Psychological interventions to reduce positive symptoms in schizophrenia: systematic review and network-meta-analysis

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Abstract

Psychological treatments are increasingly regarded as necessary interventions for schizophrenia. However, a comprehensive evaluation of the available evidence is lacking and the benefit of psychological interventions for patients with current positive symptoms is still debated. The present study aims to evaluate efficacy, acceptability and tolerability of psychological treatments for schizophrenia by applying a network-meta-analysis approach, that can integrate direct and indirect comparisons. We searched EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, Cochrane Library, WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for randomised controlled trials on psychological treatments for positive symptoms of schizophrenia, published up to January 10, 2018. We included studies on adults with a diagnosis of schizophrenia presenting positive symptoms. Primary outcome was change in positive symptoms measured with validated rating scales. We performed random-effects network meta-analysis to calculate standardized mean differences (SMDs) or risk ratios (RRs) with 95% confidence intervals (CIs). The study protocol was registered with PROSPERO, number CRD42017067795.

We included 53 randomised controlled trials on seven psychological interventions, for a total of 4068 participants receiving the psychological treatment mainly as add-on to antipsychotics. The network meta-analysis showed that cognitive behavioural therapy (40 studies) reduced positive symptoms more than inactive control (SMD -0.29; CI -0.55, -0.03), treatment as usual (SMD -0.30; CI -0.45, -0.14) and supportive therapy (SMD -0.47; CI -0.91, -0.03). Cognitive behavioural therapy was associated with a higher dropout rate compared with treatment as usual (RR 0.74; CI 0.58, 0.95). Confidence in the estimates ranges from moderate to very low.

Cognitive behavioural therapy was more efficacious for positive symptoms reduction than usual care (typically including antipsychotics), although the effects were relatively small and the treatment was associated with higher dropout rates. The other treatments contributed to the network with a lower number of studies.

Our results are robust after sensitivity analyses controlling for several factors, including the role of researcher's allegiance and blinding of outcome assessor. Based on the current evidence, our results suggest that patients with positive symptoms may benefit from cognitive behavioural therapy.

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Introduction

Psychological interventions for psychosis and schizophrenia have been developed to address many aspects of the disorder, and according to guidelines from the National Institute for Health and Care Excellence in the UK and the Schizophrenia Patient Outcomes Research Team in the USA, are widely regarded as necessary interventions for schizophrenia (1, 2). The importance of research advancements in this field has also been recently pointed out by the constitution of the Lancet Psychiatry Commission on psychological treatments research in tomorrow's science (3).

A number of systematic reviews of randomized studies have been conducted on these treatments (for an overview, see Bighelli 2018(4)).

However, findings are unclear and sometimes contradictory. For example, while some reviews (5, 6) found a superiority of cognitive behavioural therapy (CBT) compared to usual care, Jauhar and colleagues could not replicate this finding when non-blinded RCTs were excluded (7). Similarly, the Cochrane review by Jones et al only found CBT to be effective in the long-term, but not in the short- or medium term (8). The work of Lynch et al., on the contrary, did not find a benefit for CBT (9).

Moreover, the current evidence presents shortcomings and limitations. Above all, all the existing reviews compared two interventions at a time using pairwise meta-analysis. This method synthesizes results only when a comparison of two treatments has already been considered in existing studies, leaving open questions for all the other possible comparisons. As a consequence, psychological treatments are mainly compared with no treatment or treatment as usual conditions. The work by Turner and colleagues attempted to consider comparisons between active treatments, by including only studies comparing two “active psychological interventions”, like cognitive behavioural therapy, befriending, cognitive remediation, psychoeducation, social skills training and supportive counseling (10). Nonetheless, since the authors applied pairwise meta-analysis to compare each intervention with the others pooled, these results again do not provide information on the comparisons that were not already considered in a trial.

Another issue is that the existing reviews included heterogeneous samples, considering patients with different set of symptoms all together. No review focused specifically on patients with current positive symptoms, which are - at least in the acute phase - at the core of the disorder. Also the review by Zimmermann and colleagues, aiming at evaluating the effect of CBT on positive symptoms, did not restrict the selection of the studies on patients presenting these symptoms (6). Therefore, no review was so far able to provide comprehensive and clinically relevant information for this specific and important group of patients.

As a result of these methodological and clinical limitations in the current evidence, it is still unclear which are the most efficacious, the most acceptable and the best tolerable psychological intervention for treating positive symptoms in schizophrenia.

Our aim is to overcome these limitations by conducting a network-meta-analysis (NMA). This methodology represents the only possibility to cover this gap in the current knowledge. A NMA integrates direct and indirect comparisons of interventions (11), and informs about differences between treatments, even when direct comparisons are not available. However, NMA requires a certain degree of homogeneity in the population, settings and methods across the studies. A careful definition of the population target of the intervention is therefore essential in order to produce information that is useful for clinical practice.

Based on this ground, we conducted a NMA of psychological interventions addressing positive symptoms of schizophrenia, in patients currently experiencing such symptoms, in order to generate results that will be relevant for this specific population.

Methods

Study design and participants

Full methods for this systematic review and network-meta-analysis are reported in the study protocol, that was *a-priori* registered at PROSPERO, number CRD42017067795 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=67795) and published (4). In reporting we followed the PRISMA extension for network meta-analyses (12, 13).

We included studies in adult individuals with a diagnosis of schizophrenia or related disorders (such as schizophreniform or schizoaffective disorders), presenting active positive symptoms, or in the phase of acute exacerbation, as defined by inclusion criteria of the trial, without restrictions on setting, sex, or ethnicity. We optimized homogeneity of studies within and across treatment comparisons by excluding studies on patients with predominant negative symptoms or concomitant medical or psychiatric illness, and patients at different stages of illness (first episode, at risk of psychosis). Studies were included if at least 80% of the patients had 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 (14). In case of a mixed population, data about patients with schizophrenia were extracted, if available. We included the trials irrespective of the diagnostic criteria used.

Interventions and comparators

As *a-priori* defined in our protocol (4) interventions were any psychological treatments that occur through interaction between therapist and patient, either face-to-face individually or in group, with the primary aim to reduce positive symptoms.

Comparators were classified as follows: 1. Interventions with a primary aim different from improving the positive symptoms (e.g. cognition, knowledge of the illness, adherence to medication, functioning). These comparators (e.g. cognitive remediation, psychoeducation) were primarily analysed as separate nodes. In a sensitivity analysis they were combined. 2. Inactive controls defined as interventions intended to control for non-specific aspects of the therapy (befriending, recreation and support, social activity therapy, supportive counselling); these conditions are also sometimes referred as 'psychological placebos'. 3. Treatment as usual. 4. Waiting list. This classification was undertaken because it has been shown that efficacy effect sizes in psychotherapy trials depend on the type of the control group (15).

Outcomes

The primary outcome was the change in positive symptoms of schizophrenia, as measured by rating scales such as the positive subscale of Positive and Negative Syndrome Scale (PANSS (16)), positive subscale of Brief Psychiatric Rating Scale (BPRS (17)), or any other published scale. Secondary outcomes were study dropout for any reason (all-cause discontinuation), effects on overall symptoms of schizophrenia, negative symptoms, response (as defined in the study), relapse (operationalized by rating scales, or, if not available, rehospitalization due to psychopathology),

adherence and insight, changes in depressive symptoms, quality of life, functioning, adverse events that might be related to psychological treatment (following a classification proposed by Linden and colleagues (18)), and mortality (measured as death for any reason, death due to natural causes, death due to suicide). All outcomes have been measured at study endpoint, as defined in each study.

Search strategy and selection criteria

We searched EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, Cochrane Library, WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for randomised controlled trials published up to Jan 10, 2018, that compared psychological interventions with each other or with a non-pharmacological control condition in people with schizophrenia. We applied no language restrictions, in order to avoid the problem of 'language bias' (19). As an exception, we did not search Chinese databases, since serious concerns have been raised on the trustworthiness of Chinese trials found in these databases (20, 21).

Additionally, we searched the reference lists of previous reviews. We contacted authors of included studies published in the last 30 years for missing or additional information about their studies. The search terms included those related to schizophrenia and schizophrenia-like disorders, randomisation, and a great variety of terms related to all psychological interventions (eAppendix 1).

Data extraction and risk of bias assessment

All abstracts identified by the search were reviewed independently by two of IB, CR, SW and FS. Disagreements were resolved by discussion, and in case of doubts the full paper was retrieved for further inspection. Full reports have been obtained for all eligible papers, and were again assessed by two independent reviewers. Disagreements were discussed with SL, and in case of need study authors were contacted for further information.

Two of IB, CR, SW and FS independently extracted data from the selected studies, considering main reports and supplementary materials, entered the relevant information into a Microsoft-Access-database especially created for this study and assessed risk of bias using the Cochrane risk of bias tool (22),(23, 24). The following domains of possible bias were considered: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective reporting, researchers' allegiance (25, 26), other bias. We also assessed a global risk of bias rating for each study based on criteria applied in a network-meta-analysis of antidepressants (eAppendix 10.3) (27).

Statistical analysis

We performed random effects pairwise meta-analyses and network-meta-analysis in a frequentist framework using the netmeta package in R (version 3.4.3) (28, 29). We calculated standardized mean differences (SMDs) for continuous outcomes and risk ratios (RRs) for binary outcomes, both presented with their 95% confidence intervals (CIs). We also calculated the relative ranking for each intervention using the Surface Under the Cumulative Ranking curve (SUCRA), estimated within the frequentist framework (as P-scores) (30).

Before running NMA, we attempted to assess the transitivity assumption. This assumption implies that studies comparing different sets of interventions are sufficiently similar to provide valid indirect inferences, which we tried to ensure by applying narrow inclusion criteria and making populations as similar as possible within and across treatment comparisons. We also considered whether the potential effect modifiers (listed below) were distributed similarly across the available direct comparisons.

We assumed a common heterogeneity parameter across the various treatment comparisons, and presented the between study variance τ^2 for each outcome. We characterised the amount of heterogeneity as low, moderate or high using the first and third quantiles of their empirical distributions (31). Statistical inconsistency was evaluated separating direct evidence from indirect evidence provided by the entire network, and then testing the agreement of these two pieces of evidence (32); the magnitude of inconsistency factors (the difference in direct and indirect SMD) and their respective p-values were used to identify the presence of inconsistency. We also applied the design-by-treatment interaction model, that evaluates inconsistency in the network jointly (33).
To explore potential sources of heterogeneity or inconsistency, we planned *a priori* subgroup analyses for the primary outcome on the following potential effect modifiers: number of sessions, study duration, setting (individual vs group), expertise of the therapist, baseline severity. Sensitivity analyses were performed excluding open-label studies, studies that presented only completer analyses, studies at overall high risk of bias (27), studies with high risk of bias in researchers' allegiance, studies focused on treatment-resistant patients and studies with a non-active comparison group. We also assessed small-trial-effects (potentially associated with publication bias) by examining funnel plots of pairwise meta-analyses and comparison-adjusted funnel plots, if 10 or more studies were included (34). Additionally, we assessed the confidence in estimates of the main outcome with Confidence in Network Meta-Analysis (CINeMA) (http://cinema.ispm.ch), an adaptation of the Grading of Recommendations Assessment, Development and Evaluation framework (GRADE) specifically developed for NMA (35).
Extended information about the included studies and data analysis can be found in the eAppendix, available online at http://www.psykl.mri.tum.de/node/69.

Results

Characteristics of included studies

21772 references were identified by the search (last update January 2018), and 2754 articles were retrieved in full text (Figure 1). We included 62 randomised controlled trials, of which 53 had usable data and were included in the NMA (involving 4068 participants), conducted between 1996 and 2018 (Table 1). They provided comparisons of the following psychological treatments (described in eAppendix 2): CBT (N=40) (36–53, 53–73), metacognitive training (N=6) (74–79), mindfulness (N=2) (80, 81), acceptance and commitment therapy (N=2) (82, 83), experience focused counselling (N=1) (84), hallucination focused integrative treatment (N=1) (85), AVATAR therapy (N=1)(86). The mean sample size was 76.5 participants (range 6-218), and the median trial duration was 13 weeks (range 4-44 weeks). Of 3941 participants with gender indicated, 2361 were men (59.9%). The mean duration of illness was 12.4 years, and the mean age of participants was 37.4 years. Nine studies included only inpatients, 15 only outpatients and 14 both (15 did not provide information on patients' status). The majority of patients had moderate schizophrenic symptoms, with a mean reported PANSS baseline score of 68.26 (87, 88). Thanks to collaboration of the authors, we were able to include unpublished data for some studies (44, 45, 49–51, 65, 69, 75, 78).

Risk of bias assessment

The risk of bias assessment for the included studies are presented in eAppendix 3. Half of the studies (26, 50%) reported details on the randomisation procedures, and were judged as having a low risk of

bias. Most of the studies did not report details about actions to conceal treatment allocation, and were judged as unclear (39 studies, 75%). As expected in psychological treatments, personnel and patients were not blinded to treatment assignment in any study. In 18 studies the outcome assessors were blinded (34.6%), and the others were open label. We judged 34 (65.4%) studies to have a high risk of bias in terms of attrition and 18 (34.6%) in selective reporting. Thirty-three studies (63.5%) were conducted by the authors of the treatment under investigation. Six, 27 and 21 of the included studies were considered to be at low, moderate and high overall risk of bias. After evaluation of possible effects moderators, we considered the characteristics of the studies sufficiently similar.

Primary outcome: positive symptoms

Figure 2 shows the network of treatments for the primary outcome. Two studies were not considered in the analyses, because they were not connected to the rest of the network, contributing neither direct nor indirect evidence (37, 75). Network meta-analysis results show that for the primary outcome CBT was associated with a higher decrease in positive symptoms than inactive control, treatment as usual (TAU) and supportive therapy (with low, moderate and low confidence in the estimates, respectively – see eAppendix 12) (Figure 3). One study on hallucination focused integrative treatment (HFIT) showed a decrease in symptoms in comparison to TAU and supportive therapy (moderate and low confidence in the estimate). All other relative treatment effects were very imprecise, but on average they favor the active psychological treatment over the inactive control interventions. SUCRA values are presented in eAppendix 6.

The heterogeneity variance τ^2 was 0.0514, hence considered to be low to moderate (31). Design-by-treatment interaction test did not reveal significant inconsistency ($p = 0.35$). By splitting direct and indirect evidence for each comparison, we found no evidence for disagreement between these two pieces of evidence for any of the comparisons. Evaluations of heterogeneity and inconsistency are reported in eAppendix 7. None of the methods we used suggested important inconsistency, but given the low number of studies for most of the comparisons, the power of these tests is low.

The assessments of confidence in the estimates using CINeMA highlighted moderate to very low confidence, primarily due to study limitations (high risk of bias) and imprecision (eAppendix 12).

The interpretation of subgroup analyses is limited due to restricted number of studies available for the different subgroups. We did not detect any important indication that the advantage of CBT over TAU is moderated by number of sessions, study duration, setting (individual vs group), therapist's expertise and severity at baseline (eAppendix 9).

Similarly, exclusion of studies for the different sensitivity analyses left a low number of trials for most of the treatments, but results from CBT were robust after excluding open label studies, studies presenting only completer analyses, studies with high risk of bias, studies at high risk of bias for researchers' allegiance, or studies focused on treatment resistant patients (eAppendix 10).

The results of a post-hoc sensitivity analysis pooling the "Active control" comparators did not differ from the main analysis (eAppendix 8).

Investigation of small study effect and publication bias with conventional funnel plot did not reveal any association between study precision and effect size (only possible for CBT versus TAU). However, the comparison-adjusted funnel plot suggests that small studies that did not show a benefit for the newer psychological treatment over the older treatment are underrepresented in our data (possibly remain unpublished) (eAppendix 11).

Secondary outcomes

For secondary outcomes, CBT and inactive control were less acceptable than TAU in terms of all-cause-discontinuation. All treatments had fewer dropouts than social skills training (with the exception of AVATAR therapy, acceptance and commitment therapy and supportive therapy) (Figure 3). CBT was associated with a higher reduction of overall symptoms compared to waitlist and TAU, and with higher reduction in negative symptoms compared with TAU (Figure 4). HFIT and CBT were associated with larger probability to respond to treatment compared with TAU or Inactive control. When looking at adherence and insight, metacognitive training, social skills training, CBT and TAU produced a higher improvement in comparison to supportive therapy. For quality of life and functioning, CBT was more efficacious than TAU. No significant differences were observed for depression. Mortality was in general a rare event, and did not differ between treatments. Very few data were available for relapse, adverse events and other mortality outcomes. Network plots, results and SUCRAs for all secondary outcomes are presented in eAppendix 4 to 6. Heterogeneity variance assessed with τ^2 ranged from 0 to 0.0649, being evaluated from none to low-to-moderate. The design-by-treatment interaction model revealed some inconsistency for the secondary outcome of depression ($p = 0.03$) (eAppendix 7).

Discussion

To our knowledge, this is the first network meta-analysis on psychological treatments for patients with positive symptoms of schizophrenia.

With 40 studies, CBT was the most represented among the included treatments. We found indeed significant efficacy for CBT in comparison with TAU in many outcomes (positive, overall and negative symptoms, response, quality of life and functioning), higher efficacy in comparison with inactive control for positive symptoms and response, and in comparison with supportive therapy for adherence. There was no convincing proof of efficacy of other treatments, probably due to the small number of studies.

In our results, CBT was also associated with higher dropout rates than TAU (18.76% versus 12%). CBT might actually be less acceptable, and not all patients might be willing to engage in such a demanding treatment; however, we argue that to compare the dropout rates with the ones in TAU could be misleading. Patients in the TAU arm - by definition - continue their usual care, and they might have less reason to leave in comparison with patients assigned to a new intervention, that they could find demanding or challenging, or have high expectations and be discouraged if they do not see results in a few sessions. As a confirmation to this hypothesis, the inactive control condition (where patients participate to sessions like befriending and recreation activities) has also a higher dropout rate than TAU. Regarding other treatments, the low number of studies, and therefore low power of analyses, makes the results to be interpreted with caution.

It must also be noted that the patients in the included studies were only moderately ill on the average, compared with patients in a meta-analysis comparing antipsychotic drugs with placebo where they were markedly ill (88). It seems that severely ill patients are not enrolled in psychotherapy studies, and they are probably also not offered a psychological treatment as the first line in real-life clinical practice. Interpretation of subgroup and sensitivity analyses was limited by low number of studies available. However, results on CBT remained stable after all pre-planned sensitivity analyses, corroborating the robustness of the results for this intervention. We also tested the potential role of conflict of interest and researchers' allegiance (26), by excluding the studies in which the authors test the efficacy of an intervention that was developed by themselves, and did not find significantly different results from the main analysis.

One open and increasingly relevant issue is whether psychological interventions might cause harm (18). We collected all the available data about adverse events potentially connected to the psychological intervention, but we found this aspect very poorly reported in the trials. We claim that future studies should collect and report this information, in order to answer this still unclear question (89).

Our results are in agreement with findings from some previous pairwise meta-analyses, where CBT was found to be efficacious for overall, positive and negative symptoms of schizophrenia in comparison with control conditions (5, 6, 7), but not when compared with other psychological therapies (8). However, the results of previous studies and reviews regarding the efficacy of CBT for schizophrenia have been debated, not all reviews found it to be effective (9), and the question whether it should be used in these patients is still controversial. In this context, the role of blinding studies may be particularly critical (9). Here, our results are in contrast with the findings of Jauhar and colleagues (7): when excluding studies with a non-blind outcome assessor, they found no differences between CBT and TAU. On the contrary, we found that the superiority for CBT over TAU is maintained also in blinded studies (SMD -0.27; CI -0.41 to -0.13, eAppendix 10.1). We could replicate this result not only when considering the simple declaration of authors about blindness of outcome assessor, but also when considering studies with low risk of bias for outcome assessor, requiring a more detailed description on how the blinding was maintained (SMD -0.25; CI -0.38 to -0.12, eAppendix 10.1.1). We could not find any other explanation for this difference, that should be probably related to the different inclusion criteria of Jauhar's review, which was not restricted to patients with positive symptoms. It seems that the selection of the population made the difference on this issue.

Our findings have the following limitations. First, available data for other treatments than CBT and for CBT versus other nodes than TAU are based on few studies only, leading to low power to detect possible differences. Therefore results should be interpreted carefully, in particular when looking at sensitivity and subgroup analyses. For this reason we did not focus our interpretation on hierarchies that could be misleading when there are no statistically significant differences among active treatments, and should be interpreted cautiously. Second, the classification of psychological treatments is a challenging issue. We used the criterion of considering treatments that primarily address positive symptoms, consistently with the aim of this work and our primary outcome, and *a-priori* defined this strategy in the protocol (4). Third, our focus was on the treatment of positive symptoms, and the findings observed on other outcomes might be secondary to the effect of the treatment of these symptoms. For example, a patient might experience withdrawal, lack of spontaneity, depressive symptoms or a lower functioning due to the difficulties connected with delusions or hallucinations. When these are treated, the quality of life and the other symptoms may benefit as well. For this reason we focus our interpretations mainly on positive symptoms. Fourth, patients in the included trials were also receiving antipsychotic medication. We collected the available information on the use of antipsychotics, however, it was rarely given and never provided for experimental and control arm separately. The only exception to this is the study of Morrison and colleagues (73), that included patients not receiving antipsychotic medication (a post-hoc sensitivity analysis excluding this study did not materially change the results). As a result, it was not possible to assess the role of pharmacological treatment as a possible moderator. However, we assume that the intake of medications can be considered similar across study arms, thanks to randomisation. Furthermore, we argue that the situation in the included studies resembles what happens in real life clinical practice, where psychological interventions are intended to be used as add-on to pharmacological therapy, and participants usually continue their habitual medication.

On the other hand, this work presents outstanding strengths. First, the study was carefully planned in agreements with PRISMA guidelines, and followed a sound methodology that was *a-priori* published in the protocol (4). This included comprehensive outcome measures and the evaluation of quality at study level (RoB) and confidence in results at outcome level (CINeMA). Second, the consideration of control conditions like TAU and waiting list as separate allowed to ascertain their relative efficacy. This is particularly important, as waitlist has been found to be connected with a nocebo effect (15). Third, the strict selection criteria led to a very consistent population, as confirmed by very low heterogeneity, coherence across direct and indirect comparisons, and by side-splitting test and design-by-treatment interaction test; this makes us confident that the results are robust and clinically meaningful.

This was the first attempt to perform an NMA of psychological treatments for positive symptoms in schizophrenia. It must be noted that the focus on a specific population is necessary in order to produce meaningful information for patients in real life; with this premise our results are applicable specifically to patients with positive symptoms. Given the increased importance attributed to individualized treatments (90), we argue that this selective approach is the most appropriate in order to provide valid information for specific groups of patients. Different psychological interventions may be effective to treat different outcomes in subpopulations of patients presenting different characteristics. Future works might expand the focus of reviewing the efficacy of psychological treatments for other populations of schizophrenic patients.

Contributors

IB, GS, CB, TAF and SL designed the study; GPW provided substantial clinical advice in the conception of the work. IB and MH set up the database. IB, CR, SF and FS screened the literature search, acquired reports of relevant trials, selected included studies and extracted data. IB and FS contacted trial investigators for additional information. IB and GS performed all statistical analyses; IB, GS, MH, JST, MK, TAF, CB and SL analyzed and interpreted the data. IB and SL wrote the draft and the final version of the manuscript. All authors critically reviewed the report for important intellectual content and approved the final submitted version.

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Declaration of interests

MH has received speaker's honoraria from Janssen and Lundbeck. TAF has received lecture fees from Janssen, Meiji, Mitsubishi-Tanabe, Merck Sharp & Dohme, and Pfizer; and research support from Mitsubishi-Tanabe. SL has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, TEVA, Geodon Richter, Recordati, LTS Lohmann, and Boehringer Ingelheim; and for lectures from

Janssen, Lilly, Lundbeck, Otsuka, SanofiAventis, and Servier. All other authors declare no competing interests.

Table 1. Characteristics of studies

	Country	Study treatments (number of patients)	Trial duration (weeks)	Number of sessions	Diagnosis	Study design	Risk of Bias*	Characteristics of patients
ACTRN12616000976 482 (75)	Australia	Metacognitive Training (28), Cognitive Remediation (28)	4	4	schizophrenia spectrum disorder (DSM-V)	SB	Moderate	baseline PANSS total score 62.48, positive symptoms 15.21, negative symptoms 13.95
Bach 2002 (82)	USA	Acceptance and Commitment Therapy (n=40), TAU (n=40)	16	4	auditory hallucinations or delusions (clinical diagnosis), (81.25% diagnosed with schizophrenia, schizoaffective disorder or delusional disorder)	OL	High	Inpatients; 51 (64%) men, 29 (36%) women; mean age 39.3 years
Barrowclough 2006 (36)	UK	Cognitive Behavioural Therapy (n=57), TAU (n=56)	26	10.4	schizophrenia or schizoaffective disorder (DSM-IV)	SB	Moderate	82 (73%) men, 31 women (27%); mean age 38.83 years; baseline PANSS total score 63.8, positive symptoms 17.4, negative symptoms 14.1; duration of illness 13.67 years
Bechdolf 2004 (37)	Germany	Cognitive Behavioural Therapy (n=40), Psychoeducation (n=48)	8	11.9 (Cognitive Behavioural Therapy), 6.4 (Psychoeducatio n)	episode of a schizophrenic or related disorder (ICD-10)	SB	High	Inpatients; 40 (45%) men, 48 women (55%); mean age 31.8 years; baseline PANSS total score 63.75, positive symptoms 14.35, negative symptoms 16.95; duration of illness 4.45 years; 100% taking AP
Birchwood 2014 (91)	UK	Cognitive Behavioural Therapy (n=98), TAU (n=99)	39	19	schizophrenia or schizoaffective disorder (ICD-10)	SB	Moderate	113 (57%) men, 84 women (43%); mean age 37.35 years; baseline PANSS total score 71.73, positive symptoms 19.38, negative symptoms 16.02; duration of illness 15.21 years
Briki 2014 (74)	France	Metacognitive Training (n=35), Supportive Therapy (n=33)	8	14.6	schizophrenia or schizoaffective disorders (DSM-IV-TR)	SB	High	Inpatients and outpatients; 33 (66%) men, 17 women (34%); mean age 41.1 years; baseline PANSS positive symptoms score 20.84, negative symptoms 19.9; duration of illness 16.2 years
Chadwick 2009 (80)	UK	Mindfulness (n=11), WL (n=11)	10	10	Psychotic disorder (NA)	OL	High	mean age 41.6; duration of illness 17.7 years; 100% taking AP
Chadwick 2016 (81)	UK	Mindfulness (n=54), TAU (n=54)	16	12	schizophrenia or schizoaffective disorder (ICD-10)	SB	Low	53 (49.5%) men, 54 women (50.5%); mean age 42; baseline PSYRATS hallucinations score 30.28; 100% taking AP
Craig 2018 (86)	UK	AVATAR therapy (n= 75), Supportive Counselling (n=75)	12	5.6 (AVATAR therapy), 5.1 (Supportive Counselling)	schizophrenia spectrum disorder, affective disorder with psychotic symptoms (ICD-10)	SB	Low	Outpatient; 102 (68%) men, 48 (32%) women; mean age 42.7 years; baseline SAPS score 39.81, SANS 28.7; duration of illness 20.15 years; 100% taking AP
Drury 1996 (70)	UK	Cognitive Therapy[1] (n=30), Recreation and support (n= 32)	12	NA	Functional psychosis (DSM-IV)	OL	High	Inpatient; 25 (63%) men, 15 women (37%); mean age 30.7 years; baseline PAS positive symptoms score 6; duration of illness 6.15 years; 100% taking AP
Durham 2003 (39)	Scotland	Cognitive Behavioural Therapy (n=22), Supportive Therapy (n=23), TAU (n=21)	39	20	schizophrenia, schizoaffective disorder, delusional disorder (ICD-10 and DSM-IV)	SB	High	Inpatients and outpatients; 45 (68%) men, 21 women (32%); mean age 36.3 years; baseline PANSS total score 96.63, PSYRATS total 35.57; duration of illness 13 years; 100% taking AP
England 2007 (71)	NA (author's	Cognitive nursing	18	12	schizophrenia or	SB	Moderate	Outpatient; mean age 41 years; baseline BPRS-18 total

	affiliation in Canada)	intervention[1] (n=44), TAU (n=21)			schizoaffective disorder (DSM-IV)			score 51.05
Favrod 2014 (76)	Switzerland	Metacognitive Training (n=26), TAU (n=26)	8	7	schizophrenia spectrum disorder (ICD-10)	SB	Moderate	Outpatient; 34 (65%) men, 18 women (35%); mean age 39.55 years; baseline PSYRATS delusions score 17.7; 100% taking AP
Foster 2010 (40)	UK	Cognitive Behavioural Therapy (n= 12), TAU (n=12)	4	4	schizophrenia, schizoaffective disorder or delusional disorder (Clinical Diagnosis)	OL	High	Inpatients and outpatients; 14 (58%) men, 10 women (42%); mean age 36.3 years; baseline PSYRATS total score 35.57; 87.5% taking AP
Freeman 2014 (41)	UK	Cognitive Behavioural Therapy (n=15), TAU (n=15)	8	6	schizophrenia, schizoaffective disorder or delusional disorder (i.e. a diagnosis of non-affective psychosis) (Clinical Diagnosis)	SB	Low	Outpatients; 20 (67%) men, 10 women (33%); mean age 41.5 years; baseline PSYRATS total score 18.25; 100% taking AP
Freeman 2015a (92)	UK	Cognitive Behavioural Therapy (n=73), TAU (n=77)	8	5.5	schizophrenia, schizoaffective disorder or delusional disorder (i.e. a diagnosis of non-affective psychosis) (Clinical Diagnosis)	SB	High	Inpatients and outpatients; 86 (57%) men, 64 women (43%); mean age 36.3 years; baseline PANSS total score 41.5, PSYRATS total 18.35; 94.12% taking AP
Freeman 2015b (43)	UK	Cognitive Behavioural Therapy (n=24), TAU (n=26)	12	7.3	schizophrenia, schizoaffective disorder, delusional disorder (Clinical Diagnosis)	SB	Moderate	Outpatients; 34 (68%) men, 16 women (32%); mean age 40.9 years; baseline PANSS total score 81.65, baseline PSYRATS total 41.6; 91.83% AP
Garety 2008a (44)	UK	Cognitive Behavioural Therapy (n=27), Family Intervention (n=28), TAU (n=28)	39	13.9	Non-affective psychosis (DSM-IV and ICD–10)	SB	Moderate	Inpatients and outpatients; 60 (72%) men, 23 (28%) women; mean age 36.4 years; baseline PANSS total score 67.31, positive symptoms 17.16, negative symptoms 15.58; duration of illness 11.57 years
Garety 2008b (44)	UK	Cognitive Behavioural Therapy (n=106), TAU (n=112)	39	14.3	Non-affective psychosis (DSM-IV and ICD–10)	SB	Moderate	Inpatients and outpatients; 151 (69%) men, 67 (31%) women; mean age 38.1 years; baseline PANSS total score 64.29, positive symptoms 18.51, negative symptoms 12.38; duration of illness 10.4 years
Gottlieb 2017 (45)	USA	Cognitive Behavioural Therapy (n=19), TAU (n=18)	24	10	schizophrenia, schizoaffective disorder, or psychosis not otherwise specified diagnosis (NA)	SB	Moderate	Outpatients; 23 (62%) men, 14 women (38%); mean age 42.04 years; baseline BPRS-24 total score 54.92, PSYRATS 53.06, BPRS negative symptoms 6.23; 100% taking AP
Habib 2015 (46)	Pakistan	Cognitive Behavioural Therapy (n=21), TAU (n=21)	21	13	Schizophrenia (DSM-IV-TR)	SB	High	Inpatients; 25 (60%) men, 17 women (40%); mean age 31.85 years; baseline PANSS total 56.34, positive symptoms 21.1, negative symptoms 14.14; duration of illness 8.7 years
Haddock 1999 (47)	UK	Cognitive Behavioural Therapy (n=10), Supportive counselling (n=11)	5	10.2	schizophrenia or schizoaffective disorder (DSM-VI)	SB	Moderate	Inpatients; 19 (90%) men, 2 women (10%); mean age 29.05 years; baseline BPRS total score 53.1; 100% taking AP
Haddock 2009 (48)	UK	Cognitive Behavioural Therapy (n=38), Social	26	17 (Cognitive Behavioural	schizophrenia or schizoaffective disorder	SB	Moderate	Inpatients and outpatients; 66 (86%), 11 (14%) women; mean age 34.8 years; baseline PANSS total score 63.81,

		Activity Therapy (n=39)		Therapy), 17.4 (Social Activity Therapy)	(DSM-VI)			positive symptoms 27.6, negative symptoms 13.04; 100% taking AP
Hazell 2016 (49)	England	Cognitive Behavioural therapy (n=15), Waitlist (n=15)	12	8	schizophrenia and related disorders	SB	Moderate	Only protocol, authors confirmed that inclusion criteria are met and provided some outcome data, but no descriptive of patients are available in detail
Jenner 2004 (85)	Netherlands	Hallucination Focused Integrative Treatment (n=39), TAU (n=39)	39	11	nonaffective psychosis, including schizophrenia, schizoaffective, or psychotic disorder not otherwise specified (DSM-IV)	OL	High	Outpatients; 41 (54%), 35 (46%) women; mean age 36.35 years; baseline PANSS total score 60.2, positive symptoms 16.05, negative symptoms 13.25
Krakvik 2013 (50)	Norway	Cognitive Behavioural Therapy (n=23), Waitlist (n=22)	26	20	schizophrenia, schizoaffective disorder, or persistent delusional disorder (ICD-10)	OL	Moderate	Inpatients and outpatients; 29 (64%) men, 16 (36%) women; mean age 36.35 years; baseline PANSS total score 60.2, positive symptoms 16.05, negative symptoms 11.75
Kuipers 1997 (51)	UK	Cognitive Behavioural Therapy (n=28), TAU (n=32)	39	18.6	Paranoid schizophrenia (DSM-III-R)	OL	High	Inpatients and outpatients; 38 (63%) men, 22 (37%) women; mean age 25.45 years; duration of illness 13.05 years; 95% taking AP
Kumar 2010 (77)	India	Metacognitive Training (n=8), TAU (n=8)	4	8	Paranoid schizophrenia (ICD-10)	NA	High	Inpatients; 16 (100%) men; mean age 32.82 years; baseline PANSS total score 98.18, positive symptoms 27.94, negative symptoms 22.25; duration of illness 7.07 years
Lecomte 2008 (52)	Canada	Cognitive Behavioural Therapy (n=48), Social Skills Training (n=54), WL (n=27)	13	24	Schizophrenia spectrum disorder	SB	Moderate	Outpatients; 93 (72%) men, 36 (28%) women; mean age 24.49 years; baseline BPRS-E total score 41.67, BPRS positive symptoms 2, negative symptoms 1.8; duration of illness 2.69; 100% taking AP
Lee 2012 (93)	South Korea	Cognitive behavioural Social Skills Training[1] (n=12), TAU (n=13)	7	12	Schizophrenia (DSM-IV-TR)	SB	Moderate	Inpatients; 8 (40%) men, 12 (60%) women; mean age 52.22 years; baseline BPRS total score 33.28, SAPS positive symptoms 42.24, SANS negative symptoms 50.05; duration of illness 19.19 years; 100% taking AP
Lee 2013 (53)	South Korea	Cognitive Behavioural Therapy (n=25), Supportive Therapy (n=25)	32	20.1	Schizophrenia (DSM-IV)	SB	Moderate	Inpatients and outpatients; 21 (57%) men, 16 (43%) women; mean age 41.25 years; baseline PANSS total score 61.25, positive symptoms 18.95, negative symptoms 13.85; duration of illness 15.8 years; 100% taking AP
Levine 1998 (72)	NA (author's affiliation in Israel)	Cognitive Therapy[1] (n=6), Supportive Therapy[2] (n=6)	6	6	paranoid schizophrenic patients (DSM-III-R)	NA	High	12 (100%) men; mean age 34.5 years; baseline PANSS total score 57.95, positive symptoms 15.45, negative symptoms 13.3; duration of illness 10.92 years; 100% taking AP
Li 2015 (54)	China	Cognitive Behavioural Therapy (n=96), Supportive Therapy[2] (n=96)	24	15	Schizophrenia (DSM-IV)	SB	Moderate	Inpatients and outpatients; 72 (38%) men, 120 (63%) women; mean age 31.36 years; baseline PANSS total score 72.6, positive symptoms 23.43, negative symptoms 20.4; duration of illness 8.21; 100% taking AP
McLeod 2007 (55)	UK	Cognitive Behavioural Therapy (n=10), Waitlist (n=10)	12	8	Schizophrenia (DSM-IV)	NA	High	Inpatients and outpatients; 3 (30%) men, 7 (70%) women
Morrison 2014 (73)	UK	Cognitive Therapy[1] (n=37), TAU (n=37)	39	13.3	schizophrenia, schizoaffective disorder, or	SB	Moderate	39 (53%) men, 35 (47%) women; mean age 31.32 years; baseline PANSS total score 71.76, positive symptoms

					delusional disorder; diagnostic uncertainty in early phases of psychosis (Early intervention for psychosis service) (ICD-10 or PANSS)			20.98, negative symptoms 14.52; 0% taking AP
Penn 2009 (56)	USA	Cognitive Behavioural Therapy (n=32), Supportive Therapy[2] (n=33)	12	8.3	schizophrenia or schizoaffective disorder (DSM-IV)	SB	Low	Outpatients; 33 (51%) men, 32 (49%) women; mean age 40.65 years; baseline PANSS total score 61.75, positive symptoms 17.55, negative symptoms 13.9; duration of illness 15.4 years
Pinninti 2010 (57)	USA	Cognitive Behavioural Therapy (n=18), TAU (n=15)	12	11.93	schizophrenia or schizoaffective disorder (DSM-IV)	SB	Moderate	Outpatients; 11 (44%) men, 14 (56%) women; mean age 40.49 years; baseline PSYRATS positive symptoms score 32.3; duration of illness 21.4 years; 100% taking AP
Pot-Kolder 2018 (94)	Netherlands	Virtual-reality-based Cognitive behavioural therapy[1] (58), Waitlist (58)	12	16	psychotic disorder (DSM-IV)	SB	Low	82 (71%) men, 34 (29%) women; mean age 38 years; duration of illness 14.1 years; 95.5% taking AP
Rector 2003 (58)	Canada	Cognitive Behavioural Therapy (n=24), TAU (n=21)	26	20	diagnosis of schizophrenia or schizoaffective disorder (DSM-IV)	SB	Moderate	Outpatients; 20 (48%) men, 22 (52%) women; mean age 51.6 years; baseline PANSS total score 63.4, positive symptoms 14.8, negative symptoms 15.95; duration of illness 15.1 years; 100% taking AP
Schnackenberg 2017 (84)	Germany	Experienced Focused Counselling (n=12), TAU (n=10)	44	NA	Schizophrenia and schizoaffective disorder	OL	High	7 (58%) men, 5 (42%) women; mean age 42.17 years; baseline BPRS-E total score 59.03, PSYRATS hallucinations 27.65; duration of illness 18.3 years; 100% taking AP
Sensky 2000 (59)	UK	Cognitive Behavioural Therapy (n=46), Befriending (n=44)	39	19	Schizophrenia (ICD-10 research and DSM-IV)	SB	Moderate	53 (59%) men, 37 (41%) women; mean age 39.5 years; baseline CPRS schizophrenia change scale total score 10.7, SANS 33.45; duration of illness 14.5 years
Shawyer 2016 (83)	Australia	Acceptance and Commitment Therapy (n=49), Befriending (n=47)	13	7	schizophrenia or schizoaffective disorder (DSM-IV-TR)	SB	Low	Outpatients; 59 (61%) men, 37 (39%) women; mean age 34.3 years; baseline PANSS total score 78.25, positive symptoms 21.8, negative symptoms 18; 100% taking AP
So 2015 (78)	Hong Kong	Metacognitive Training (n=23), Waitlist (n=21)	4	3.15	schizophrenia spectrum disorder (Clinical Diagnosis)	SB	Moderate	Outpatients; 24 (55%) men, 20 (45%) women; mean age 33.99 years; baseline PANSS total score 74.9, positive symptoms 20.65; 97.73% taking AP
Startup 2004 (60)	UK	Cognitive Behavioural Therapy (n=47), TAU (n=43)	26	12.9	schizophrenia, schizophreniform, schizoaffective (DSM-IV)	OL	High	Inpatients; 68 (76%) men, 22 (24%) women; mean age 30.8 years; baseline BPRS-16 total score 45.75, SAPS positive symptoms 10.7, SANS negative symptoms 8.9; duration of illness 6.95 years
Tarrier 1998 (95)	UK	Cognitive Behavioural Therapy (n=33), Supportive Counselling (n=26), TAU (n=28)	10	20	schizophrenia, schizoaffective psychosis, or delusional disorder (DSM-III-R)	SB	Moderate	54 (75%) men, 18 (25%) women; mean age 39.54 years; baseline BPRS hallucinations positive symptoms 21.4, SANS negative symptoms 11.55; duration of illness 14.14 years; 100% taking AP
Trower 2004 (62)	UK	Cognitive Behavioural Therapy (n=18), TAU (n=20)	26	16	schizophrenia or related disorder (ICD-10)	SB	High	24 (63%) men, 14 (37%) women; mean age 35.85 years; baseline PANSS total 78,6, positive symptoms 21,35, negative symptoms 21,15; duration of illness 11.7 years
Turkington 2000 (63)	UK	Cognitive Behavioural Therapy (n=13),	8	6	Schizophrenia (ICD-10 research criteria)	SB	Moderate	Inpatients and outpatients; 9 (50%) men, 9 (50%) women, mean age 40.8 years; duration of illness 11.1 years

		Befriending (n=6)						
Valmaggia 2005 (64)	Netherlands, Belgium	Cognitive Behavioural Therapy (n=36), Supportive Counselling (n=26)	23	16	Schizophrenia (DSM-IV)	SB	Moderate	Inpatients; 41 (71%) men, 17 (29%) women; mean age 35.48 years; baseline PANSS total score 65.4, positive symptoms 17.85, negative symptoms 13.91; duration of illness 9.2 years; 100% taking AP
van der Gaag 2011 (65)	Netherlands	Cognitive Behavioural Therapy (n=110), TAU (n=106)	26	13	schizophrenia or schizoaffective disorder (DSM-IV-TR)	SB	High	153 (71%) men, 63 (29%) women; mean age 36.99 years; baseline PANSS total score 69.3, PSYRATS total 31.35; duration of illness 10.58 years
van Oosterhout 2014 (79)	Netherlands	Metacognitive Training (n=75), TAU (n=79)	8	8	a psychotic disorder in the DSM-IV schizophrenia spectrum (DSM-IV-TR)	SB	Moderate	Inpatients and outpatients; 110 (71%) men, 44 (29%) women; mean age 37.55 years; baseline PSYRATS - Delusions score 13
Velligan 2015 (66)	USA	Cognitive Behavioural Therapy (n=43), Cognitive Adaptation Training (n=41), Cognitive Behavioural Therapy +Cognitive Adaptation Training (n=40), TAU (n=42)	39	26.6 (CBT), 27.5 (Cognitive Adaptation Training), 27.5 (CBT+ Cognitive Adaptation Training)	schizophrenia or schizoaffective disorder (DSM-IV)	SB	High	74 (52%) men, 68 (48%) women; mean age 40.62 years
Wahass 1997 (67)	Saudi Arabia	Cognitive Behavioural Therapy (n=3), TAU (n=3)	9	25	Schizophrenia (ICD-10)	OL	Moderate	Inpatients; 6 (100%) men, mean age 32.55 years; 100% taking AP
Wittorf 2010 (68)	Germany	Cognitive Behavioural Therapy (n=50), Supportive Therapy (n=50)	33	20	schizophrenia, schizophreniform disorder, schizoaffective disorder, or delusional disorder (DSM-IV)	SB	High	Outpatients; 35 (52%) men, 32 (48%) women; mean age 37.78 years; baseline PANSS total score 63.85, positive symptoms 17.24, negative symptoms 14.48; 94% taking AP Med
Wykes 2005 (69)	UK	Cognitive Behavioural Therapy (n=45), TAU (n=40)	10	7	Schizophrenia (DSM-IV)	OL	High	Outpatients; 50 (59%) men, 35 (41%) women; mean age 39.7 years; baseline PSYRATS hallucination score 27.95

[1] based on the description of the intervention, considered with CBT in the analyses; [2] based on the description of the intervention, considered with supportive counselling in the analyses. TAU=Treatment as usual, WL=Waitlist, OL=open label, SB=single blind, NA=not available, AP=Antipsychotics medication, PANSS=Positive and Negative Syndrome Scale, SAPS=Scale for the Assessment of Positive Symptoms, PSYRATS=Psychotic Symptoms Rating Scale, SANS=Scale for the Assessment of Negative Symptoms, PAS=Psychiatric Assessment Scale

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