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Psychosocial treatments for relapse prevention in schizophrenia: study protocol for a systematic review and network meta-analysis of randomized evidence

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ABSTRACT

Introduction

There is evidence that different psychosocial interventions could reduce the risk of relapse in 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 psychosocial treatments for relapse prevention in schizophrenia according to their efficacy, acceptability and tolerability.

Methods and analysis

We will include all RCTs comparing a psychosocial treatment aimed at preventing relapse in patients with schizophrenia with another psychosocial 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. acutely ill patients). Primary outcome will be the number of patients experiencing a relapse. Secondary outcomes will be acceptability (dropout), change in overall, positive, negative and depressive symptoms, quality of life, adherence, 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 Published and unpublished studies will be sought through database searches, trial registries and websites.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 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 CINeMA. 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: [will be available at the time of publication]

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first network meta-analysis on psychosocial treatments for relapse prevention in schizophrenia; the findings from this study have the potential to inform and influence clinical decision-making and guideline development.
- The analysis will benefit from maximum statistical power by combining direct and indirect comparisons in a network meta-analysis, measuring the relative effects of the different treatments.
- There is risk of heterogeneity and inconsistency, given the different psychosocial interventions that will be included: however, we try to control variability by carefully framing the inclusion criteria about population, interventions and focus of the single studies, and we will evaluate consistency employing local as well as global methods.
- The limitations of individual studies will be addressed with the Cochrane risk of bias tool and the credibility of the results for the primary outcome will be assessed using the CINeMA web application, an adaptation of the GRADE framework; these approaches are considered the gold standard for critical appraisal of evidence quality.

INTRODUCTION

Schizophrenia is characterized by acute episodes often followed by symptom improvement (1), but requires generally maintenance treatment in order to prevent recrudescence of symptomatology.

A five-year analysis of 11291 patients with schizophrenia found a 13.4% rehospitalisation rate within one month, 38.9% within one year and 64.1% within 5 years (2).

Pharmacological interventions have been the mainstay of treatment for schizophrenia, and play an essential role also in the prevention of relapses. According to a recent meta-analysis of 65 randomised trials, patients treated with antipsychotics experienced a psychotic relapse within one year in the 27% of the cases (3).

Moreover, antipsychotics have a number of limitations (high incidence of disabling side effects, poor adherence to treatment) (3) and can be problematic in many situations (such as medical comorbidities, tolerability problems and pregnancy).

The resulting burden for patients, relatives and society is dramatic, because relapses often lead to costly hospitalisations, patients lose their jobs and relationships are challenged (4, 5).

In this context, psychosocial interventions might have an important role to reduce the risk of relapses.

Several systematic reviews and meta-analyses have examined the comparative efficacy and acceptability of psychosocial interventions from randomized controlled trials (RCTs) in schizophrenia considering relapses among other outcomes. Different interventions like family therapy (6), psychoeducation (7, 8) and cognitive behavioural therapy (9, 10) have been compared with so called no treatment conditions (waiting-list, treatment as usual (TAU)) (9, 7), and in some cases also with other psychosocial treatments pooled together (10, 6), showing promising results.

A review of 25 studies examining family interventions found a 20% reduction of relapse when involving the relatives in the treatment during maintenance phase (6).

Psychoeducation was found to be successful in reduction of relapses in a Cochrane review analysing 11 studies in the medium term and 6 studies in the long term comparing psychoeducation with standard care (RR 0.70, 95% CI 0.61 to 0.81; RR 0.73, 95% CI 0.62 to 0.85) (7); brief psychoeducation also showed positive results in the medium term for people with severe mental illnesses (8). Cognitive behavioural therapy was found to reduce relapse rates in the medium term when compared to standard care (9), but not when compared to other psychosocial therapies (10).

However, evidence is still fragmentary and a comprehensive ranking of all treatments evaluated in RCTs is lacking.

In fact, all the available reviews applied pairwise meta-analysis as a method, and can therefore provide information only on comparisons of two treatments that have been considered in existing studies, and several interventions lack of head-to-head comparisons. For example, both individual psychoeducation and family interventions have shown efficacy in the reduction of relapses, but the two have never been compared with each other.

As a result, it is still currently unclear which are the most efficacious, the most acceptable and the best tolerable psychosocial treatments for relapse prevention in schizophrenia. Better understanding of the comparative efficacy of these active treatments would be important for clinical practice and for meaningful allocation of resources.

To overcome this gap in the current knowledge, we will perform a network meta-analysis comparing all the interventions with each other and produce hierarchies of the effects of the various psychosocial treatments. 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.

Objectives

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

1. relapse and hospitalisations
2. other efficacy measures, such as overall symptoms, positive symptoms, negative symptoms, depression, quality of life, adherence, functioning
3. acceptability (dropout) and tolerability.

METHODS AND ANALYSIS

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 (11, 12). This systematic review and NMA is registered in the PROSPERO database (registration number: [the protocol will be registered by the time of publication]). The record in PROSPERO will be updated with any amendment made to the protocol.

Criteria for considering studies for this review

Types of studies

Randomized controlled studies (RCTs) will be included. We will accept open and blinded RCTs; this choice is particularly relevant in trials on psychological interventions, in which only the assessor of outcome can be blind, but not the clinicians providing the intervention. The effect of a non-blind assessor will be examined excluding these studies in a sensitivity analysis. 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 psychosocial treatments. Studies in which the domain "Risk of bias arising from the randomization process" was at high risk of bias (e.g. randomization by the date of birth or day of the week) will be excluded. There will be no language restriction in order to avoid the problem of 'language bias' (13). Studies will be considered for inclusion irrespective of setting (in- or outpatients) and participant gender, nationality, ethnicity.

For all the selection criteria (participants, interventions, comparators, outcomes, study design), we will pay attention to the joint randomizability of the interventions for the studied populations namely if the included participants are in principle jointly randomizable to a hypothetical huge trial comparing all the included interventions.

Types of participants

Individuals aged 18 years or older with a diagnosis of schizophrenia or related disorders (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 (14).

We will include trials irrespective of the diagnostic criteria used. Here we will follow the strategy of the Cochrane Schizophrenia Group (15) 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 exclude studies where all patients, according to the study inclusion criteria:
(1) are acutely ill (e.g. showing agitation/aggression), but we will include studies if the description of the treatment implies that they are stable enough to receive the intervention (e.g., psychoeducation initiated during hospital stay, but it is clear it will be offered to the patients when they are stable enough in order to take part in the sessions), (2) have comorbid psychiatric disorders, including substance abuse, (3) have a concomitant medical illness, (4) are prodromal or "at risk for psychosis".

Types of interventions

We will include any psychosocial intervention whose main target in the included study is relapse prevention. We expect to include specific psychotherapies (e.g. cognitive behavioral therapy designed for relapse prevention, compliance therapy), non-specific psychotherapies (e.g. supportive therapy), group psychotherapies (e.g. family intervention, psychoeducation), interventions focused on psychosocial functioning (e.g. social skills training), interventions including the broader context in which the patient lives (e.g. case management and assertive community treatment).
The interventions mentioned above are typical examples. Nevertheless, if during the screening process we identify studies meeting inclusion criteria that examine other interventions we will include them as long as they are deemed jointly randomizable with those mentioned above.
The interventions can be of any length. Psychosocial treatments as defined above will be compared to each other and to any non-pharmacological control condition. Control conditions will include: no additional treatment (e.g. 'treatment as usual'- TAU), waiting list and inactive treatments (e.g. psychological placebo). When TAU is used as a waiting list, we will classify this condition as waiting list.

Outcome measures

Primary outcome

Our primary outcome is relapse. In case more measures of relapse are reported, we will give priority to measures defined in the following order: a) operationalized criteria, b) psychiatric hospital admissions c) clinical judgement, d) need for additional medication or for extra psychotherapy sessions/meetings with the therapist. Other definitions that we cannot foresee at the protocol stage will also be discussed and considered for inclusion. We will extract the number of patients who relapsed, and the definition that was used by the authors.

Dropouts will be considered as having relapsed in a sensitivity worst case scenario analysis, unless it is clear that they have already been counted among relapsed patients by the authors of the study.

Primary outcome relapse will be reported separately up to 6 months (26 weeks), up to 12 months (between 26 and 52 weeks - primary time point), more than 12 months.
We want to include studies in which the psychosocial treatment aims at preventing relapse. Therefore, studies will be included if relapse or rehospitalisation are measured among the primary outcomes according to the protocol or methods of the trial.

Where not explicitly reported in the study methods or protocol, the judgement about whether relapse or rehospitalization can be considered as primary or co-primary outcome will be made observing:

- Whether it is mentioned in the title (for example, “psychoeducation for relapse prevention in schizophrenia”)
- Whether it is the only outcome measured in the study
- Whether it is declared among study aims (for example, “the main objective of this study was to examine the efficacy of family intervention to prevent rehospitalisation”).
- Whether the power calculation was planned to detect differences in the outcome relapse or rehospitalization.

Studies in which there is a declared primary outcome other than relapse or rehospitalization will be excluded. The exact criterion used for the judgement about inclusion of each study will be reported for the seek of transparency.

For a study to be included, the assessment of the outcome must have been performed at minimum 12 weeks from randomisation.

Secondary outcomes

1. Acceptability: number of premature discontinuation (‘dropout’), reported separately for due to any reason, due to inefficacy and due to worsening of clinical conditions. 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’ (15) 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 for the assessment of overall schizophrenic symptomatology;
3. Change in positive symptoms, measured by the respective subscale of the PANSS, or the “Scales for Assessment of Positive Symptoms” (SAPS) or any other published scale;
4. 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;
5. Depressive symptoms, measured by the Calgary Depression Scale for Schizophrenia, the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Scale or other published symptom scales;
6. Quality of life, measured by any published rating scale (e.g. “Heinrichs quality of life scale”, Quality of Life Scale (QOLS);
7. Adherence, measured by any published rating scale (e.g. “Adherence Therapy Patients Satisfaction Questionnaire”, “Adherence Rating Scale”);
8. Overall functioning measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale, or any other published rating scale.
9. Tolerability: adverse events. We will collect any reported adverse event that may be connected to the intervention, using a recently published classification (16): 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 psychosocial treatment will also be considered.
10. Mortality. We will examine this outcome in terms of a) death for any reason, b) death due to natural causes and c) due to suicide.

Secondary outcomes will be measured at study endpoint. If multiple timepoints are given, we will take that between 26-52 weeks and the closest to 52 weeks.

We will give preference to the mean change from baseline to endpoint measures, and, if not available, we will take the mean values at endpoint. All continuous outcomes will be measured with rating scales that have been published in a peer-reviewed journal, because it has been shown that non-validated schizophrenia scales exaggerate differences (17). Examples of scales that we will use are the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) for overall symptoms, and their respective subscales for positive and negative symptoms (see above).

Search strategy

Electronic searches

The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, and the clinical trials registers Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). A draft search strategy for PsycINFO is presented in Table 1.

Reference lists and other sources

We will also inspect previous reviews concerning psychosocial interventions for relapse prevention/maintenance treatment 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 20 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, at least two reviewers will independently assess them for eligibility against the review criteria. If disagreement cannot be clarified by discussion, it will be resolved with a third reviewer (SL) or seeking further information from the 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;
- 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 psychosocial 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

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

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 (18) 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 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. For our primary outcome relapse this means we will consider patients who dropped out as having relapsed in a sensitivity worst case scenario analysis, unless the authors have already included data of these patients.

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 (19). 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 (20). 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 (19).

Risk of bias assessment

Risk of bias will be assessed for each included study using the revised Cochrane risk of bias tool, RoB2 (21). IB and a second reviewer will independently assess the following domains:

1. Risk of bias arising from the randomization process
2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
3. Risk of bias due to missing outcome data
4. Risk of bias in measurement of the outcome
5. Risk of bias in selection of the reported result
6. Overall risk of bias, as calculated by the algorithm described in (21).

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. We will not include in the data analyses studies whose "Risk of bias arising from the randomization process" was at high risk of bias (e.g. randomization by the date of birth or day of the week). Effects of studies with high risk of bias in the Overall domain 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 sessions.

Pairwise meta-analyses

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. If very few RCTs are available or 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 applied. As heterogeneity is likely, a random effects model will be used.

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 we will compare the empirical distribution to predictive distributions (22–24). 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 are equally likely to be randomised to any of the interventions of interest (i.e. jointly randomisable). When additional evidence of intransitivity is lacking and potential effect modifiers have similar distributions across the included studies, NMA is likely to give valid results. We will maximize 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 acutely ill patients or patients with a comorbid disorder.

Assessment of the transitivity assumption will be done by investigating the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons (25).

These variables include administration mode and frequency of the treatment (individual/group setting, number of sessions), baseline severity and blinding (see below, "Investigation of heterogeneity and inconsistency"), which will also be assessed in subgroup analyses. We will investigate if these variables are similarly distributed across studies grouped by comparison.

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 (26). If undertaking a NMA is deemed appropriate as described above, we will conduct a random-effects NMA in a frequentist setting to synthesize all evidence for each outcome. If the estimation of the relative treatment effects is precise, then we will obtain a ranking of all treatments using the surface under the cumulative ranking curve (SUCRA) and the mean ranks. We will assume a single heterogeneity parameter for each network. We will present the summary ORs or SMDs 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.

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.

To evaluate inconsistency, we will employ both local and global methods (27). We will employ the "separating indirect from direct evidence approach (SIDE)", which separates direct evidence from indirect evidence and then evaluates their agreement to evaluate local consistency (28). We will also evaluate consistency in the entire network with the design-by-treatment interaction test (29). 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 (30). 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. The following potential effect modifiers of the primary outcome will be explored by subgroup analyses:

a) Studies conducted in first episode patients
b) Studies using different definitions of relapse (if relevant)
c) Setting: individual vs group
d) Setting: inpatients vs outpatients (at enrolment in the study)
e) Number of sessions
f) Baseline severity (PANSS or BPRS score at baseline)

Sensitivity analyses on the primary outcome will be performed as follows:

a) Exclusion of studies in which the outcome assessor was not blind (open studies)
b) Exclusion of studies that presented only completer analyses
c) Exclusion of studies with high risk of bias in the Overall domain
d) Exclusion of studies with researchers' allegiance (31–33)

e) Patients who dropped out from the study considered as having relapsed (unless data about these patients were already considered by study authors in the outcome provided in the study)
f) Hospitalizations and relapse defined define with other critera analysed separately
g) Exclusion of studies where relapse or hospitalization was not defined explicitly as primary outcome, but based on our judgement.

Publication bias

To assess small study effects and publication bias we will use funnel plots of pairwise meta-analyses if there are 10 or more studies included. We will also use a comparison adjusted funnel plot for relative treatment effects between all active and control interventions (34).

Statistical software

The analysis and presentation of results will be performed using R (meta and netmeta packages).

Assessing of the confidence in the evidence from NMA

The confidence in the relative treatment effect estimated in NMA for the primary outcome will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework (27, 35), implemented in the web application (http://cinema.ispm.ch/model/CINeMA_paper.pdf). This tool evaluates the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity and incoherence.

PATIENT AND PUBLIC INVOLVEMENT

Representatives from the Organisation "BASTA - Bündnis für psychisch erkrankte Menschen" (http://www.bastagegenstigma.de/) were involved since the stage of grant application with regular meetings. We explained them the basis of systematic reviews methodology, in order that they can understand the process and provide suggestions. We asked them to provide the patients' perspective about the relevance of the topic, the choice and the importance of the appropriate outcomes. They were involved again for the preparation of this protocol, and one of them (WPH) is a co-author. We will collaborate at the preparation of a lay version of the results, that will be disseminated also through the newsblog of BASTA.

ETHICS AND DISSEMINATION

This review does not require ethical approval. Findings will be published in peer reviewed scientific journals, granting open access, and the dataset will be made publicly available.

Contributors: IB and SL designed this study, drafted and critically revised the protocol. GS provided substantial methodological and statistical advice. AR, GPW, CB and TAF contributed with clinical and methodological input in planning the study. WPH provided input from patients' point of view. All authors contributed to and have approved the final manuscript.

Collaborators: Samantha Roberts helped us to conduct the literature searches. Johannes Schneider-Thoma, Maximilian Huhn, Spyridon Siafis and Helena García-Mieres provided help and suggestions. Members of the patient organization BASTA contributed providing the patients' perspective.

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Competing interests: SL has received honoraria as a consultant/advisor and/or for lectures from LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson and Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Sunovion, Recordati, and Gedeon Richter. TAF reports personal fees from Meiji, Mitsubishi-Tanabe, MSD and Pfizer and a grant from Mitsubishi-Tanabe, outside the submitted work, and has a patent 2018-177688 pending.

Table 1. Draft search strategy for PsycINFO

1	exp Schizophrenia/
2	exp psychosis/
3	schizo$.mp.
4	or/1-3
5	exp psychotherapy/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp PSYCHOANALYSIS/ or exp psychotherapeutic counseling/ or hypnosis/ or free association/
6	(abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap$ or anger control or anger management or animal therap$ or art therap$ or assertive$ training or attention training technique or autogenic training or autosuggestion or aversion therap$ or balint group or befriending or behavio?r contracting or behavio?r modification or behavio?r regulation or behavio?r therap$ or bibliotherap$ or biofeedback or body psychotherap$ or brief psychotherap$ or caregiver support or cbt or client cent$ or cognitive behavio?r$ or cognitive intervention$ or cognitive rehabilit$ or cognitive remediation or cognitive technique$ or cognitive therap$ or cognitive treatment$ or colo?r therap$ or compassionate mind training or conjoint therap$ or contingency management or conversational therap$ or conversion therap$ or coping skills or counsel?ing or countertransference or couples therap$ or covert sensitization or crisis intervention or dance therap$ or dialectic$ or eclectic or emotion$ focus$ or emotional freedom technique or encounter group therap$ or existential therap$ or experiential psychotherap$ or exposure therap$ or expressive psychotherap$ or eye movement desensiti?ation or family intervention$ or family therap$ or feminist therap$ or free association or freudian or geriatric psychotherap$ or gestalt therap$ or griefwork or group intervention$ or group psychotherap$ or group therap$ or guided image$ or holistic psychotherap$ or humanistic psychotherap$ or hypnosis or hypnotherap$ or hypnoti?zability or imagery or implosive therap$ or individual psychotherap$ or insight therap$ or integrated psychological therapy or integrative psychotherap$ or integrative therap$ or interpersonal or jungian or kleinian or logotherap$ or marathon group therap$ or marital therap$ or meditation or mental healing or metacognitive therap$ or metacognitive training or milieu therap$ or mindfulness or morita therap$ or multimodal or music therap$ or narrative therap$ or nondirective therap$ or object relations or person cent$ therap$ or personal construct therap$ or persuasion therap$ or pet therap$ or play therap$ or primal therap$ or problem solving or psychoanaly$ or psychodrama or psychodynamic or psychoeducat$ or psychologic$ or psychological therap$ or psychosocial treatment or psychotherap$ or psychotherapeutic counsel$ or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment$ or rational emotive or reality therap$ or reciprocal inhibition or rehabilitat$ or relationship therap$ or relaxation or reminiscence therap$ or rogerian or role play$ or self analys$ or self esteem or sensitivity training or sex therap$ or sleep phase chronotherap$ or social skills education or social skills training or socioenvironmental therap$ or sociotherap$ or solution focused or stress management or support group$ or supportive therap$ or systematic desensiti?ation or systemic therap$ or therapeutic communit$ or transactional analysis or transference or transtheoretical or validation therap$ or (dream$ adj3 analys$) or (support adj3 psycho$)).mp.
7	or/5-6
8	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
9	(random$ adj5 (assign$ or allocat$)).mp.
10	randomi$.mp.
11	crossover.mp.
12	or/8-11
13	4 and 7 and 12

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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	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
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	12
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	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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	8 – Table 1

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
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	8
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	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8
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	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

*** 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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Psychosocial treatments for relapse prevention in schizophrenia: study protocol for a systematic review and network meta-analysis of randomized evidence

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Psychosocial treatments for relapse prevention in schizophrenia: study protocol for a systematic review and network meta-analysis of randomized evidence

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ABSTRACT

Introduction

There is evidence that different psychosocial interventions could reduce the risk of relapse in 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 psychosocial treatments for relapse prevention in schizophrenia according to their efficacy, acceptability and tolerability.

Methods and analysis

We will include all RCTs comparing a psychosocial treatment aimed at preventing relapse in patients with schizophrenia with another psychosocial 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. acutely ill patients). Primary outcome will be the number of patients experiencing a relapse. Secondary outcomes will be acceptability (dropout), change in overall, positive, negative and depressive symptoms, quality of life, adherence, 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 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 CINeMA. 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: CRD42019147884

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first network meta-analysis on psychosocial treatments for relapse prevention in schizophrenia; the findings from this study have the potential to inform and influence clinical decision-making and guideline development.
- The analysis will benefit from maximum statistical power by combining direct and indirect comparisons in a network meta-analysis, measuring the relative effects of the different treatments.
- There is risk of heterogeneity and inconsistency, given the different psychosocial interventions that will be included: however, we try to control variability by carefully framing the inclusion criteria about population, interventions and focus of the single studies, and we will evaluate consistency employing local as well as global methods.
- The limitations of individual studies will be addressed with the Cochrane risk of bias tool and the credibility of the results for the primary outcome will be assessed using the CINeMA web application, an adaptation of the GRADE framework; these approaches are considered the gold standard for critical appraisal of evidence quality.

INTRODUCTION

Schizophrenia is characterized by acute episodes often followed by symptom improvement (1), but requires generally maintenance treatment in order to prevent recrudescence of symptomatology.

A five-year analysis of 11291 patients with schizophrenia found a 13.4% rehospitalisation rate within one month, 38.9% within one year and 64.1% within 5 years (2).

Pharmacological interventions have been the mainstay of treatment for schizophrenia, and play an essential role also in the prevention of relapses. According to a recent meta-analysis of 65 randomised trials, patients treated with antipsychotics experienced a psychotic relapse within one year in the 27% of the cases (3).

Moreover, antipsychotics have a number of limitations (high incidence of disabling side effects, poor adherence to treatment) (3) and can be problematic in many situations (such as medical comorbidities, tolerability problems and pregnancy).

The resulting burden for patients, relatives and society is dramatic, because relapses often lead to costly hospitalisations, patients lose their jobs and relationships are challenged (4, 5).

In this context, psychosocial interventions might have an important role to reduce the risk of relapses.

Several systematic reviews and meta-analyses have examined the comparative efficacy and acceptability of psychosocial interventions from randomized controlled trials (RCTs) in schizophrenia considering relapses among other outcomes. Different interventions like family therapy (6), psychoeducation (7, 8) and cognitive behavioural therapy (9, 10) have been compared with so called no treatment conditions (waiting-list, treatment as usual (TAU)) (9, 7), and in some cases also with other psychosocial treatments pooled together (10, 6), showing promising results.

A review of 25 studies examining family interventions found a 20% reduction of relapse when involving the relatives in the treatment during maintenance phase (6).

Psychoeducation was found to be successful in reduction of relapses in a Cochrane review analysing 11 studies in the medium term and 6 studies in the long term comparing psychoeducation with standard care (RR 0.70, 95% CI 0.61 to 0.81; RR 0.73, 95% CI 0.62 to 0.85) (7); brief psychoeducation also showed positive results in the medium term for people with severe mental illnesses (8). Cognitive behavioural therapy was found to reduce relapse rates in the medium term when compared to standard care (9), but not when compared to other psychosocial therapies (10).

However, evidence is still fragmentary and a comprehensive ranking of all treatments evaluated in RCTs is lacking.

In fact, all the available reviews applied pairwise meta-analysis as a method, and can therefore provide information only on comparisons of two treatments that have been considered in existing studies, and several interventions lack of head-to-head comparisons. For example, both individual psychoeducation and family interventions have shown efficacy in the reduction of relapses, but the two have never been compared with each other.

As a result, it is still currently unclear which are the most efficacious, the most acceptable and the best tolerable psychosocial treatments for relapse prevention in schizophrenia. Better understanding of the comparative efficacy of these active treatments would be important for clinical practice and for meaningful allocation of resources.

To overcome this gap in the current knowledge, we will perform a network meta-analysis comparing all the interventions with each other and produce hierarchies of the effects of the various psychosocial treatments. 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.

Objectives

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

1. relapse and hospitalisations
2. other efficacy measures: overall symptoms, positive symptoms, negative symptoms, depressive symptoms, quality of life, adherence, overall functioning
3. acceptability (dropout) and tolerability (adverse events).

METHODS AND ANALYSIS

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 (11, 12). This systematic review and NMA is registered in the PROSPERO database (registration number: CRD42019147884). The record in PROSPERO will be updated with any amendment made to the protocol. The methods are consistent with the protocol of a previous NMA by our group on psychological intervention for the positive symptoms of schizophrenia (13).

Criteria for considering studies for this review

Types of studies

Randomized controlled studies (RCTs) will be included. We will accept open and blinded RCTs; this choice is particularly relevant in trials on psychological interventions, in which only the assessor of outcome can be blind, but not the clinicians providing the intervention. The effect of a non-blind assessor will be examined excluding these studies in a sensitivity analysis. 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 psychosocial treatments. Studies described as randomized, but in which a closer evaluation with the RoB 2.0 leads to a “high risk of bias” judgement in the domain “Risk of bias arising from the randomization process” will be excluded. There will be no language restriction in order to avoid the problem of ‘language bias’ (14). Studies will be considered for inclusion irrespective of setting (in- or outpatients) and participant gender, nationality, ethnicity.

For all the selection criteria (participants, interventions, comparators, outcomes, study design), we will pay attention to the joint randomizability of the interventions for the studied populations namely if the included participants are in principle jointly randomizable to a hypothetical huge trial comparing all the included interventions.

Types of participants

Individuals aged 18 years or older with a diagnosis of schizophrenia or related disorders (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 (15).

We will include trials irrespective of the diagnostic criteria used. Here we will follow the strategy of the Cochrane Schizophrenia Group (16) 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 exclude studies where all patients, according to the study inclusion criteria:
(1) are acutely ill (e.g. showing agitation/aggression), but we will include studies if the description of the treatment implies that they are stable enough to receive the intervention (e.g., psychoeducation initiated during hospital stay, but it is clear it will be offered to the patients when they are stable enough in order to take part in the sessions), (2) have comorbid psychiatric disorders, including substance abuse, (3) have a concomitant medical illness, (4) are prodromal or "at risk for psychosis".

Types of interventions

We will include any psychosocial intervention whose main target in the included study is relapse prevention. We expect to include specific psychotherapies (e.g. cognitive behavioral therapy designed for relapse prevention, compliance therapy), non-specific psychotherapies (e.g. supportive therapy), group psychotherapies (e.g. family intervention, psychoeducation), interventions focused on psychosocial functioning (e.g. social skills training), interventions including the broader context in which the patient lives (e.g. case management and assertive community treatment).
The interventions mentioned above are typical examples. Nevertheless, if during the screening process we identify studies meeting inclusion criteria that examine other interventions we will include them as long as they are deemed jointly randomizable with those mentioned above.
The interventions can be of any length. Psychosocial treatments as defined above will be compared to each other and to any non-pharmacological control condition. Control conditions will include: no additional treatment (e.g. 'treatment as usual'- TAU), waiting list and inactive treatments (e.g. psychological placebo). When TAU is used as a waiting list, we will classify this condition as waiting list.

Outcome measures

Primary outcome

Our primary outcome is relapse. In case more measures of relapse are reported, we will give priority to measures defined in the following order: a) operationalized criteria, b) psychiatric hospital admissions c) clinical judgement, d) need for additional medication or for extra psychotherapy sessions/meetings with the therapist. Other definitions that we cannot foresee at the protocol stage will also be discussed and considered for inclusion. We will extract the number of patients who relapsed, and the definition that was used by the authors.

Dropouts will be considered as having relapsed in a sensitivity worst case scenario analysis, unless it is clear that they have already been counted among relapsed patients by the authors of the study.

Primary outcome relapse will be reported separately up to 6 months (26 weeks), up to 12 months (between 26 and 52 weeks - primary time point), more than 12 months.

We want to include studies in which the psychosocial treatment aims at preventing relapse. Therefore, studies will be included if relapse or rehospitalisation are measured among the primary outcomes according to the protocol or methods of the trial.

Where not explicitly reported in the study methods or protocol, the judgement about whether relapse or rehospitalization can be considered as primary or co-primary outcome will be made observing:

- Whether it is mentioned in the title (for example, “psychoeducation for relapse prevention in schizophrenia”)
- Whether it is the only outcome measured in the study
- Whether it is declared among study aims (for example, “the main objective of this study was to examine the efficacy of family intervention to prevent rehospitalisation”).
- Whether the power calculation was planned to detect differences in the outcome relapse or rehospitalization.

Studies in which there is a declared primary outcome other than relapse or rehospitalization will be excluded. The exact criterion used for the judgement about inclusion of each study will be reported for the seek of transparency.

For a study to be included, the assessment of the outcome must have been performed at minimum 12 weeks from randomisation.

Secondary outcomes

1. Acceptability: number of premature discontinuation (‘dropout’), reported separately for due to any reason, due to inefficacy and due to worsening of clinical conditions. 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’ (16) 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 for the assessment of overall schizophrenic symptomatology;
3. Change in positive symptoms, measured by the respective subscale of the PANSS, or the “Scales for Assessment of Positive Symptoms” (SAPS) or any other published scale;
4. 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;
5. Depressive symptoms, measured by the Calgary Depression Scale for Schizophrenia, the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Scale or other published symptom scales;
6. Quality of life, measured by any published rating scale (e.g. “Heinrichs quality of life scale”, Quality of Life Scale (QOLS);
7. Adherence, measured by any published rating scale (e.g. “Adherence Therapy Patients Satisfaction Questionnaire”, “Adherence Rating Scale”);
8. Overall functioning measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale, or any other published rating scale.
9. Tolerability: adverse events. We will collect any reported adverse event that may be connected to the intervention, using a recently published classification (17): 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 psychosocial treatment will also be considered.

10. Mortality. We will examine this outcome in terms of a) death for any reason, b) death due to natural causes and c) due to suicide.

Secondary outcomes will be measured at study endpoint. If multiple timepoints are given, we will take that between 26-52 weeks and the closest to 52 weeks.

We will give preference to the mean change from baseline to endpoint measures, and, if not available, we will take the mean values at endpoint. All continuous outcomes will be measured with rating scales that have been published in a peer-reviewed journal, because it has been shown that non-validated schizophrenia scales exaggerate differences (18). Examples of scales that we will use are the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS) for overall symptoms, and their respective subscales for positive and negative symptoms (see above).

Search strategy

Electronic searches

The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, and the clinical trials registers Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). A draft search strategy for PsycINFO is presented in Table 1. The date of the last search update will be provided in the final publication.

Reference lists and other sources

We will also inspect previous reviews concerning psychosocial interventions for relapse prevention/maintenance treatment 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 20 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, at least two reviewers will independently assess them for eligibility against the review criteria. If disagreement cannot be clarified by discussion, it will be resolved with a third reviewer (SL) or seeking further information from the 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;
- 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 psychosocial 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

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

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 (19) 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 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. For our primary outcome relapse this means we will consider patients who dropped out as having relapsed in a sensitivity worst case scenario analysis, unless the authors have already included data of these patients.

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 (20). 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 (21). 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 (20).

Risk of bias assessment

Risk of bias will be assessed for each included study using the revised Cochrane risk of bias tool, RoB 2.0 (22). IB and a second reviewer will independently assess the following domains:

1. Risk of bias arising from the randomization process
2. Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
3. Risk of bias due to missing outcome data
4. Risk of bias in measurement of the outcome
5. Risk of bias in selection of the reported result
6. Overall risk of bias, as calculated by the algorithm described in (22).

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. Effects of studies with high risk of bias in the Overall domain 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 sessions.

Pairwise meta-analyses

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. If very few RCTs are available or 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 applied. As heterogeneity is likely, a random effects model will be used.

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 we will compare the empirical distribution to predictive distributions (23–25). 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 are equally likely to be randomised to any of the interventions of interest (i.e. jointly randomisable). When additional evidence of intransitivity is lacking and potential effect modifiers have similar distributions across the included studies, NMA is likely to give valid results. We will maximize 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 acutely ill patients or patients with a comorbid disorder.

Assessment of the transitivity assumption will be done by investigating the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons (26).
These variables include administration mode and frequency of the treatment (individual/group setting, number of sessions), baseline severity and blinding (see below, "Investigation of heterogeneity and inconsistency"), which will also be assessed in subgroup analyses. We will investigate if these variables are similarly distributed across studies grouped by comparison.

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 (27). If undertaking a NMA is deemed appropriate as described above, we will conduct a random-effects NMA in a frequentist setting to synthesize all evidence for each outcome. If the estimation of the relative treatment effects is precise, then we will obtain a ranking of all treatments using the surface under the cumulative ranking curve (SUCRA) and the mean ranks. We will assume a single heterogeneity parameter for each network. We will present the summary ORs or SMDs 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.

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.
To evaluate inconsistency, we will employ both local and global methods (28). We will employ the "separating indirect from direct evidence approach (SIDE)", which separates direct evidence from indirect evidence and then evaluates their agreement to evaluate local consistency (29). We will also evaluate consistency in the entire network with the design-by-treatment interaction test (30). 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 (31). 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. The following potential effect modifiers of the primary outcome will be explored by subgroup analyses:
a) Studies conducted in first episode patients
b) Studies using different definitions of relapse (if relevant)
c) Setting: individual vs group
d) Setting: inpatients vs outpatients (at enrolment in the study)
e) Number of sessions
f) Baseline severity (PANSS or BPRS score at baseline)

Sensitivity analyses on the primary outcome will be performed as follows:
a) Exclusion of studies in which the outcome assessor was not blind (open studies)
b) Exclusion of studies that presented only completer analyses
c) Exclusion of studies with high risk of bias in the Overall domain

d) Exclusion of studies with researchers' allegiance (32–34)
e) Patients who dropped out from the study considered as having relapsed (unless data about these patients were already considered by study authors in the outcome provided in the study)
f) Hospitalizations and relapse defined define with other criteria analysed separately
g) Exclusion of studies where relapse or hospitalization was not defined explicitly as primary outcome, but based on our judgement.

Publication bias

To assess small study effects and publication bias we will use funnel plots of pairwise meta-analyses if there are 10 or more studies included. We will also use a comparison adjusted funnel plot for relative treatment effects between all active and control interventions (35).

Statistical software

The analysis and presentation of results will be performed using R (meta and netmeta packages).

Assessing of the confidence in the evidence from NMA

The confidence in the relative treatment effect estimated in NMA for the primary outcome will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework (28, 36), implemented in the web application (http://cinema.ispm.ch/model/CINeMA_paper.pdf). This tool evaluates the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity and incoherence.

PATIENT AND PUBLIC INVOLVEMENT

Representatives from the Organisation "BASTA - Bündnis für psychisch erkrankte Menschen" (http://www.bastagegenstigma.de/) were involved since the stage of grant application with regular meetings. We explained them the basis of systematic reviews methodology, in order that they can understand the process and provide suggestions. We asked them to provide the patients' perspective about the relevance of the topic, the choice and the importance of the appropriate outcomes. They were involved again for the preparation of this protocol, and one of them (WPH) is a co-author. We will collaborate at the preparation of a lay version of the results, that will be disseminated also through the newsblog of BASTA.

ETHICS AND DISSEMINATION

This review does not require ethical approval. Findings will be published in peer reviewed scientific journals, granting open access, and the dataset will be made publicly available.

Contributors: IB and SL designed this study, drafted and critically revised the protocol. GS provided substantial methodological and statistical advice. AR, GPW, CB and TAF contributed with clinical and methodological input in planning the study. WPH provided input from patients' point of view. All authors contributed to and have approved the final manuscript.

Collaborators: Samantha Roberts helped us to conduct the literature searches. Johannes Schneider-Thoma, Maximilian Huhn, Spyridon Siafis and Helena García-Mieres provided help and

suggestions. Members of the patient organization BASTA contributed providing the patients' perspective.

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Competing interests: SL has received honoraria as a consultant/advisor and/or for lectures from LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson and Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Sunovion, Recordati, and Gedeon Richter. TAF reports personal fees from Meiji, Mitsubishi-Tanabe, MSD and Pfizer and a grant from Mitsubishi-Tanabe, outside the submitted work, and has a patent 2018-177688 pending.

Table 1. Draft search strategy for PsycINFO

1	exp Schizophrenia/
2	exp psychosis/
3	schizo$.mp.
4	or/1-3
5	exp psychotherapy/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp PSYCHOANALYSIS/ or exp psychotherapeutic counseling/ or hypnosis/ or free association/
6	(abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap$ or anger control or anger management or animal therap$ or art therap$ or assertive$ training or attention training technique or autogenic training or autosuggestion or aversion therap$ or balint group or befriending or behavio?r contracting or behavio?r modification or behavio?r regulation or behavio?r therap$ or bibliotherap$ or biofeedback or body psychotherap$ or brief psychotherap$ or caregiver support or cbt or client cent$ or cognitive behavio?r$ or cognitive intervention$ or cognitive rehabilit$ or cognitive remediation or cognitive technique$ or cognitive therap$ or cognitive treatment$ or colo?r therap$ or compassionate mind training or conjoint therap$ or contingency management or conversational therap$ or conversion therap$ or coping skills or counsel?ing or countertransference or couples therap$ or covert sensitization or crisis intervention or dance therap$ or dialectic$ or eclectic or emotion$ focus$ or emotional freedom technique or encounter group therap$ or existential therap$ or experiential psychotherap$ or exposure therap$ or expressive psychotherap$ or eye movement desensiti?ation or family intervention$ or family therap$ or feminist therap$ or free association or freudian or geriatric psychotherap$ or gestalt therap$ or griefwork or group intervention$ or group psychotherap$ or group therap$ or guided image$ or holistic psychotherap$ or humanistic psychotherap$ or hypnosis or hypnotherap$ or hypnoti?zability or imagery or implosive therap$ or individual psychotherap$ or insight therap$ or integrated psychological therapy or integrative psychotherap$ or integrative therap$ or interpersonal or jungian or kleinian or logotherap$ or marathon group therap$ or marital therap$ or meditation or mental healing or metacognitive therap$ or metacognitive training or milieu therap$ or mindfulness or morita therap$ or multimodal or music therap$ or narrative therap$ or nondirective therap$ or object relations or person cent$ therap$ or personal construct therap$ or persuasion therap$ or pet therap$ or play therap$ or primal therap$ or problem solving or psychoanaly$ or psychodrama or psychodynamic or psychoeducat$ or psychologic$ or psychological therap$ or psychosocial treatment or psychotherap$ or psychotherapeutic counsel$ or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment$ or rational emotive or reality therap$ or reciprocal inhibition or rehabilitat$ or relationship therap$ or relaxation or reminiscence therap$ or rogerian or role play$ or self analys$ or self esteem or sensitivity training or sex therap$ or sleep phase chronotherap$ or social skills education or social skills training or socioenvironmental therap$ or sociotherap$ or solution focused or stress management or support group$ or supportive therap$ or systematic desensiti?ation or systemic therap$ or therapeutic communit$ or transactional analysis or transference or transtheoretical or validation therap$ or (dream$ adj3 analys$) or (support adj3 psycho$)).mp.
7	or/5-6
8	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
9	(random$ adj5 (assign$ or allocat$)).mp.
10	randomi$.mp.
11	crossover.mp.
12	or/8-11
13	4 and 7 and 12

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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	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
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	12
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	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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	8 – Table 1

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
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	8
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	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-8
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	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-12
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

*** 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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