case, conventional pairwise meta-analysis will be the most straightforward approach. As heterogeneity is likely, a random effects model will be used. In a second step we will then perform a network meta-analysis within a frequentist framework.

Assessment of heterogeneity

The heterogeneity (variability in relative treatment effects within the same treatment comparison) will be measured with the tau-squared (the variance of the random effects distribution). The heterogeneity variance will be assumed common across the various treatment comparisons (grouped by comparison type) and the empirical distributions will be used to characterize the amount of heterogeneity as low, moderate or high using the first and third quantiles (51–53). Potential reasons for heterogeneity will be explored by subgroup analysis (see below).

Assessment of the transitivity assumption

Joint analysis of treatments can be misleading if the network is substantially intransitive. We assume that patients who fulfill the inclusion criteria outlined in criteria for considering studies for this review section are equally likely to be randomised to any of the interventions that we plan to compare. We will need to investigate the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons (54). We have maximized the chances of transitivity in our network with regard to clinical variables by limiting our samples to participants with schizophrenia and excluding specific subgroups like first episode patients or patients with prevalent negative symptoms. Other clinical or methodological variables that may influence the

efficacy of psychological interventions include administration mode and frequency of the treatment (like number of sessions and experience of the therapist), baseline severity (see below, "Investigation of heterogeneity and inconsistency"), and blinding, which will also be assessed in sensitivity analyses. We will investigate if these variables are similarly distributed across studies grouped by comparison. The comparability of studies comparing the intervention with treatment as usual or waiting list conditions with those that provide head-to-head evidence will be examined carefully.

Network meta-analysis

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and can therefore provide estimates with maximum power and increased precision (55). If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers (refer Assessment of transitivity assumption section), we will conduct a random-effects NMA to synthesize all evidence for each outcome, and obtain a comprehensive ranking of all treatments. We will assume a single heterogeneity parameter for each network. We will present the summary SMDs or RRs for all pairwise comparisons in a league table. We will also estimate the prediction intervals to assess how much the common heterogeneity affects the relative effect with respect to the extra uncertainty anticipated in a future study. To rank the various treatments for each outcome, we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks.

Assessment of inconsistency

The strategical and conceptual evaluation of transitivity will be supplemented with a statistical evaluation of consistency, the agreement between direct and indirect evidence. We will employ local as well as global methods to evaluate consistency (56). Local methods detect 'hot spots' of inconsistency, evidence loops that are inconsistent or comparisons for which direct and indirect evidence disagree. We will employ a method that separates direct evidence from indirect evidence provided by the entire network and then evaluate the agreement of these two pieces of evidence (57). We will also evaluate consistency in the entire network by calculating the design-by-treatment interaction test and I-squared for network heterogeneity, inconsistency, and for both (58). Tests for inconsistency are known to have low power, and empirical evidence has suggested that 10% of evidence loops published in the medical literature are expected to be inconsistent (60). Therefore, interpretation of the statistical inference about inconsistency will be carried out with caution and possible sources of inconsistency will be explored even in the absence of evidence for inconsistency.

Investigation of heterogeneity and inconsistency

We expect small amounts of heterogeneity and inconsistency to be present given the variety of study settings we plan to include. The following potential effect modifiers of the primary outcome will be explored by subgroup analyses:

a) Number of sessions
b) Study duration
c) Setting: individual vs group
d) Expertise of the therapist
e) Baseline severity (PANSS or BPRS score at baseline)
f) Different types of patients, with a different clinical outline concerning symptoms (if identified).

Sensitivity analyses

We will explore the following sensitivity analyses by excluding:
a) studies in which the outcome assessor was not blind (open studies)
b) studies that presented only completer analyses
c) studies characterized as pertaining to high risk of bias
d) studies with high risk of bias in researchers' allegiance
e) studies focused on treatment resistant patients (study defined)
f) studies with a non-active comparison group.

Publication bias

We will first examine funnel plots of pairwise MAs if there are 10 or more studies included. We will also explore the association between study size and effect size with a comparison-adjusted funnel plot that has been adapted to network meta-analysis (59).

Evaluating the quality of the evidence

The quality of evidence contributing to each network estimate will be evaluated using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework specifically developed for network meta-analysis (56). We will characterize the credibility of a body of evidence based on the study limitations, imprecision, heterogeneity/inconsistency, indirectness, and publication bias.

Statistical software

The analysis and presentation of results will be performed using the Stata packages network and network_graphs, the R package netmeta.

ETHICS AND DISSEMINATION

This review does not require ethical approval. Findings will be published in peer reviewed scientific journals, granting open access, and the database will be made publicly available (in agreement with European Research Council Guidelines on Implementation of Open Access to Scientific Publications and Research Data (http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/oa-pilot/h2020-hi-erc-oa-guide_en.pdf).

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Authors' contributions: IB and SL designed this study, drafted and critically revised the protocol. IB will screen search results for inclusion, conduct data extraction and data analysis, and draft the final manuscript. SL will assist with data extraction and analysis, and revise the final manuscript. CR and SW will screen search results for inclusion and conduct data extraction. GS provided substantial methodological advice in planning the study, and will assist with data analysis. CB and TF contributed with clinical and methodological input in planning the study. All authors contributed to and have approved the final manuscript.

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Competing interests: SL in the past 3 years has received honoraria for consulting from Roche, TEVA, Otsuka, Lundbeck, and LB Pharma; for lectures from Otsuka, Lundbeck, Janssen, ICON, Lilly, Sanofi Aventis, AOP Orphan, Roche, and Servier; and for a publication from Roche. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer and consultancy fees from Takeda Science Foundation. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Mitsubishi-Tanabe.

Search terms for Pubmed

("Schizophrenia"[Mesh] OR "Paranoid Disorders"[Mesh] OR schizo*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract]) AND ("Psychotherapy"[Mesh] or "Behavior Therapy"[Mesh] or "Cognitive Therapy"[Mesh] or "Complementary Therapies"[Mesh] or "Psychoanalysis"[Mesh] or "Counseling"[Mesh] or "Hypnosis"[Mesh] or "Association"[Mesh] or "Association Learning"[Mesh] OR abreaction[Title/Abstract] OR "acceptance[Title/Abstract] AND commitment therapy"[Title/Abstract] OR "acting out"[Title/Abstract] OR adlerian[Title/Abstract] OR "analytical psychotherapy"[Title/Abstract] OR "analytical psychotherapies"[Title/Abstract] OR "anger control"[Title/Abstract] OR "anger management"[Title/Abstract] OR "animal therapy"[Title/Abstract] OR "animal therapies"[Title/Abstract] OR "art therapy"[Title/Abstract] OR "art therapies"[Title/Abstract] OR "assertive training"[Title/Abstract] OR "assertiveness training"[Title/Abstract] OR "attention training technique"[Title/Abstract] OR "autogenic training"[Title/Abstract] OR autosuggestion[Title/Abstract] OR "aversion therapy"[Title/Abstract] OR "aversion therapies"[Title/Abstract] OR "balint group"[Title/Abstract] OR befriending[Title/Abstract] OR "behavior contracting"[Title/Abstract] OR "behavior modification"[Title/Abstract] OR "behavior regulation"[Title/Abstract] OR "behavior therapy"[Title/Abstract] OR "behavior therapies"[Title/Abstract] OR "behaviour contracting"[Title/Abstract] OR "behaviour modification"[Title/Abstract] OR "behaviour regulation"[Title/Abstract] OR "behaviour therapy"[Title/Abstract] OR "behaviour therapies"[Title/Abstract] OR bibliotherapy[Title/Abstract] OR bibliotherapies[Title/Abstract] OR biofeedback[Title/Abstract] OR "body psychotherapy"[Title/Abstract] OR "body psychotherapies"[Title/Abstract] OR "brief psychotherapy"[Title/Abstract] OR "brief psychotherapies"[Title/Abstract] OR "caregiver support"[Title/Abstract] OR cbt[Title/Abstract] OR "client centre"[Title/Abstract] OR "client center"[Title/Abstract] OR "cognitive behavior"[Title/Abstract] OR "cognitive behaviorial"[Title/Abstract] OR "cognitive intervention"[Title/Abstract] OR "cognitive interventions"[Title/Abstract] OR "cognitive rehabilitation"[Title/Abstract] OR "cognitive remediation"[Title/Abstract] OR "cognitive technique"[Title/Abstract] OR "cognitive techniques"[Title/Abstract] OR "cognitive therapy"[Title/Abstract] OR "cognitive therapies"[Title/Abstract] OR "cognitive treatment"[Title/Abstract] OR "cognitive treatments"[Title/Abstract] OR "color therapy"[Title/Abstract] OR "color therapies"[Title/Abstract] OR "colour therapy"[Title/Abstract] OR "colour therapies"[Title/Abstract] OR "compassionate mind training"[Title/Abstract] OR "conjoint therapy"[Title/Abstract] OR "conjoint therapies"[Title/Abstract] OR "contingency management"[Title/Abstract] OR "conversational therapy"[Title/Abstract] OR "conversational therapies"[Title/Abstract] OR "conversion therapy"[Title/Abstract] OR "conversion therapies"[Title/Abstract] OR "coping skills"[Title/Abstract] OR counseling[Title/Abstract] OR counselling[Title/Abstract] OR countertransference[Title/Abstract] OR "couples therapy"[Title/Abstract] OR "couples therapies"[Title/Abstract] OR "covert sensitization"[Title/Abstract] OR "covert sensitisation"[Title/Abstract] OR "crisis intervention"[Title/Abstract] OR "dance therapy"[Title/Abstract] OR "dance therapies"[Title/Abstract] OR dialectic[Title/Abstract] OR dialectical[Title/Abstract] OR "dream analysis"[Title/Abstract] OR eclectic[Title/Abstract] OR "emotion focused"[Title/Abstract] OR "emotionally focused"[Title/Abstract] OR "emotional freedom technique"[Title/Abstract] OR "encounter group therapy"[Title/Abstract] OR "encounter group therapies"[Title/Abstract] OR "existential therapy"[Title/Abstract] OR "existential therapies"[Title/Abstract] OR "experiential

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 (title)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16-17
Sponsor	5b	Provide name for the review funder and/or sponsor	16-17
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	16-17
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9, 11, 12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12, 13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized controlled trials

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Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction

There is rising awareness that we need multi-disciplinary approaches integrating psychological treatments for schizophrenia, but a comprehensive evidence base on their relative efficacy is lacking. We will conduct a network meta-analysis (NMA), integrating direct and indirect comparisons from randomised controlled trials (RCTs) to rank psychological treatments for schizophrenia according to their efficacy, acceptability and tolerability.

Methods and analysis

We will include all RCTs comparing a psychological treatment aimed at positive symptoms of schizophrenia with another psychological intervention or with a no treatment condition (waiting list, treatment as usual). We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. first episode patients, or patients with psychiatric comorbidities). Primary outcome will be the change in positive symptoms on a published rating scale. Secondary outcomes will be acceptability (dropout), change in overall and negative symptoms of schizophrenia, response, relapse, adherence, depression, quality of life, functioning and adverse events. Published and unpublished studies will be sought through database searches, trial registries and websites. Study selection and data extraction will be conducted by at least two independent reviewers. We will conduct random-effects NMA to synthesize all evidence for each outcome and obtain a comprehensive ranking of all treatments. NMA will be conducted in Stata and R within a frequentist framework. The risk of bias in studies will be evaluated using the Cochrane Risk of Bias tool and the credibility of the evidence will be evaluated using an adaptation of the GRADE framework to NMA, recommended by the Cochrane guidance. Subgroup and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination

No ethical issues are foreseen. Results from this study will be published in peer-reviewed journals and presented at relevant conferences.

PROSPERO registration number: CRD42017067795

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will conduct a random-effects network meta-analysis to synthesize all available published or unpublished randomized controlled trials for each pre-specified outcome, and obtain a comprehensive ranking of all treatments.
- This will be the first network meta-analysis on psychological treatments for schizophrenia; the findings from this study have the potential to inform and influence clinical decision-making and guideline development.
- The risk of heterogeneity and inconsistency is high, given the different psychological interventions that will be included: however, we try to control variability by carefully framing the inclusion criteria about population and interventions, and we will evaluate consistency employing local as well as global methods.

- The limitations of primary studies will be addressed with the Cochrane risk of bias tool and the quality of evidence for network estimates will be assessed with an appropriate adaptation of the GRADE framework; these approaches are considered the gold standard for critical appraisal of evidence quality.

INTRODUCTION

Schizophrenia is a debilitating, and often life-long disorder that ranks among the top 20 causes of disability according to the World Health Report (1). Although pharmacological interventions have been the mainstay of treatment for schizophrenia, antipsychotics have a number of limitations (limited response, high incidence of disabling side effects, poor adherence to treatment) (2) and are problematic in many situations (such as medical comorbidities, tolerability problems and pregnancy). Besides, there has been growing recognition of the importance of psychological processes in psychosis, both as contributors to onset and persistence, and in terms of the negative psychological impact of a diagnosis of schizophrenia on the individual's well-being, psychosocial functioning and life opportunities. Psychological interventions for psychosis and schizophrenia have been developed to address these aspects, and, in accordance with guidelines from the National Institute for Health and Care Excellence in the United Kingdom (3) and the Schizophrenia Patient Outcomes Research Team in the United States (4), psychological treatments are widely regarded as a necessary intervention for schizophrenia.

A broad range of interventions that can be defined as "psychological" have been studied in the treatment of schizophrenia. These interventions can be provided at different stages of the illness and address different aspects, like social and cognitive functioning, adherence to medication and symptoms of schizophrenia. Table 1 presents the panorama of existing systematic reviews of randomized controlled trials that have been conducted on the topic. These reviews have mainly included studies comparing the intervention under examination with so called no treatment conditions (waiting-list, treatment as usual (TAU)) (5, 6). Other reviews included also active comparisons with other psychological treatments (7–9). An attempt to provide information on active comparisons was made by Turner and colleagues, who performed separate meta-analysis when there were at least five eligible randomized controlled trials comparing one intervention to another psychological intervention (10). However, all the available reviews applied pairwise meta-analysis as a method, being able to pool results only when a comparison of two treatments was considered in existing studies. The comparative efficacy and tolerability of the existing interventions has not been checked yet; as a result, it is still currently unclear which are the most efficacious, the most acceptable and the best tolerable psychological treatments for schizophrenia.

To overcome this gap in the current knowledge, a network meta-analysis would be necessary to consider both direct and indirect comparisons, and produce hierarchies of the effects of the various psychological treatments in the various efficacy and tolerability outcomes. Such hierarchies are essential for guidelines, which should ideally be able to indicate which treatment is likely to be the best, the second best and so on for a given outcome. Only the method of network meta-analysis can provide such hierarchies by combining all the randomised evidence. Our aim is to produce such a network meta-analysis of all psychological interventions for schizophrenia in multiple outcomes. We focus here on the interventions primarily aimed at treating positive symptoms in the acute phase of the illness.

Intervention	Existing reviews	RCT*	Comparator
Acceptance and commitment therapy	Ongoing Cochrane review (11)	-	TAU, pharmacological intervention, another psychosocial intervention
Adherence interventions	Gray 2016 (12)	6	TAU, didactic health education
Active comparisons (Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling)	Turner 2014 (10)	48	Befriending, CBT, Cognitive remediation, Psychoeducation, Social skills training, Supportive counseling, Family intervention, Art therapy, Body psychotherapy, Occupational therapy, Problem-solving therapy
Art therapy	Ruddy 2005 (6)	2	Standard care
Assertive community treatment	Marshall 1998 (13)	20**	TAU, hospital-based rehabilitation, case management
Befriending	-		
Bibliotherapy	-		
Body oriented psychological therapy	-		
Case management	Dieterich 2017 (14)	40**	Assertive Community Treatment, Assertive Outreach model, Case Management model, standard community care
Cognitive behavioural therapy	Zimmermann 2005 (positive symptoms) (9)	15	Waiting-list, TAU or another therapeutic treatment
	Jones 2012 (7)	20	Active (Psychoeducation, Family Intervention, Supportive Psychotherapy, Supportive Counselling, Cognitive Remediation) and nonactive control treatments (Recreation and support, social activities, befriending, non-specific counselling)
	Jauhar 2013 (15)	52	Waiting list, TAU or an intervention designed to control for the non-specific effects of psychotherapy (recreation and support, group support, befriending, supportive counselling/therapy, social activity therapy and goal-focused supportive contact) or active treatments (cognitive remediation, psychoeducation)
	Van der Gaag 2014 (individually tailored) (16)	18	Any control condition was accepted
	Hazell 2016 (low intensity) (17)	8	TAU, supportive psychotherapy
	Kennedy 2016 (auditory hallucinations) (18)	2	Non-specialized therapy (focused on supportive interactions and social integration)
Cognitive remediation	Cella 2016 (19)	45	TAU, active control (e.g. computer games) another active treatment (e.g. CBT)
Dance therapy	Ren 2013 (20)	1	Standard care plus supportive counselling
Family interventions	Pitschel-Walz 2001 (21)	25	TAU, patient intervention, other family interventions
	Pharoah 2006 (22)	25	TAU, discussion groups, psychoeducation, supportive psychotherapy, psychosocial support
Group psychotherapeutic treatments	Orfanos 2015 (23)	34	TAU, other groups (active discussion group, support group, counselling group, occupational

			therapy group or problem-solving discussion group)
Integrated psychological Therapy (IPT)	Roder 2006 (24)	16	TAU, placebo-attention condition, other active treatments
Psychological and psychosocial interventions for negative symptoms in psychosis	Lutgens 2017 (8)	95	TAU, active comparator (including psychoeducation, supportive therapy, cognitive remediation)
Metacognitive training	Eichner 2016 (25)	12	TAU, Wait list control, Supportive Therapy, Newspaper discussion group, CogPack (=Cognitive remediation)
Mindfulness	Aust 2017 (26)	11**	Active control intervention (e.g. Befriending, Progressive Muscle Relaxation), TAU
Music therapy	Geretsegger 2017 (27)	18	Placebo defined as an alternative therapy designed to control for effects of the therapist's attention; TAU or no treatment
Psychodynamic therapy	Malmberg 2012 (28)	4	Reality-adaptive, supportive psychotherapy, Hospital comparison, Ataraxic drugs, electro convulsive therapy, Milieu therapy, individual vs. group
Psychoeducation	Pekkala 2006 (29)	10	TAU, supportive psychotherapy, behavioral intervention, leisure-time group
Social skills training	Almerie 2015 (30)	13	TAU, structured activities, discussion group, interaction group, no treatment control
Supportive therapy	Buckley 2015 (31)	24	Standard care, any other treatment (biological, psychological or social) such as medication, problem-solving therapy, psychoeducation, social skills training, CBT, family therapy or psychodynamic psychotherapy
Systemic therapy	Pinquart 2016 (5)	7	No treatment

Table 1. Existing reviews about psychological treatments for schizophrenia.
RCT: randomized controlled trial; TAU: treatment as usual.
*number of RCTs on schizophrenic patients; **RCTs about patients with severe mental illness including schizophrenia

Objectives

To estimate relative treatment effects and obtain a hierarchy for the psychological treatments in patients with schizophrenia, in terms of:

1. Efficacy on positive symptoms
2. Acceptability
3. Other efficacy measures, such as overall symptoms, negative symptoms, response, relapse, adherence, depression, quality of life, functioning
4. Tolerability.

METHODS AND ANALYSIS

Criteria for considering studies for this review

Methods for this systematic review have been developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions (32, 33). This systematic review and NMA is registered in the PROSPERO database

(registration number: CRD42017067795); the record in PROSPERO will be updated with any amendment made to the protocol.

Types of studies

We will include all randomised trials (RCTs) in which participants with schizophrenia received a psychological intervention as defined below (see *Types of interventions*). Studies whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week) will be excluded. We will accept open and blinded RCTs; this choice is particularly relevant in trials on psychological interventions, in which in best case only the assessor of outcome can be blind, but not the therapist. Open RCTs will be excluded in a sensitivity analysis. We will include both trials in which psychological interventions were compared with a control condition and trials in which they were compared with another intervention. There will be no language restriction in order to avoid the problem of 'language bias' (34). In case we retrieve references in languages in which we are not fluent, study authors will be contacted to check inclusion criteria and eventually ask for study data. As an exception, we will not search Chinese databases, since serious concerns have been raised on the trustworthiness of Chinese trials found in these databases (35, 36). Chinese studies found in Western databases will be considered for inclusion. In the case of cross-over studies we will use only the first cross-over phase in order to avoid the problem of carry-over effects which are very likely in schizophrenia and with psychological treatments. We will exclude cluster randomized trials.

Types of participants

Our aim is to collect information on the efficacy of psychological treatments on patients with positive symptoms. In order to select this population, we operationalized the inclusion criteria as follows. We will include adults, however defined by study authors, with a diagnosis of schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders); there is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (37). We will include trials irrespective of the diagnostic criteria used. Here we will follow the strategy of the Cochrane Schizophrenia Group (38) to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-V, because these criteria are not meticulously used in clinical routine either. This decision should increase generalizability and representativeness.

Studies including participants with other diagnoses part of the psychosis spectrum will be included only if participants with a diagnosis of schizophrenia, schizophreniform or schizoaffective disorders were more than 80% of the participants considered. We will include studies recruiting patients with positive symptoms, either delusions, hallucinations or both, or in the phase of acute exacerbation of positive symptoms, however defined by inclusion criteria of the trial.

We will exclude studies focused on specific subpopulations of patients, such as (1) studies recruiting patients in which negative symptoms are predominant, according to authors' definition, (2) studies on patients with comorbid psychiatric disorders including substance abuse, (3) studies recruiting patients with concomitant medical illnesses, (4) trials enrolling stable patients (relapse prevention studies), (5) studies on first episode patients, (6) trials on patients who show prodromal signs of psychosis (also defined as "at risk for psychosis"). Among other reasons, we exclude first episode patients because they were found to have significantly higher response rates to treatments compared to chronic patients (39, 40).

Types of interventions

Any psychological intervention that occurs through interaction between therapist and patient, either face-to-face individually or in group, with the primary aim to reduce positive symptoms. Interventions with an explicit primary aim different from positive symptoms (e.g. functioning, cognition, adherence to medication, knowledge of the illness) will be excluded. The identified treatments will be classified after identification of eligible studies. Psychological treatments will be compared to each other and to any non-pharmacological control condition considered in the included studies. Comparators will include the so called "treatment as usual", waiting list and inactive treatments. The effect of "non-active" comparators will be analysed in a sensitivity analysis (41). Patients also receiving treatment as usual, including pharmacological interventions, will be included. If psychological treatments that we do not include among the interventions (e.g. psychoeducation, supportive therapy) are used as control condition in the studies, they will be included as nodes in order to strengthen the network, but will not be part of our decision set.

Outcome measures

Outcomes will be measured at study endpoint, as defined in each study.

Primary outcome

Change in positive symptoms of schizophrenia, examined accordingly to the respective subscale of the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) or the Scales for Assessment of Positive Symptoms (SAPS) or any other published scale.

As not all studies will have used the same scale, we will extract data according to the following hierarchy: mean change of the PANSS positive symptoms subscale from baseline to endpoint, if not available mean change of the BPRS positive symptoms subscale, or if again not available the mean values at endpoint of the PANSS/BPRS positive symptoms subscale. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal, because it has been shown that non-validated schizophrenia scales exaggerate differences (42).

Secondary outcomes

Given the focus on treatments for positive symptoms, the results of this review will be informative for the treatment of positive symptoms. They will also describe how these interventions can have an effect on a number of other outcomes. With this aim, the following secondary outcomes will be assessed:

1. Acceptability, defined as the percentage of patients leaving the study early ('dropout') for any reason. All-cause discontinuation due to any reason combines efficacy, tolerability, and other factors and can therefore be considered as a measure of 'acceptability of treatment' (38) or of overall "effectiveness";
2. Change in overall symptoms, measured by rating scales such as the PANSS or the BPRS, or any other published scale (e.g. the Manchester Scale) for the assessment of overall schizophrenic symptomatology. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal;

3. Change in negative symptoms, measured by the respective subscale of the PANSS, or the "Scales for Assessment of Negative Symptoms" (SANS) or any other published scale;
4. Response, measured by the percentage of responders defined by reduction on the PANSS, BPRS or CGI scores, accepting the criteria used by study authors;
5. Percentage of patients with relapse, by definitions operationalized by rating scales, and, if not available, number of rehospitalisations due to psychopathology. We will not include data from studies that used non-operationalized relapse criteria (e.g. "clinical judgement");
6. Adherence, measured by any published rating scale (e.g. "Adherence Therapy Patients Satisfaction Questionnaire", "Adherence Rating Scale");
7. Depression, measured by the Calgary Depression Scale for Schizophrenia, the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Scale or other published symptom scales;
8. Quality of life, measured by any published rating scale (e.g. "Heinrichs quality of life scale", Quality of Life Scale (QOLS);
9. Functioning, measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale, or any other published rating scale.
10. Tolerability, measured as the percentage of patients experiencing adverse events. Adverse events associated with psychological treatments are not covered as comprehensively as in trials on pharmacological treatments (43). However, there is a raising awareness of the importance of considering possible harms associated with psychological interventions (44). Therefore we will collect any available information in clinical studies about this outcome, using a classification proposed by Linden and colleagues (44): a) emergence of new symptoms; b) deterioration of existing symptoms; c) lack of improvement or deterioration of illness; d) prolongation of treatment; e) patient's non-compliance; f) strains in the patient-therapist relationship; g) very good patient-therapist relationship, therapy dependency; h) strains or changes in family relations; i) strains or changes in work relations; l) any change in the life circumstances of the patient; m) stigmatization. Suicide attempts and any other possible adverse event related to psychological treatment will also be considered.
11. Mortality. Psychosocial treatments may actually reduce or, by contrast, increase overall mortality, in particular connected to suicidality. To test this, we will examine this outcome in terms of a) death for any reason, b) death due to natural causes and c) due to suicide.

Search strategy

Electronic searches

The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PUBMED. The search terms that will be used for PubMed are provided as Supplement material. We will also search the following international databases:

1. WHO International Clinical Trials Registry Platform (ICTRP)
2. BIOSIS
3. Cochrane Collaboration Controlled Trials Register
4. ClinicalTrials.gov.

Reference lists and other sources

References of all selected studies will be inspected for other published reports and citations of unpublished studies. We will also inspect previous reviews conducted on psychological treatments for schizophrenia to check if some studies meet our inclusion criteria as well. In addition, we will contact the first author of each included study published in the last 30 years for missing information about their studies.

Identification and selection of studies

Studies identified through electronic and manual searches will be listed with citation, titles and abstracts, in Citavi; duplicates will be excluded. The eligibility for inclusion process will be conducted in two separate stages:

1. Two authors will independently inspect title and abstracts identified in the literature searches, and exclude those not pertinent. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection and the article will proceed to the next stage;
2. Once the full articles are obtained, two reviewers will independently assess them for eligibility. Disagreements will be resolved by discussion, and, if needed, a third senior author will be involved. When required, further information will be obtained from study authors.

Data extraction

Two authors will independently extract data from all selected trials. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient we will contact the study authors.

The following data will be collected from each included study:

- Study citation, year(s) of study, registration number to trials registries, year of publication, location, setting, number of centers, sample size, diagnostic criteria, funding/sponsor (industry or academic);
- Methodology, including study design (type of RCT), number of arms, risk of bias (see below);
- Characteristics of study participants, including gender, age, details on diagnosis, number randomized to each arm, sociodemographic characteristics, whether psychological treatments naïve at baseline, or with previous experience with the experimental intervention);
- Characteristics of intervention, including number and frequency of sessions, therapy setting, expertise of therapist, researcher allegiance at study arm level;
- Outcome measures, including information on whether an Intention to Treat (ITT) approach has been used and how it was defined.

The two reviewers will independently input data into an Access database especially created for this study. The software will automatically detect any inconsistencies, and they will be resolved by discussion.

Measurement of treatment effect

Relative treatment effects

- Continuous outcomes: For continuous outcomes we will use the standardized mean difference (SMD), because we expect that the studies use different rating scales of overall schizophrenia symptomatology.

- Dichotomous outcomes: The effect size for dichotomous outcomes will be the risk ratio (RR) and its 95% confidence intervals (CIs).

Relative treatment ranking

We will estimate the probability for each intervention to be ranked at each possible place, given the relative effect sizes as estimated in NMA. As described in Salanti et al (45) we will obtain a hierarchy of the competing interventions using the Surface Under the Cumulative Ranking curve (SUCRA) and mean ranks. SUCRA values will be expressed as percentage, showing the relative probability of an intervention to be among the best options.

Dealing with missing outcome data and missing statistics

For continuous outcomes we will extract data for all randomized patients if possible, and we will give preference to data based on mixed-effect models of repeated measurements of multiple imputations over last-observation-carried-forward data.

We will use published standard deviations (SDs), where available. When standard errors instead of SDs are presented, the former will be converted to SDs (46). If both are missing we will estimate SDs from p-values or confidence intervals, as described in Section 7.7.3 of the Cochrane Handbook for Systematic Reviews (47). If none of these options is viable we will contact the original authors. When no information can be obtained we will derive SDs from those of the other studies using a validated imputation technique (46).

For dichotomous outcomes, everyone allocated to the intervention will be counted whether they completed the follow up or not. If the authors applied such a strategy, we will use their results. If the original authors presented only the results of the per-protocol or completer population, we will assume that those participants lost to follow-up would not have changed in a given outcome. In terms of efficacy this means that they would be conservatively considered to have not responded to treatment or control. In terms of tolerability it would mean that participants would not have developed a side-effect.

Risk of bias assessment

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool (47, 48). The following domains will be considered:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants: was knowledge of the allocated treatment adequately prevented during the study? Given the peculiarity of the included studies, in which the therapist cannot be blind, we will consider under this item only if a way was found to keep patients unaware of the treatment they were receiving (even if we expect this will not be likely);
4. Blinding of outcome assessors: were outcome evaluated by blind raters? Were adequate measures taken to prevent them to discover treatment allocation during the study?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective reporting: are reports of the study free from suggestion of selective outcome reporting?
7. Researcher's allegiance: do the researchers involved have a vested interest for the psychological treatment under investigation? We will additionally consider this point as possible source of bias, since it has been claimed to be relevant in trials on psychological interventions (49)(50, 51). An

evaluation of high risk of bias will be given, for example, when the authors are founders of the therapy or have written a manual for that therapy.

A description of what was reported about the same domains in each study will be provided, and a judgement on the risk of bias will be made for each one of them, based on the following three categories: 'high risk of bias', 'low risk of bias' and 'unclear risk of bias' where information are not sufficient to make a judgement. Two independent review authors will assess the risk of bias in selected studies. Any disagreement will be resolved through discussion. Where necessary, the authors of the studies will be contacted for further information. Studies will be classified as having low risk of bias if none of the domains above was rated as high risk of bias and three or less were rated as unclear risk; moderate if one was rated as high risk of bias or none was rated as high risk of bias but four or more were rated as unclear risk, and all other cases will be assumed to pertain to high risk of bias (52). We will not include studies in the data analyses whose sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week). Effects of high risk of bias in the other domains will be analyzed by sensitivity analyses.

Data analysis

Characteristics of the included studies

We will produce descriptive statistics and study population characteristics across all eligible trials, describing the types of comparisons and other clinical or methodological variables, such as age, duration of illness, co-medication, country, duration of study and number of session.

Two-step procedure

In a first step we will perform series of conventional pair-wise meta-analyses by combining studies that compared the same interventions, including the comparison between active treatments and the different control arms. In subgroups with very few RCTs available or if the requirements of network meta-analysis are not met it can be that network meta-analysis will not be appropriate and in this case, conventional pairwise meta-analysis will be the most straightforward approach. As heterogeneity is likely, a random effects model will be used. In a second step we will then perform a network meta-analysis within a frequentist framework.

Assessment of heterogeneity

The heterogeneity (variability in relative treatment effects within the same treatment comparison) will be measured with the tau-squared (the variance of the random effects distribution). The heterogeneity variance will be assumed common across the various treatment comparisons (grouped by comparison type) and the empirical distributions will be used to characterize the amount of heterogeneity as low, moderate or high using the first and third quantiles (53–55). Potential reasons for heterogeneity will be explored by subgroup analysis (see below).

Assessment of the transitivity assumption

Joint analysis of treatments can be misleading if the network is substantially intransitive. We assume that patients who fulfill the inclusion criteria outlined in criteria for considering studies for this review section are equally likely to be randomised to any of the interventions that we plan to compare. We will need to investigate the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons (56). We have maximized the chances of

transitivity in our network with regard to clinical variables by limiting our samples to participants with schizophrenia and excluding specific subgroups like first episode patients or patients with prevalent negative symptoms. Other clinical or methodological variables that may influence the efficacy of psychological interventions include administration mode and frequency of the treatment (like number of sessions and experience of the therapist), baseline severity (see below, "Investigation of heterogeneity and inconsistency"), and blinding, which will also be assessed in sensitivity analyses. We will investigate if these variables are similarly distributed across studies grouped by comparison. The comparability of studies comparing the intervention with treatment as usual or waiting list conditions with those that provide head-to-head evidence will be examined carefully.

Network meta-analysis

Network meta-analysis combines direct and indirect evidence for all relative treatment effects and can therefore provide estimates with maximum power and increased precision (57). If the collected studies appear to be sufficiently similar with respect to the distribution of effect modifiers (refer Assessment of transitivity assumption section), we will conduct a random-effects NMA to synthesize all evidence for each outcome, and obtain a comprehensive ranking of all treatments. We will assume a single heterogeneity parameter for each network. We will present the summary SMDs or RRs for all pairwise comparisons in a league table. We will also estimate the prediction intervals to assess how much the common heterogeneity affects the relative effect with respect to the extra uncertainty anticipated in a future study. To rank the various treatments for each outcome, we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks.

Assessment of inconsistency

The strategical and conceptual evaluation of transitivity will be supplemented with a statistical evaluation of consistency, the agreement between direct and indirect evidence. We will employ local as well as global methods to evaluate consistency (58). Local methods detect 'hot spots' of inconsistency, evidence loops that are inconsistent or comparisons for which direct and indirect evidence disagree. We will employ a method that separates direct evidence from indirect evidence provided by the entire network and then evaluate the agreement of these two pieces of evidence (59). We will also evaluate consistency in the entire network by calculating the design-by-treatment interaction test and I-squared for network heterogeneity, inconsistency, and for both (60). Tests for inconsistency are known to have low power, and empirical evidence has suggested that 10% of evidence loops published in the medical literature are expected to be inconsistent (61). Therefore, interpretation of the statistical inference about inconsistency will be carried out with caution and possible sources of inconsistency will be explored even in the absence of evidence for inconsistency.

Investigation of heterogeneity and inconsistency

We expect small amounts of heterogeneity and inconsistency to be present given the variety of study settings we plan to include. The following potential effect modifiers of the primary outcome will be explored by subgroup analyses:

a) Number of sessions
b) Study duration
c) Setting: individual vs group
d) Expertise of the therapist
e) Baseline severity (PANSS or BPRS score at baseline)

f) Different types of patients, with a different clinical outline concerning symptoms (if identified).

Sensitivity analyses

We will explore the following sensitivity analyses by excluding:

a) studies in which the outcome assessor was not blind (open studies)

b) studies that presented only completer analyses

c) studies characterized as pertaining to high risk of bias

d) studies with high risk of bias in researchers' allegiance

e) studies focused on treatment resistant patients (study defined)

f) studies with a non-active comparison group.

Publication bias

We will first examine funnel plots of pairwise MAs if there are 10 or more studies included. We will also explore the association between study size and effect size with a comparison-adjusted funnel plot that has been adapted to network meta-analysis (62).

Evaluating the quality of the evidence

The quality of evidence contributing to each network estimate will be evaluated using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework specifically developed for network meta-analysis (58). We will characterize the credibility of a body of evidence based on the study limitations, imprecision, heterogeneity/inconsistency, indirectness, and publication bias.

Statistical software

The analysis and presentation of results will be performed using the Stata packages network and network_graphs, the R package netmeta.

ETHICS AND DISSEMINATION

This review does not require ethical approval. Findings will be published in peer reviewed scientific journals, granting open access, and the database will be made publicly available (in agreement with European Research Council Guidelines on Implementation of Open Access to Scientific Publications and Research Data (http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/oa-pilot/h2020-hi-erc-oa-guide_en.pdf).

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Authors' contributions: IB and SL designed this study, drafted and critically revised the protocol. IB will screen search results for inclusion, conduct data extraction and data analysis, and draft the final manuscript. SL will assist with data extraction and analysis, and revise the final manuscript. CR and SW will screen search results for inclusion and conduct data extraction. GS provided substantial methodological advice in planning the study, and will assist with data analysis. CB and TF contributed with clinical and methodological input in planning the study. All authors contributed to and have approved the final manuscript.

Collaborators: Samantha Roberts helped us to conduct the literature searches. Maximilian Huhn, Johannes Schneider-Thoma, Marc Krause and Costanza Carmi provided help and suggestions.

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Competing interests: SL in the past 3 years has received honoraria for consulting from Roche, TEVA, Otsuka, Lundbeck, and LB Pharma; for lectures from Otsuka, Lundbeck, Janssen, ICON, Lilly, Sanofi Aventis, AOP Orphan, Roche, and Servier; and for a publication from Roche. TAF has received lecture fees from Eli Lilly, Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer and consultancy fees from Takeda Science Foundation. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mochida and Mitsubishi-Tanabe.

Search terms for Pubmed

("Schizophrenia"[Mesh] OR "Paranoid Disorders"[Mesh] OR schizo*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract]) AND ("Psychotherapy"[Mesh] or "Behavior Therapy"[Mesh] or "Cognitive Therapy"[Mesh] or "Complementary Therapies"[Mesh] or "Psychoanalysis"[Mesh] or "Counseling"[Mesh] or "Hypnosis"[Mesh] or "Association"[Mesh] or "Association Learning"[Mesh] OR abreaction[Title/Abstract] OR "acceptance[Title/Abstract] AND commitment therapy"[Title/Abstract] OR "acting out"[Title/Abstract] OR adlerian[Title/Abstract] OR "analytical psychotherapy"[Title/Abstract] OR "analytical psychotherapies"[Title/Abstract] OR "anger control"[Title/Abstract] OR "anger management"[Title/Abstract] OR "animal therapy"[Title/Abstract] OR "animal therapies"[Title/Abstract] OR "art therapy"[Title/Abstract] OR "art therapies"[Title/Abstract] OR "assertive training"[Title/Abstract] OR "assertiveness training"[Title/Abstract] OR "attention training technique"[Title/Abstract] OR "autogenic training"[Title/Abstract] OR autosuggestion[Title/Abstract] OR "aversion therapy"[Title/Abstract] OR "aversion therapies"[Title/Abstract] OR "balint group"[Title/Abstract] OR befriending[Title/Abstract] OR "behavior contracting"[Title/Abstract] OR "behavior modification"[Title/Abstract] OR "behavior regulation"[Title/Abstract] OR "behavior therapy"[Title/Abstract] OR "behavior therapies"[Title/Abstract] OR "behaviour contracting"[Title/Abstract] OR "behaviour modification"[Title/Abstract] OR "behaviour regulation"[Title/Abstract] OR "behaviour therapy"[Title/Abstract] OR "behaviour therapies"[Title/Abstract] OR bibliotherapy[Title/Abstract] OR bibliotherapies[Title/Abstract] OR biofeedback[Title/Abstract] OR "body psychotherapy"[Title/Abstract] OR "body psychotherapies"[Title/Abstract] OR "brief psychotherapy"[Title/Abstract] OR "brief psychotherapies"[Title/Abstract] OR "caregiver support"[Title/Abstract] OR cbt[Title/Abstract] OR "client centre"[Title/Abstract] OR "client center"[Title/Abstract] OR "cognitive behavior"[Title/Abstract] OR "cognitive behaviorial"[Title/Abstract] OR "cognitive intervention"[Title/Abstract] OR "cognitive interventions"[Title/Abstract] OR "cognitive rehabilitation"[Title/Abstract] OR "cognitive remediation"[Title/Abstract] OR "cognitive technique"[Title/Abstract] OR "cognitive techniques"[Title/Abstract] OR "cognitive therapy"[Title/Abstract] OR "cognitive therapies"[Title/Abstract] OR "cognitive treatment"[Title/Abstract] OR "cognitive treatments"[Title/Abstract] OR "color therapy"[Title/Abstract] OR "color therapies"[Title/Abstract] OR "colour therapy"[Title/Abstract] OR "colour therapies"[Title/Abstract] OR "compassionate mind training"[Title/Abstract] OR "conjoint therapy"[Title/Abstract] OR "conjoint therapies"[Title/Abstract] OR "contingency management"[Title/Abstract] OR "conversational therapy"[Title/Abstract] OR "conversational therapies"[Title/Abstract] OR "conversion therapy"[Title/Abstract] OR "conversion therapies"[Title/Abstract] OR "coping skills"[Title/Abstract] OR counseling[Title/Abstract] OR counselling[Title/Abstract] OR countertransference[Title/Abstract] OR "couples therapy"[Title/Abstract] OR "couples therapies"[Title/Abstract] OR "covert sensitization"[Title/Abstract] OR "covert sensitisation"[Title/Abstract] OR "crisis intervention"[Title/Abstract] OR "dance therapy"[Title/Abstract] OR "dance therapies"[Title/Abstract] OR dialectic[Title/Abstract] OR dialectical[Title/Abstract] OR "dream analysis"[Title/Abstract] OR eclectic[Title/Abstract] OR "emotion focused"[Title/Abstract] OR "emotionally focused"[Title/Abstract] OR "emotional freedom technique"[Title/Abstract] OR "encounter group therapy"[Title/Abstract] OR "encounter group therapies"[Title/Abstract] OR "existential therapy"[Title/Abstract] OR "existential therapies"[Title/Abstract] OR "experiential

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treatments"[Title/Abstract] OR psychotherapy[Title/Abstract] OR psychotherapies[Title/Abstract] OR "psychotherapeutic counsel"[Title/Abstract] OR "psychotherapeutic counseling"[Title/Abstract] OR "psychotherapeutic counselling"[Title/Abstract] OR "psychotherapeutic processes"[Title/Abstract] OR "psychotherapeutic training"[Title/Abstract] OR "psychotherapeutic treatment"[Title/Abstract] OR "psychotherapeutic treatments"[Title/Abstract] OR "rational emotive"[Title/Abstract] OR "reality therapy"[Title/Abstract] OR "reality therapies"[Title/Abstract] OR "reciprocal inhibition"[Title/Abstract] OR rehabilitation[Title/Abstract] OR rehabilitating[Title/Abstract] OR "relationship therapy"[Title/Abstract] OR "relationship therapies"[Title/Abstract] OR relaxation[Title/Abstract] OR "reminiscence therapy"[Title/Abstract] OR "reminiscence therapies"[Title/Abstract] OR rogerian[Title/Abstract] OR "role play"[Title/Abstract] OR "role plays"[Title/Abstract] OR "role playing"[Title/Abstract] OR "self analysis"[Title/Abstract] OR "self analysing"[Title/Abstract] OR "self esteem"[Title/Abstract] OR "sensitivity training"[Title/Abstract] OR "sex therapy"[Title/Abstract] OR "sex therapies"[Title/Abstract] OR "sleep phase chronotherapy"[Title/Abstract] OR "sleep phase chronotherapies"[Title/Abstract] OR "social skills education"[Title/Abstract] OR "social skills training"[Title/Abstract] OR "socioenvironmental therapy"[Title/Abstract] OR "socioenvironmental therapies"[Title/Abstract] OR sociotherapy[Title/Abstract] OR sociotherapies[Title/Abstract] OR "solution focused"[Title/Abstract] OR "stress management"[Title/Abstract] OR "support group"[Title/Abstract] OR "support groups"[Title/Abstract] OR "supportive therapy"[Title/Abstract] OR "supportive therapies"[Title/Abstract] OR "systematic desensitization"[Title/Abstract] OR "systematic desensitisation"[Title/Abstract] OR "systemic therapy"[Title/Abstract] OR "systemic therapies"[Title/Abstract] OR "therapeutic community"[Title/Abstract] OR "therapeutic communities"[Title/Abstract] OR "transactional analysis"[Title/Abstract] OR transference[Title/Abstract] OR transtheoretical[Title/Abstract] OR "validation therapy"[Title/Abstract] OR "validation therapies"[Title/Abstract]) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh]))

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1 (title)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	5
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16-17
Sponsor	5b	Provide name for the review funder and/or sponsor	16-17
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	16-17
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9, 11, 12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12, 13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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