Psychological and psychosocial interventions for treatment-resistant schizophrenia

a systematic review and network meta-analysis

Psychological and psychosocial interventions for treatment-resistant schizophrenia: a systematic review and network meta-analysis

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Summary

Background Many patients with schizophrenia have symptoms that do not respond to antipsychotics. This condition is called treatment-resistant schizophrenia and has not received specific attention as opposed to general schizophrenia. Psychological and psychosocial interventions as an add-on treatment to pharmacotherapy could be useful, but their role and comparative efficacy to each other and to standard care in this population are not known. We investigated the efficacy, acceptability, and tolerability of psychological and psychosocial interventions for patients with treatment-resistant schizophrenia.

Methods In this systematic review and network meta-analysis (NMA), we searched for published and unpublished randomised controlled trials (RCTs) through a systematic database search in BIOSIS, CINAHL, Embase, LILACS, MEDLINE, PsychInfo, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform for articles published from inception up to Jan 31, 2020. We also searched the Cochrane Schizophrenia Group registry for studies published from inception up to March 31, 2022, and PubMed and Cochrane CENTRAL for studies published from inception up to July 31, 2023. We included RCTs that included patients with treatment-resistant schizophrenia. The primary outcome was overall symptoms. We did random-effects pairwise meta-analyses and NMAs to calculate standardised mean differences (SMDs) or risk ratios with 95% CIs. No people with lived experience were involved throughout the research process. The study protocol was registered in PROSPERO, CRD42022358696.

Findings We identified 30 326 records, excluding 24 526 by title and abstract screening. 5762 full-text articles were assessed for eligibility, of which 5540 were excluded for not meeting the eligibility criteria, and 222 reports corresponding to 60 studies were included in the qualitative synthesis. Of these, 52 RCTs with 5034 participants (1654 [33·2%] females and 3325 [66·8%] males with sex indicated) comparing 20 psychological and psychosocial interventions provided data for the NMA. Mean age of participants was 38·05 years (range 23·10–48·50). We aimed to collect ethnicity data, but they were scarcely reported. According to the quality of evidence, cognitive behavioural therapy for psychosis (CBTp; SMD –0·22, 95% CI –0·35 to -0·09, 35 trials), virtual reality intervention (SMD –0·41, –0·79 to –0·02, four trials), integrated intervention (SMD –0·70, –1·18 to –0·22, three trials), and music therapy (SMD –1·27, –1·83 to –0·70, one study) were more efficacious than standard care in reducing overall symptoms. No indication of publication bias was identified.

Interpretation We provide robust findings that CBTp can reduce the overall symptoms of patients with treatment-resistant schizophrenia, and therefore clinicians can prioritise this intervention in their clinical practice. Other psychological and psychosocial interventions showed promising results but need further investigation.

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Introduction

Schizophrenia is a chronic and serious mental illness affecting almost 24 million people worldwide, characterised by positive, negative, affective, and cognitive symptoms leading to serious functional disability.[1] Pharmacological interventions with antipsychotics have been the mainstay of treatment since their introduction in the 1950s. However, antipsychotics are not always effective in treating the symptoms of the illness.[2] This phenomenon is called treatment-resistant schizophrenia. The exact epidemiology of treatment-resistant schizophrenia is not clear, further complicated by the different existing criteria used to define non-response or treatment resistance.[3] In subgroup analyses, we analysed the stringency of the treatment-resistant schizophrenia criterion as a moderator. As is shown in the results of consensus papers,[3,4] the definition of treatment-resistant schizophrenia can be separated into three categories: a minimum, moderate, and optimum definition of treatment-resistant schizophrenia. 30·0–36·7% of people with schizophrenia have symptoms that do not respond to antipsychotics.[5–7] A considerable effort to treat

Research in context

Evidence before this study

Schizophrenia is a global chronic and severe mental illness, mainly treated with antipsychotic medication. Many people with schizophrenia have symptoms that do not respond satisfactorily to pharmacological treatments. As an add-on intervention, psychological and psychosocial treatments can have a crucial role in treating patients with treatment-resistant schizophrenia. However, among the many interventions that have been developed, which treatments are efficacious is still unclear. We searched PubMed on June 8, 2022 for studies published from database inception with the search terms "schizophrenia" and "treatment resistant" and filtered for meta-analysis article types, and we included and inspected 1830 references. We then searched PROSPERO on June 8, 2022, for studies published from database inception with the search terms "schizophrenia" and "treatment resistant" and retrieved 32 references. We found no network meta-analysis and two small pairwise meta-analyses investigating a single intervention (cognitive behavioural therapy) versus a control group (treatment as usual, a waiting list in which participants received the same treatment as the ones in the experimental condition after the end of the intervention phase, or another therapeutic treatment). We therefore found no evidence of previous studies on the comparative effectiveness of psychological and psychosocial interventions in people with treatment-resistant schizophrenia.

Added value of this study

This study is the first network meta-analysis providing an overall picture of all the available evidence on the comparative efficacy, acceptability, and tolerability of psychosocial and psychological interventions for people with schizophrenia whose symptoms did not respond to treatment with antipsychotics. We included 52 randomised controlled trials in 5812 participants with treatment-resistant schizophrenia and compared 20 psychological and psychosocial interventions for the efficacy, acceptability, and tolerability of the outcome. For the primary outcome of overall symptoms, we additionally investigated several potential effect modifiers. We found a small but clear benefit in improving the overall symptoms of schizophrenia for cognitive behavioural therapy for psychosis (CBTp) compared with treatment as usual.

Implications of all the available evidence

We recommend that clinicians consider prioritising CBTp when planning and formulating treatment in clinical practice for patients with schizophrenia whose symptoms did not respond to medication.

this particular population has been made since the 1980s by introducing clozapine, which was superior to chlorpromazine in a pivotal trial.[8] Much research followed to test antipsychotic effectiveness in treatment-resistant schizophrenia, including a recent network meta-analysis (NMA) by Dong and colleagues.[9] Clozapine and olanzapine were found to be good options for treating patients who did not benefit from previous treatment with antipsychotics. However, both antipsychotics contributed to weight gain, and the clozapine was correlated with sedative effects.[9] Clozapine is also associated with other serious adverse events, including agranulocytosis, constipation, pancreatitis, orthostatic hypotension, and myocarditis.[10] The serious side-effects associated with the gold standard of antipsychotics for treatment-resistant schizophrenia underscore that no ideal treatment for this population exists. Therefore, finding effective psychological treatments as add-ons to antipsychotic medication for people with treatment-resistant schizophrenia is of crucial importance.

See Online for appendix

To the best of our knowledge, only two small reviews[11,12] on psychological interventions have been conducted in patients with treatment-resistant schizophrenia, but they were restricted to cognitive behavioural therapy (CBT) and used a simple pairwise meta-analysis. As a result, the current evidence does not answer the question of which psychological treatments are likely to be the best in the different outcome parameters (eg, symptoms of schizophrenia or functioning) for treatment-resistant schizophrenia. We therefore did an NMA to investigate all psychological and psychosocial interventions for treatment-resistant schizophrenia, combining direct and indirect evidence and providing information on the comparative efficacy of different psychological treatments even when a direct comparison has not been addressed with a trial.

Methods

Search strategy and selection criteria

In this systematic review and NMA, we included all randomised controlled trials (RCTs) that compared psychological or psychosocial interventions in adults with a diagnosis of schizophrenia or related disorders (eg, schizophreniform or schizoaffective disorders). Any psychological or psychosocial intervention would be eligible for inclusion (eg, CBT for psychosis [CBTp], occupational therapy, or social skills training; a complete list of the searched interventions is provided in the appendix p 9). These interventions have been listed in the Cochrane Common Mental Disorders group appendices of psychological therapies.[13] We later classified the included interventions according to the descriptions provided (appendix p 160). Open and blinded RCTs were accepted; open RCTs were excluded in a sensitivity analysis. Cluster randomised trials were excluded because their special design would easily violate the transitivity principle in the NMA. We also excluded studies with a high risk of bias in the randomisation process.

No restrictions in terms of gender, ethnicity, language, country, or setting were applied. Studies recruiting participants with specific psychiatric comorbidities were excluded. Furthermore, participants needed to be treatment-resistant by the inclusion criteria of the studies. If we found treatment-resistant definitions in the abstract, introduction, or discussion, we contacted the authors to confirm whether all participants had treatment-resistant schizophrenia. Treatment-resistant definitions given by the authors were accepted and then categorised into three levels by at least two independent reviewers, described in abridged form as level 1, non-response stated, level 2, no response to at least two antipsychotics, and level 3, retrospective and prospective criteria (appendix p 51).

The control groups were classified by the intensity of the treatment into three groups. First, a waiting-list group, in which participants received the same treatment as those in the experimental condition after the end of the intervention phase. Second, a group given treatment as usual, a control condition that includes routine standard treatment, which can be wide-ranging, from treatment with medication alone to extensive treatment with psychological elements (a secondary paper about the role of control groups, including treatment as usual, in the same population is being prepared). Third, an inactive control group, including control conditions in which participants had contact with a therapist or clinician, but not including a specific therapeutic component (eg, recreational therapy, reading task, or activity groups that did not involve any psychological interventions).

The primary outcome was overall symptoms of schizophrenia measured by validated rating scales at end of treatment, including the Positive and Negative Syndrome Scale (PANSS),[14] the Brief Psychiatric Rating Scale (BPRS),[15] and the Schizophrenia Change Scale.[16] We examined positive symptoms, negative symptoms, and depressive symptoms, treatment response (defined by each study; eg, a reduction in PANSS or BPRS from baseline score),[17] relapse, quality of life, functioning, and adherence as secondary efficacy outcomes, dropout as a measure for acceptability, and adverse events potentially connected to the intervention (reported according to a published classification)[18] and mortality (for any reason, due to natural causes or suicide) as tolerability outcomes.

To identify eligible studies, we searched electronic databases, performed manual searches, and used personal contacts. We did a systematic database search in BIOSIS, CINAHL, Embase, LILACS, MEDLINE, PsychInfo, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform for articles published from inception until Jan 31, 2020. We searched the Cochrane Schizophrenia Group registry for studies published from inception until March 31, 2022, and in PubMed and Cochrane CENTRAL for studies published from inception until July 31, 2023 (appendix p 9).

Two reviewers (NHS and SFM) independently screened the identified references and selected the final included studies at the title and abstract level. Any disagreements were resolved by discussion. When doubt still remained, we acquired the full article for further inspection. Once the full articles were obtained, the two reviewers independently decided whether the studies met the review inclusion criteria. If disagreements could not be clarified by discussion, they were resolved with a third senior reviewer (IB). Two reviewers (NHS and either AS or IB) independently extracted the data from the included studies using a Microsoft Access database specifically developed for this project. The risk of bias was assessed by two reviewers (NHS and AS) using the Cochrane Risk of Bias tool 2 (RoB2)[19] for the primary outcome. If we found discrepancies that could not be solved by discussion, a third reviewer (IB) resolved the disagreement. A reviewer (NHS) sent emails to the authors of the included studies to request missing or additional data (appendix p 51).

Data analysis

We carried out random-effects pairwise meta-analyses and an NMA in a frequentist framework using the package netmeta in R, version 2.8-2.[20] Standardised mean differences (SMDs) for continuous outcomes and risk ratios (RRs) for binary outcomes were calculated and presented with their 95% CIs. We calculated the relative ranking for each intervention within the frequentist framework (using p scores) and used them to present the results according to this order.[21]

Before the NMA, we assessed the transitivity assumption by evaluating whether studies comparing different sets of interventions were sufficiently similar to provide valid indirect inferences, which we tried to ensure by applying narrow inclusion criteria. We also compared the distribution of main effect modifiers across studies grouped by interventions (baseline severity, inpatient status, masking of outcome assessor, treatment-resistant definition, female patient percentage, publication year, sample size, mean age, and study duration).

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 the empirical distributions of τ^2.[22,23]

Statistical inconsistency was assessed by separating indirect from direct evidence and testing the agreement of these two pieces of evidence (SIDE splitting).[24] The magnitude of inconsistency factors and their respective p values were applied to recognise the presence of inconsistency. We also used the design-by-treatment interaction model, which evaluated the inconsistency of the network.[25] To explore potential sources of heterogeneity or inconsistency, we did a priori planned subgroup

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analyses for the primary outcome on the following potential effect modifiers: number of sessions; studies using manualised and non-manualised intervention; baseline severity; and treatment-resistant definition.[26]

Sensitivity analyses were done by excluding studies in which outcome assessors were not masked, studies presented only completer analyses, studies included a high risk of bias in the overall domain, studies with researcher allegiance (in which the investigated intervention was developed by the authors of the study),[27] studies that did not use diagnosis operationalised criteria, and studies representing extreme outliers. We assessed small-trial effects (potentially associated with publication bias) for the primary outcome with a comparison-adjusted funnel plot ordering the treatments from newest to oldest. We then tested for asymmetry in RRs using Egger's test.[28,29]

We evaluated the confidence in the relative treatment effect estimated in the NMA for the primary outcome using the Confidence in Network Meta-Analysis framework,[30] implemented in the web application CINeMA.[31] The study protocol was registered in PROSPERO, CRD42022358696.[26] As the current study has been registered and was designed with no contact with the participants of the study, ethical approval and patient consent were not required.

For more on **CINeMA** see http://cinema.ispm.ch

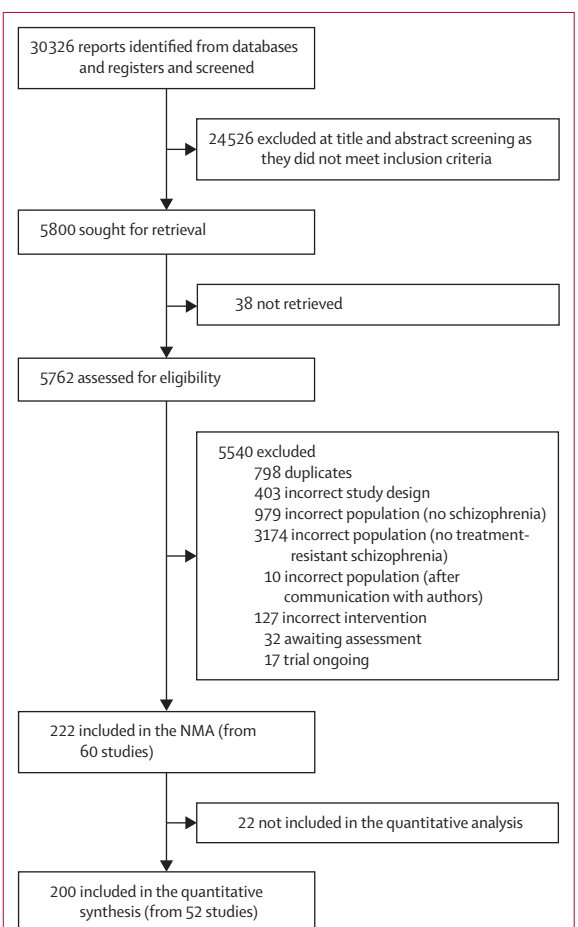

Figure 1: **Study selection**
NMA=network meta-analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After screening 30326 records (including 410 articles by hand search), we retrieved and assessed for eligibility 5762 full-text articles, from which we excluded 5540 reports for several reasons (study design, not relating to treatment-resistant schizophrenia, or the incorrect intervention). 222 records reporting 60 RCTs were included (conducted between 1973 and 2022, involving 5327 participants), of which 52 studies (conducted between 1997 and 2022, including 5034 participants) had usable data and were included in the quantitative synthesis and the NMA (figure 1; appendix p 54). For 14 studies, we were able to include unpublished data and additional information sent by the authors (appendix p 51). The included studies investigated 20 psychological and psychosocial interventions (appendix p 160).

The mean sample size per study was 90 participants (range 6–487), and the median trial duration was 13 weeks (range 4–104). Of 4979 participants with gender indicated, 1654 (33·2%) were women and 3325 (66·8%) were men. Mean duration of illness was 12·96 years (range 1·4–20·5), and mean age of participants was 38·05 years (range 23·10–48·5). The majority of patients were moderately ill, with a mean reported PANSS baseline score of 75·97 (range 58·10–126·74).[32] Ethnicity data were collected but were rarely reported. More detailed descriptions of the patient characteristics can be found in the appendix (p 54).

We present the risk of bias assessments for the included studies (appendix p 62). Overall risk of bias was judged to be low for two studies, moderate for 21 studies, and high for eight studies. No study was rated at high risk in the randomisation process domain.

The comparison of potential effect modifiers suggested that the transitivity assumption was reasonably met (appendix p 64). However, for most parameters, the number of studies per comparison was small, so there might be a certain level of intransitivity that we were not able to detect.

Hereafter, we report the results for which the 95% CI excluded the possibility of no difference between interventions. Additional data as network plots, forest plots, league tables, and p scores can be found in the appendix (pp 69–112).

31 studies with 12 interventions (n=3393 patients; figure 2) provided data for the NMA of the primary outcome of overall symptoms. SMDs compared to treatment as usual excluding no effect, according to the

quality of evidence, were –0·22 (95% CI –0·35 to –0·09) for CBTp in 1835 participants, –0·41 (–0·79 to –0·02) for virtual reality intervention in 155 participants, and –0·70 (–1·18 to –0·22) for integrated intervention (a combination of several treatments) in 90 participants (figures 3, 4). Music therapy was an outlier (–1·27, –1·83 to –0·70) on the basis of a single trial in 41 patients, which was later investigated in a post-hoc sensitivity analysis (appendix p 148). Heterogeneity in estimates between studies of the same comparison was low to moderate, whereas inconsistency in direct and indirect estimates was low (appendix p 113).

Results of the subgroup (appendix p 118) and sensitivity analyses (appendix p 134) were mainly consistent with the main analysis. CBTp remained efficacious across almost all subgroups and sensitivity analyses, followed by integrated intervention and virtual reality therapy when compared with treatment as usual (appendix p 159). An exception was that no studies using a very stringent definition of treatment resistance (level 3, retrospective and prospective treatment resistance) was available, and that in eight level-2 studies (at least two antipsychotics ineffective) no clear difference compared with treatment as usual was noted (SMD –0·16, 95% CI –0·54 to 0·23).

When looking at secondary efficacy outcomes versus treatment as usual (appendix p 73), metacognitive training, family intervention, virtual reality intervention, integrated intervention, and CBTp were efficacious for positive symptoms (46 studies with 17 treatments), music therapy, body-oriented intervention, occupational therapy, and CBTp were efficacious for negative symptoms (32 studies with 13 treatments), and only CBTp was better than treatment as usual for response (15 studies with 11 treatments) and quality of life (13 studies with six treatments) outcomes, occupational therapy and cognitive training for adherence (eight studies with seven treatments), and cognitive adaptation training for functioning (20 studies with 11 treatments). No treatment showed a difference from treatment as usual for depressive symptoms (17 studies with ten treatments) and relapse (nine studies with six treatments).

With regard to the acceptability of the interventions, we found no clear difference in terms of participants leaving the study early for any reason in comparison with treatment as usual, with the exception of social skills training, which was associated with a higher number of dropouts. However, it must be noted that many interventions tended to have a higher number of drop-outs when compared to treatment as usual, even if the possibility of no difference cannot be excluded. When observing tolerability, we could not analyse data on adverse events potentially connected to psychological interventions because those were scarcely reported in the included studies (appendix p 100). Mortality due to any reason was a rare event and did not differ between treatments (21 studies with ten treatments, 22 deaths), and the same was true for mortality due to suicide (19 studies with ten treatments, 11 deaths) and natural causes (14 studies with seven treatments, four deaths).

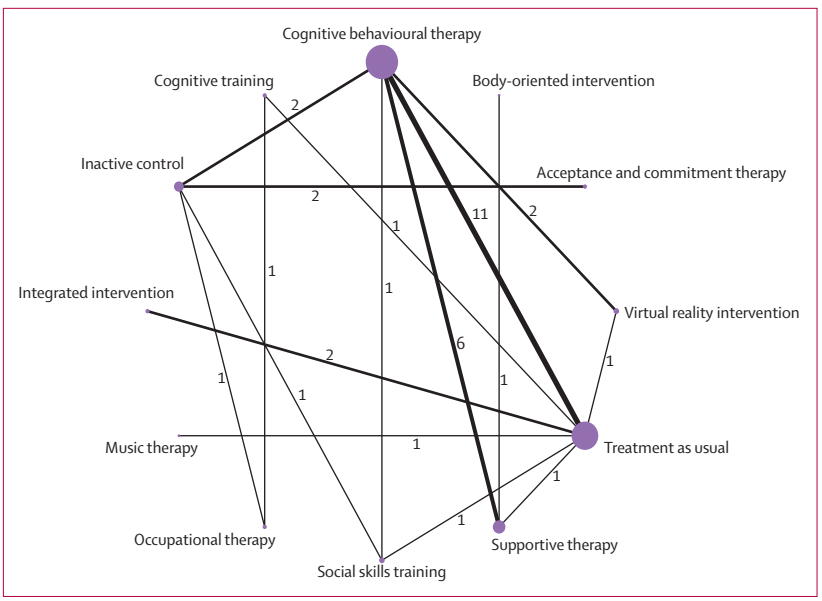

Figure 2: **Network plot of the primary outcome overall symptoms**

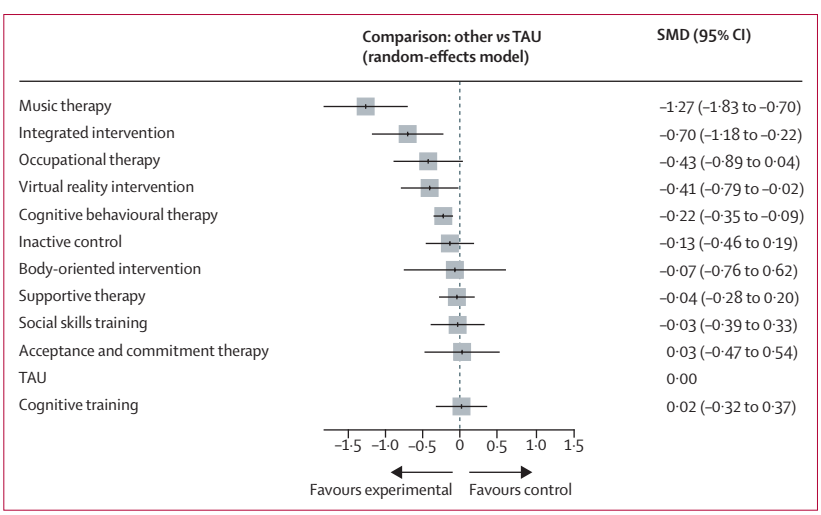

Figure 3: **Forest plot of psychological interventions versus treatment as usual for the primary outcome overall symptom**
SMD=standardised mean difference. TAU=treatment as usual.

We presented assessments for heterogeneity and inconsistency for the secondary outcomes (appendix p 113). Heterogeneity in estimates between studies of the same comparison was low to moderately high, with the exception of quality of life, for which it was high. There was no or little evidence of inconsistency in direct and indirect estimates for most of the outcomes, except for quality of life, for which we found important evidence for inconsistency (appendix p 114; for this outcome, the pairwise meta-analysis results are presented in the appendix p 92). For many secondary outcomes, the networks were thin and the power was low, so there

MT	..	..	..	..	..	..	..	..	..	–1·27 (–1·83 to –0·70)*	..
–0·57 (–1·31 to 0·18)	II	..	..	..	..	..	..	..	..	–0·70 (–1·18 to –0·22)*	..
–0·84 (–1·58 to –0·11)*	–0·28 (–0·95 to 0·32)	OT	..	..	–0·07 (–0·69 to 0·54)	..	..	..	..	..	–0·59 (–1·08 to –0·10)*
–0·86 (–1·55 to –0·17)*	–0·30 (–0·91 to 0·32)	–0·02 (–0·62 to 0·58)	VRI	–0·14 (–0·54 to 0·25)	..	..	..	..	..	–0·72 (–1·79 to 0·35)	..
–1·04 (–1·63 to –0·46)*	–0·48 (–0·98 to 0·02)	–0·20 (–0·62 to 0·27)	–0·18 (–0·55 to 0·19)	CBTp	–0·25 (–0·61 to 0·12)	..	–0·18 (–0·39 to 0·03)	–0·08 (–0·53 to 0·37)	..	–0·21 (–0·34 to –0·07)*	..
–1·13 (–1·79 to –0·48)*	–0·57 (–1·15 to 0·01)	–0·29 (–0·76 to 0·17)	–0·27 (–0·75 to 0·21)	–0·09 (–0·40 to 0·22)	IC	..	..	–0·35 (–0·99 to 0·29)	–0·17 (–0·56 to 0·22)	..	..
–1·20 (–2·09 to –0·31)*	–0·63 (–1·47 to 0·20)	–0·36 (–1·18 to 0·46)	–0·34 (–1·11 to 0·43)	–0·16 (–0·83 to 0·52)	–0·07 (–0·81 to 0·68)	BOI	–0·03 (–0·67 to 0·62)	..	..	..	..
–1·23 (–1·84 to –0·61)*	–0·66 (–1·20 to –0·12)*	–0·39 (–0·90 to 0·13)	–0·37 (–0·79 to 0·06)	–0·18 (–0·39 to 0·02)	–0·09 (–0·46 to 0·28)	–0·03 (–0·67 to 0·62)	ST	..	..	0·05 (–0·62 to 0·73)	..
–1·24 (–1·91 to –0·56)*	–0·67 (–1·28 to –0·07)*	–0·40 (–0·96 to 0·16)	–0·38 (–0·89 to 0·13)	–0·19 (–0·55 to 0·16)	–0·10 (–0·51 to 0·30)	–0·04 (–0·80 to 0·73)	–0·01 (–0·42 to 0·40)	SST	..	–0·10 (–0·62 to 0·41)	..
–1·30 (–2·06 to –0·54)*	–0·74 (–1·44 to –0·04)*	–0·46 (–1·07 to 0·14)	–0·44 (–1·06 to 0·18)	–0·26 (–0·75 to 0·24)	–0·17 (–0·56 to 0·22)	–0·10 (–0·94 to 0·74)	–0·07 (–0·61 to 0·46)	–0·06 (–0·63 to 0·50)	ACT	..	..
–1·27 (–1·83 to –0·70)*	–0·70 (–1·18 to –0·22)*	–0·43 (–0·89 to 0·04)	–0·41 (–0·79 to –0·02)*	–0·22 (–0·35 to –0·09)*	–0·13 (–0·46 to 0·19)	–0·07 (–0·76 to 0·62)	–0·04 (–0·28 to 0·20)	–0·03 (–0·39 to 0·33)	0·03 (–0·47 to 0·54)	TAU	0·06 (–0·32 to 0·44)
–1·29 (–1·95 to –0·63)*	–0·72 (–1·32 to –0·13)*	–0·45 (–0·87 to –0·03)	–0·43 (–0·94 to 0·09)	–0·25 (–0·61 to 0·12)	–0·16 (–0·59 to 0·27)	–0·09 (–0·86 to 0·68)	–0·06 (–0·48 to 0·35)	–0·05 (–0·54 to 0·44)	0·01 (–0·57 to 0·59)	–0·02 (–0·37 to 0·32)	CT

Figure 4: **League table of the primary outcome overall symptoms**

Treatments are ranked by probability of being the best in treating treatment-resistant schizophrenia (net rank). Results from the network meta-analysis (mixed [network] and indirect comparisons) are presented in the lower left triangle and results from pairwise meta-analyses (direct comparisons) are presented in the upper right triangle. Relative treatment effects are measured by standardised mean differences along with their 95% CIs. The colours of the cells in the lower triangle represent the confidence in the estimate results obtained with CINeMA; blue indicates moderate confidence, orange indicates low confidence, and red indicates very low confidence. ACT=acceptance and commitment therapy. BOI=body-oriented intervention. CBTp=cognitive behavioural therapy for psychosis. CT=cognitive training. IC=inactive control. II=integrated intervention. MT=music therapy. OT=occupational therapy. SST=social skills training. ST=supportive therapy. TAU=treatment as usual. VRI=virtual reality intervention. *Significant.

might have been inconsistencies that we were not able to detect.

No indication of small study effects was found with a comparison-adjusted funnel plot for the primary outcome (Egger's test p=0·0668; appendix p 151). The judgements about confidence in NMA (CINeMA) stretched from moderate to very low (figure 4; appendix p 152).

Discussion

To the best of our knowledge, this is the first NMA assessing the psychological and psychosocial interventions for treatment-resistant schizophrenia. We investigated 20 interventions reported in 60 RCTs with 5327 participants.

We found that CBTp, virtual reality interventions, integrated intervention, and music therapy were superior to treatment as usual in reducing overall symptoms of schizophrenia in participants with treatment-resistant schizophrenia. CBTp usually includes therapy components involving the improvement of existing coping strategies, the development and practice of new ones, the modification of delusional beliefs and beliefs about hallucinations, and the challenge of dysfunctional schemas.

Findings for CBTp were consistently effective across all sensitivity and subgroup analyses that we conducted, with the exception of studies that used a moderate versus low definition of treatment resistance when compared with treatment as usual.

Results for integrated intervention were also mainly consistent, in terms of its effectiveness, with the main analysis, showing a benefit over standard care in studies using more stringent treatment-resistance criteria. Integrated intervention is a combination of several treatments, not a special form of therapy, such as CBTp or occupational therapy. Some, but not all, different treatments within the integrated intervention that were investigated in other trials were included in the NMA. It is probable that a combination of different treatments can target several internal and external factors that potentially cause symptoms.[33]

However, it must be noted that for interventions other than CBTp with 1835 participants involved, the quantity of studies and data is not sufficient to draw strong conclusions. For the same reason, it is not possible to make conclusions on the head-to-head comparisons between interventions. This is especially true for music therapy, investigated by one single Chinese study involving 41 participants, which had very positive results.[34] We were not able to contact the authors of this study; therefore, we applied great caution in the interpretation of the results and conducted a sensitivity analysis excluding it.

CBTp was associated with a somewhat large reduction in positive symptoms (SMD –0·31, 95% CI –0·43 to –0·19; appendix p 79) but had a less clear effect on negative symptoms (SMD –0·14, –0·29 to 0·01), so that the efficacy on overall symptoms of schizophrenia is probably

driven by the effect on positive symptoms. Negative symptoms in patients with treatment-resistant schizophrenia are probably particularly challenging, because these patients have low expectations of pleasure, success, and social acceptance.[35] This result is in line with the review by Bighelli and colleagues,[36] who showed that CBTp is effective in treating positive symptoms compared with standard care, inactive control, and supportive therapy in the population of participants with positive symptoms of schizophrenia. Two small pairwise meta-analyses done in treatment-resistant schizophrenia[11,12] also found CBTp to be beneficial for general and positive symptoms compared with control conditions.

Similarly, we found CBTp to be more effective than treatment as usual in improving response rates. A previous review in a population of participants with schizophrenia and positive symptoms found lower response rates in the subgroup of patients with treatment-resistant schizophrenia.[37]

We did not find CBTp to have a role in improving functioning. This result differs from a review focusing on this outcome in the general population of patients with schizophrenia,[38] which showed a benefit for CBTp on functioning compared with standard care alone. Again, the population of patients with treatment-resistant schizophrenia seems to differ in this regard from the general population of patients with schizophrenia. Conversely, we found CBTp to be associated with better quality of life, even with some heterogeneity. Therefore, the real-world outcome of a decrease in symptoms in the quality of life of people with schizophrenia remains unclear and deserves to be further investigated.

We found that no intervention, when compared with treatment as usual, was associated with a reduction in depressive symptoms. Patients with schizophrenia whose symptoms did not respond to medication have a higher level of depression compared with the general population of people with schizophrenia, and their depression might be, therefore, more difficult to treat.[39] Moreover, psychological and psychosocial interventions might be associated with improved insight, which is known to be associated with some depressive symptoms, for instance, self-depreciation, pathological guilt, morning depression, and suicidal ideation.[40] Thus, finding a therapeutic strategy that is effective for the depressive symptoms is still challenging.[39]

For many interventions, there was a trend in the direction of a higher dropout rate in comparison with standard care, even if the CI mainly included the possibility of no difference. Psychological interventions require the active participation of the patient, which might be particularly challenging for people with symptoms that did not respond to a previous therapy.

Because of the paucity of data, it was not possible to analyse the potential adverse events of the interventions. We recommend that future studies consider not only efficacy but also potential harms of the psychological interventions and report them according to published classifications.[18]

All these findings must be considered with some limitations. Firstly, networks were mainly thinly connected, with data on some comparisons based on only few studies. These types of connections lead to low statistical power to distinguish possible differences and to properly check assumptions for NMA; caution is therefore needed when interpreting the results. Therefore, we did not interpret hierarchies based on p scores, but used them only for presentation purposes. Connected to this limitation, it must be noted that the number of studies on interventions other than CBTp was low, preventing the possibility of drawing strong conclusions on their effects in this population.

Secondly, the interventions found efficacious were not superior to the inactive control condition (eg, comparator conditions intended to control for non-specific aspects of the treatment including writing daily diaries, checking in via telephone calls, enjoying leisure time in a group setting, doing art activities such as crafting, talking about hobbies, and sports). However, only seven studies used inactive control conditions and two of them compared with CBTp. The effect size in the pairwise comparison of CBTp with inactive control (SMD –0·25, 95% CI –0·61 to 0·12) was approximately the same as that compared to treatment as usual in NMA. Nevertheless, more trials comparing CBTp with inactive controls are needed.

Thirdly, even if we strictly applied a list of inclusion criteria and detected no clear issue in transitivity, we found a certain degree of heterogeneity and inconsistency in quality of life. We investigated possible effect modifiers but did not find an evident role for any of the moderators evaluated. Different quality of life scales might measure slightly different aspects.

As a fourth limitation, the descriptions of the treatment-resistant schizophrenia population in the studies were sometimes poor, and less strict than observed in studies investigating drugs in the same population.[18] In most of the studies, the participants were identified as having persistent or resistant psychotic symptoms. Some studies provided additional details, mentioning the number of antipsychotics previously used, the duration of symptoms, or the duration of the drug treatment. We found only one RCT[41] that applied the comprehensive treatment-resistant schizophrenia definition recommended by Kane and colleagues,[4] but no usable data were reported. These poor descriptions prevented us from properly analysing the role of the different treatment-resistant schizophrenia definitions, and we cannot exclude that they might be connected with some degree of heterogeneity found in our results.

Another limitation of our study was that people with lived experience of schizophrenia were not involved at any stage. Further, we did not plan sex-based or gender-based analyses of the primary outcome.

We encountered in the included studies the well known problem of poor description of the pharmacological treatments received by the participants in parallel to the psychological intervention, so that a proper analysis of this important moderator was not possible. The results should be considered as the effect of the psychological intervention in addition to an unspecified pharmacological therapy.

Finally, although several interventions were found efficacious and could help to reduce symptoms of schizophrenia in the population with treatment-resistant schizophrenia, only the results for CBTp were supported by data from a considerable number of studies and robust when controlling for potential moderators. However, CBTp is often difficult to access because of the scarcity of the therapists. Given its effectiveness, an improvement in training possibilities and therefore in the accessibility of CBTp for patients is desirable.

Our review shows that clinicians should, therefore, consider prioritising CBTp in their clinical practice when treating patients with schizophrenia who do not benefit sufficiently from medication. Other psychological treatments such as integrated intervention and virtual reality intervention could also be considered and deserve further investigation.

Contributors

SL and IB designed the study with input from JP. NHS and IB set up the database. NHS, IB, AS, and SFM screened the literature, acquired reports of the relevant trials, identified several publications of individual studies, selected included studies, and extracted data. SS reconciled the data extraction from some unclear studies. NHS contacted trial investigators for additional information and conducted the statistical analyses with input from IB, SL, and SS. NHS, AC, IB, and SL verified and had full access to the raw data. NHS, IB, and SL analysed and interpreted the data, with advice from AC. NHS, IB, and GP-W provided input to data refinement, particularly in the treatment descriptions. NHS and IB wrote the draft and the final version of the manuscript. All authors critically reviewed the report for important intellectual content, approved the final submitted version, and accepted responsibility to submit it for publication.

Declaration of interests

In the past 3 years SL has received honoraria as an adviser, for lectures, or for educational material from Angelini, Boehringer Ingelheim, Apsen, Eisai, Ekademia, Gedeon Richter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Mitshubishi, NovoNordisk, Otsuka, Recordati, Rovi, and TEVA. GP-W received honoraria from Rovi. JP is a member of the TSC of the SINAPPS2 study, DGPPN, Referatsleiter; DGGPP, erweiterter Vorstand; DGBP, Referatsleiter; DZNE, PI; UK DRI, PI; DZPG, PI, and UniQure. All other authors declare no competing interests.

Data sharing

Please contact the corresponding author if you would like to see any data that are not included in the Article or the appendix.

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