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Review article

The role of control groups in non-pharmacological randomised controlled trials of treatment-resistant schizophrenia: A systematic review and meta-analysis

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ABSTRACT

Control groups used in randomised controlled trials investigating psychological interventions for depression and anxiety disorders have effects of their own. This has never been investigated for schizophrenia, in particular treatment-resistant schizophrenia. This systematic review and meta-analysis aimed to examine how control groups in randomised controlled trials on psychological interventions for treatment-resistant schizophrenia behave in their effects on general symptomatology. In a search of various databases until July 2023, 31 eligible studies with 3125 participants were found whose control groups were assigned to four categories: active, inactive, treatment as usual and waitlist. The analyses showed that psychological interventions had a greater effect on symptom reduction to all control groups combined. When separating the control groups, only compared to TAU and waitlist controls the psychological interventions were superior. The difference was larger when less active control groups (e.g. waitlist – or treatment as usual control groups) were used. All control groups were associated with an improvement in symptoms from pre- to post-measurement point, with the greatest improvement observed in the inactive control group. The results are preliminary, but they suggest that the choice of the control group has a considerable impact on study effects as it has been shown in other psychiatric diagnoses.

1. Introduction

The effectiveness of treating schizophrenia with antipsychotics as well as with psychological and psychotherapeutic interventions has already been demonstrated (Leucht et al., 2017; Bighelli et al., 2018). In contrast, no attention has been paid to the investigation of control groups (CGs) in randomized controlled trials (RCTs) on the treatment of schizophrenia with psychological interventions. Although, the CGs also include potentially therapeutically effective components and their influence on the symptomatology should not be underestimated (Mohr et al., 2014). In their work on CGs in RCTs on psychological interventions, the working group around Mohr (2009) offers a description of the different CGs, which includes treatment as usual (TAU)-CG, CGs with non-specific treatment components, active control treatments and waitlist control.

In meta-analyses, particular attention should be paid to the exact consideration of CGs used in the studies, since the CGs may differ in their effects on symptomatology (Michopoulos et al., 2021) and could therefore influence the effect sizes of the investigated interventions.

So far, CGs have mainly been investigated in psychotherapy studies for depression and anxiety disorders (Smits and Hofmann, 2009; Mohr et al., 2014; Cuijpers et al., 2016; Michopoulos et al., 2021). In these meta-analyses (Mohr et al., 2014; Cuijpers et al., 2016; Michopoulos et al., 2021), the experimental conditions were superior to the CGs in the effect estimates. Moreover, it could be shown that the CGs differed from each other in their effects on symptoms. For example, Mohr et al. (2014)

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showed clear effects for the interventions when compared with waiting list ($g = 0.95$, 95 % CI 0.74;1.16) and TAU ($g = 0.93$, 95 % CI 0.72;1.15) and no significant effects for the interventions when compared to more active CGs (non-specific components control ($g = 0.18$, 95 % CI −0.04;0.40), specific components control ($g = 0.35$, 95 % CI 0.11;0.58) and active comparator ($g = 0.09$, 95 % CI −0.23;0.40)). Similarly, a network meta-analysis comparing cognitive-behavioural therapy (CBT) for depression with different CGs showed that the effects of CBT differed depending on the CG used as comparator (odds ratio of response against WL (4.71, 95 % CI 3.59;6.17) and against psychological placebo (2.32, 95 % CI 1.48;3.63) (Michopoulos et al., 2021). Cuijpers et al. (2016) also showed in their meta-analysis on CBT for major depression and anxiety disorders (generalized anxiety disorder, panic disorder and social anxiety disorder) that the effect sizes differ depending on the choice of control group (major depression: CBT vs. waiting list ($g = 0.98$, 95 % CI 0.80;1.17), CBT vs. care as usual ($g = 0.60$, 95 % CI 0.45;0.75) or e.g. general anxiety disorder: CBT vs. waiting list ($g = 0.85$, 95 % CI 0.72;0.99), CBT vs. care as usual ($g = 0.45$, 95 % CI 0.26;0.64)). Smits and Hofmann (2009) found in the area of anxiety disorders that CGs with supportive but non-specific components are associated with a certain reduction in anxiety severity ($g = 0.45$, 95 % CI 0.35;0.46).

To our knowledge, the role of CGs in the area of schizophrenia has not been explored yet. Schizophrenia is a disorder that is often associated with treatment-resistant symptoms (Meltzer, 1997). The general consensus in the definition of treatment-resistant schizophrenia is the lack of response to at least two treatment attempts with two different antipsychotics in adequate doses over 6 weeks each (Howes et al., 2017; Kane et al., 2019). Psychosocial interventions, in particular cognitive behavioural therapy, are recommended for treatment-resistant schizophrenia (Keepers et al., 2021). The aim of this study is, therefore, to investigate the effects of different CGs on the difference between intervention and CG in RCTs on psychological interventions in patients with treatment-resistant schizophrenia. In addition, we investigated to what extent the patients improved in symptomatology in different control group conditions.

2. Methods

2.1. Study design and inclusion criteria

The data and the adapted methodological approach of this systematic review with meta-analysis are an extension of another study whose protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Salahuddin et al., 2022), and we follow the PRISMA reporting guidelines (Page et al., 2021; see Supplementary 1). Included studies were RCTs of psychological or psychosocial interventions in adults with a diagnosis of schizophrenia or related disorder such as schizoaffective, schizophreniform, delusional, or non-affective psychotic disorder. All patients had to be described as treatment-resistant in the inclusion criteria as defined by the study authors, to ensure a relatively homogeneous population. The description of treatment-resistant schizophrenia in the studies was then categorized into three categories: the minimum definition was the persistence of psychotic symptoms, the moderate definition was considered to be non-response to at least two antipsychotic treatments, and the optimal definition was a combination of retrospective and prospective criteria for TRS (see Supplementary 3 Table 1). There were no restrictions regarding gender, ethnicity, language, country, setting or severity of treatment-resistance. Studies that examined patients with schizophrenia in the context of a comorbid illness were excluded.

2.2. Interventions and control groups

All psychological and psychosocial interventions for treatment-resistant schizophrenia were eligible for inclusion, for example psychotherapies such as CBT, cognitive training, or music therapy, but also therapies such as counselling, psychoeducation, psychosocial interventions, case management, rehabilitation, vocational rehabilitation, or virtual reality interventions. The control groups of the studies were classified into the following four control group forms, depending on the description or the information given after communication with the authors: active CG, inactive CG, TAU-CG and waitlist CG. A detailed description of the four categories is shown in Table 1.

2.3. Outcomes

All studies that met the inclusion criteria and measured overall symptoms of schizophrenia using validated rating scales such as the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) or the Schizophrenia Change Scale (SCS; Montgomery et al., 1978) were included in this study.

2.4. Search strategy

Our search strategy was based on a broad search, aimed at identifying studies of psychological treatments in patients with schizophrenia, which were then carefully screened to select the studies which met the inclusion criteria for the present systematic review. The following databases were searched: EMBASE, BIOSIS, CINAHL, Cochrane CENTRAL, PubMed, MEDLINE, PsycINFO, LILACS, Dissertation Abstracts, ClinicalTrials.gov, World Health Organization's International Clinical Trials Registration Platform and the Cochrane Schizophrenia Group's trial registry (up to January 2020); Cochrane Schizophrenia Group's trial registry (Cochrane Schizophrenia, 2023) (that is compiled including searches in multiple databases, please see Supplementary 2b for details), up to March 2022; a last search update was conducted in PubMed and CENTRAL up to July 2023. In order not to disregard any publications, there were no language restrictions in the search. In case of missing or unclear information, the authors of studies published in the last 30 years were contacted (see Supplementary 3 Table 2). The detailed search strategy can be found in the Supplementary 2.

2.5. Data extraction and risk of bias assessment

First, all study titles and abstracts identified through the search were reviewed and checked for eligibility by two independent reviewers. Any ambiguities were discussed and, if not clarified, the associated publication was retrieved and inspected. Subsequently, the full text of all included studies was again reviewed by two independent investigators and discussed in case of discrepancy.

Data extraction was performed by two independent reviewers (NHS

Table 1
Description of the control groups.

Intervention	Description of the Intervention
Active control group	This group includes interventions that are evidence-based and have already been studied for their effectiveness. The treatment content includes psychological and psychotherapeutic elements, which differ from the experimental condition.
Inactive control group	This includes interventions that involve the same intensity of treatment in duration and contact with the therapist. However, the interventions do not include specific therapeutic elements, but rather an empathic and supportive attitude towards the patient, sharing of experiences and active listening. Occasionally, interventions may include educational content.
TAU control group	TAU is a control condition that includes routine standard treatment. This can be wide-ranging, from treatment with medication alone to extensive treatment with psychological elements.
Waitlist control group	In the waitlist control condition, patients receive the same treatment as the patients in the experimental condition after the end of the intervention phase.

and either AS or IB) using a Microsoft Access database designed specifically for schizophrenia studies. In the case of any disagreements between the two reviewers, a third experienced reviewer was consulted for clarification.

To assess study quality, two independent investigators (NHS and either AS or IB) assessed the risk of bias using the Cochrane Risk of Bias Tool 2 (RoB2; Sterne et al., 2019) (see Supplementary 5 Figure 1).

2.6. Statistical analysis

Statistical analyses were conducted using the software R Studio version 4.3.1 (R Core Team, 2023) and the meta package version 6.5–0 (Balduzzi et al., 2019). Standard mean deviations (SMDs) and 95 % confidence intervals (CIs) were calculated, and forest plots were created.

First, we conducted a meta-analysis comparing all interventions with all control groups. A subgroup analysis was made to investigate whether the magnitude of the difference depended on the control groups. For this purpose, the studies were assigned to following control group categories: active CG, inactive CG, TAU-CG and waitlist CG. Then a test for subgroup differences was carried out to investigate the impact of the different CGs.

Second, we carried out sensitivity analyses. Here, the previously described analysis was repeated excluding certain characteristics, to investigate whether these had any influence on the estimates. To control for the potentially confounding factor of diversity of psychological interventions, only studies with CBT as experimental condition were included in the sensitivity analysis. Finally, we post-hoc applied a common-effects model.

Third, we calculated the standardized mean change (SMC) in symptom severity for each of the control groups, assuming a potential correlation of 0.5 (Balk et al., 2012). A single-group meta-analysis was conducted with the SMCs from the CGs using R Studio's metagen function to determine the differences in symptom reduction between the CGs. In a single-group meta-analysis there is no comparator, but the effects of the control groups are summarised.

Heterogeneity was investigated using I^2, for which an I^2 of 30–60 % indicated potentially moderate heterogeneity, 50–90 % indicated potentially substantial heterogeneity and from 75 to 90 % indicated substantial heterogeneity (Deeks et al., 2022).

3. Results

3.1. Study selection and characteristics of the studies

The process of study selection was illustrated in Fig. 1. The literature search identified 30,326 references. After title/abstract screening, 5762

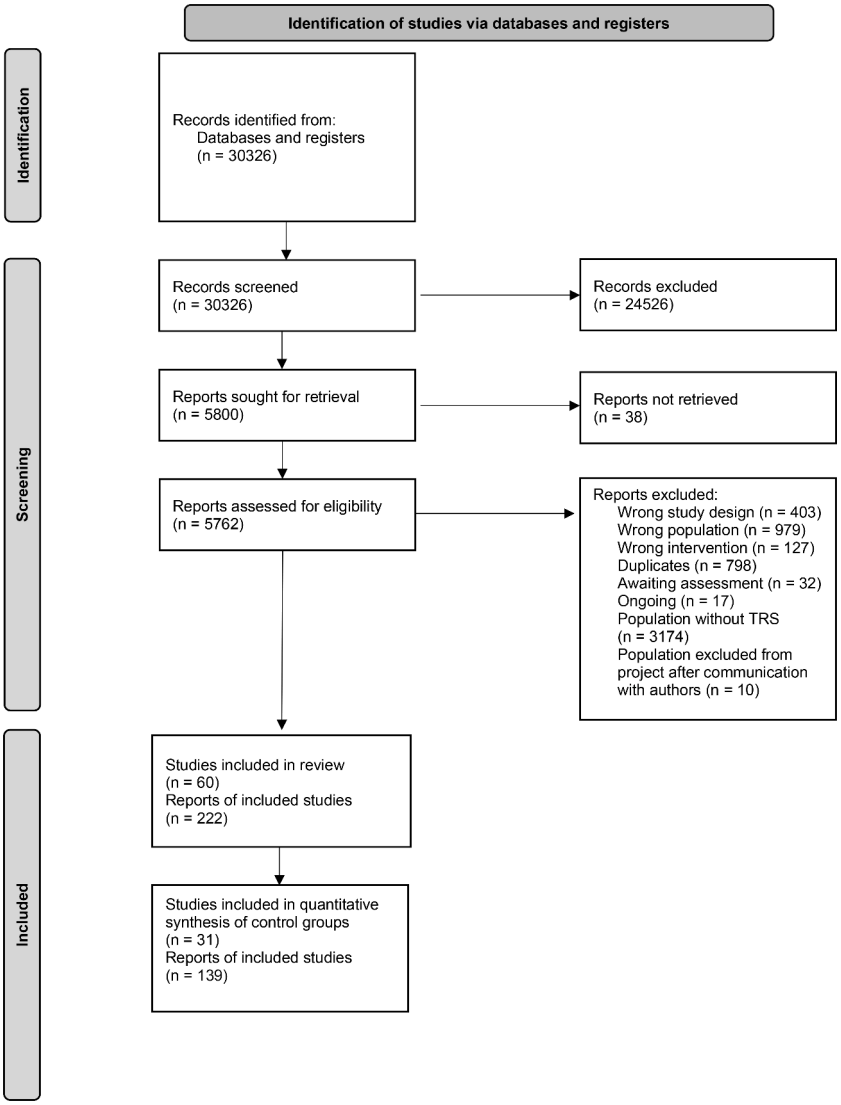

Fig. 1. PRISMA flow diagram describing the process of study selection.

references were screened as full text. In the process, 5540 references were excluded for various reasons (see Fig. 1). Of these, 9 potentially suitable studies/trial registrations (Malda et al., 2013; ChiCTR-IPR-17011541, 2017; DRKS00012523, 2018; Müller et al., 2018; Freeman et al., 2019; NCT02787135, 2019; NCT04143126, 2019; Garety et al., 2021; Smith et al., 2022) with 17 references were reported as ongoing, and a further 5 studies (Anzai et al., 2002; Farhall et al., 2009; Velligan et al., 2015; NCT03852706, 2019; Lincoln et al., 2021) with 10 references were excluded after communication with the study authors. As a result, 222 references reporting about 60 studies were included. Of these 31 studies (conducted between 1997 and 2022; 1624 participants in the psychological interventions and 1501 participants in the CGs) with 139 references had data for overall symptoms (Kuipers et al., 1997; Yang et al., 1998; Pinto et al., 1999; Sensky et al., 2000; Turkington et al., 2002; Durham et al., 2003; Rector et al., 2003; Jenner et al., 2004; Valmaggia et al., 2005; Barrowclough et al., 2006; Röhricht and Priebe, 2006; Lecomte et al., 2008; Haddock et al., 2009; Penn et al., 2009; van der Gaag et al., 2011; Ojeda et al., 2012; Shawyer et al., 2012; Kråkvik et al., 2013; Lee et al., 2013; Freeman et al., 2015b, 2015a; Khazaal et al., 2015; Shawyer et al., 2017; Du Sert et al., 2018; Klingberg et al., 2018; Morrison et al., 2018; Rakitzi and Georgila, 2019; Kayo et al., 2020; Dellazizzo et al., 2021; Vizzotto et al., 2021; Liang et al., 2022) (provided in the publications or by the study authors – see Supplementary 3) and could be included in the quantitative analyses. Two studies (Durham et al., 2003; Lecomte et al., 2008) had three study arms and the remaining 29 studies had two study arms, for a total of 33 comparisons. Four studies were categorised as applying an active CG condition and included CBT (Dellazizzo et al., 2021; Liang et al., 2022), social skills training (Lecomte et al., 2008), and occupational therapy (Ojeda et al., 2012). 13 studies were categorised as an inactive CG and included supportive therapy (Pinto et al., 1999; Durham et al., 2003; Penn et al., 2009; Lee et al., 2013; Klingberg et al., 2018), social activity therapy (Haddock et al., 2009), inactive controls (Kayo et al., 2020; Vizzotto et al., 2021), supportive counselling (Valmaggia et al., 2005; Röhricht and Priebe, 2006) and befriending (Sensky et al., 2000; Shawyer et al., 2012, 2017). For the original descriptions of the active and inactive CGs from the included studies see Supplementary 4 Table 6 and Table 7. The inactive CGs (e.g. supportive therapy, supportive counselling, befriending) and TAU CGs are separate categories. 14 studies used TAU-CG (Kuipers et al., 1997; Yang et al., 1998; Turkington et al., 2002; Durham et al., 2003; Rector et al., 2003; Jenner et al., 2004; Barrowclough et al., 2006; van der Gaag et al., 2011; Freeman et al., 2015a, 2015b; Khazaal et al., 2015; Du Sert et al., 2018; Morrison et al., 2018; Rakitzi and Georgila, 2019) and two studies were categorised as a waitlist CG (Lecomte et al., 2008; Kråkvik et al., 2013). The characteristics of the included studies investigated interventions and their participants were shown in Supplementary 4, (Table 5). The mean sample size per study was 48.8 participants (range 7–257) and the mean trial duration was 20.9 weeks. The mean age of the 3125 participants was 37.3 years and 1099 of these were female (35.2 %). All participants were treatment-resistant by inclusion criteria of the studies (see Supplementary 3 Table 1). The overall RoB2 (Sterne et al., 2019) rating in the 31 included studies with data was “low” in four studies (13 %) (Khazaal et al., 2015; Shawyer et al., 2017; Klingberg et al., 2018; Morrison et al., 2018), “some concerns” in 20 studies (64 %) (Kuipers et al., 1997; Yang et al., 1998; Pinto et al., 1999; Sensky et al., 2000; Durham et al., 2003; Rector et al., 2003; Jenner et al., 2004; Valmaggia et al., 2005; Barrowclough et al., 2006; Lecomte et al., 2008; Haddock et al., 2009; Penn et al., 2009; Ojeda et al., 2012; Shawyer et al., 2012; Kråkvik et al., 2013; Freeman et al., 2015a, 2015b; Dellazizzo et al., 2021; Vizzotto et al., 2021; Liang et al., 2022) and “high” in seven studies (23 %) (Turkington et al., 2002; Röhricht and Priebe, 2006; van der Gaag et al., 2011; Lee et al., 2013; Du Sert et al., 2018; Rakitzi and Georgila, 2019; Kayo et al., 2020) (see Supplementary 5 Figure 1).

3.2. Psychological interventions compared with control groups

Overall, the psychological interventions had a greater effect on symptom reduction to all CGs combined (SMD = −0.20, 95 % CI −0.32;−0.08). When separating the CGs, only compared to TAU-CG and waitlist CG the psychological interventions were superior. The heterogeneity of the effects can be classified as moderate (I^2 = 51 %). The difference between interventions and controls increased with decreasing assumed efficacy of the four CGs. The lowest difference was found in the active CG (SMD = 0.07, 95 % CI −0.29;0.44, I^2 = 57 %), followed by the inactive CG (SMD = −0.08, 95 % CI −0.21;0.05, I^2 = 0 %), TAU-CG (SMD = −0.33, 95 % CI −0.53;−0.14), and finally waitlist CG (−0.50, 95 % CI −1.18;0.18, I^2 = 51 %, test for subgroup differences p = 0.07) (see Fig. 2).

3.2.1. Sensitivity analyses

A potential confounding factor and explanation for the heterogeneity in the previous analyses could be the diversity of the psychological interventions that were analysed together. Therefore, a sensitivity analysis considering only CBT as intervention was conducted. Of the 31 studies included in the analysis, 18 studies (Kuipers et al., 1997; Sensky et al., 2000; Turkington et al., 2002; Durham et al., 2003; Rector et al., 2003; Valmaggia et al., 2005; Barrowclough et al., 2006; Lecomte et al., 2008; Haddock et al., 2009; Penn et al., 2009; van der Gaag et al., 2011; Shawyer et al., 2012; Kråkvik et al., 2013; Lee et al., 2013; Freeman et al., 2015a, 2015b; Klingberg et al., 2018; Morrison et al., 2018) investigated CBT as experimental condition. These 18 studies included 2310 participants and allowed for 20 comparisons, as two studies had three arms. Overall, CBT showed greater symptom reduction compared to the CGs (SMD = −0.17, 95 % CI −0.26;−0.07) with low heterogeneity (I^2 = 14 %). The hierarchy of intervention versus control differences was the same as in the primary analysis and the mean effect sizes were similar (active CG: SMD = −0.08, 95 % CI −0.56;0.41; inactive CG: SMD = −0.11, 95 % CI −0.26;0.04; TAU-CG: SMD = −0.17, 95 % CI −0.32;−0.03, waitlist-CG: SMD −0.50, 95 % CI −1.18;0.18), although the test for subgroup differences was not significant (I^2 = 14 %; p = 0.68; see Supplementary 6 Figure 2).

The test for subgroup difference for all studies was significant if a common-effects model was used (post-hoc analysis, I^2 = 51 %; p = 0.03; see Figure 2).

3.3. Results change in overall symptoms in control groups

The SMC of the control groups was calculated for 31 studies with 1501 participants in the control groups and used for the single-group meta-analysis.

Overall, the CGs were associated with a reduction in the mean pre-post comparison (SMC = −0.29, 95 % CI −0.39;−0.20, I^2 = 64 %; see Fig. 3).

As hypothesized, the lowest change from pre to post measurement was found in the waitlist CG (SMC =−0.16, 95 % CI −0.44;0.12), followed by the TAU-CG (SMC = −0.20, 95 % CI −0.34;−0.06). However, the active CG came next (SMC = −0.27, 95 % CI −0.44;−0.09) and the inactive CG had the highest reduction in overall symptoms (SMC = −0.46, 95 % CI −0.63;−0.29). The p-value of the test for subgroup differences was 0.1, see Fig. 3.

4. Discussion

To the best of our knowledge this is the first meta-analysis to investigate the role of CGs in schizophrenia studies and especially in studies on treatment-resistant schizophrenia. 31 studies with 3125 participants were examined in the present analysis.

Overall, the psychological interventions showed a superiority in the reduction of overall symptoms compared to all CGs combined. Nevertheless, there was a difference in the effect between the CGs, with

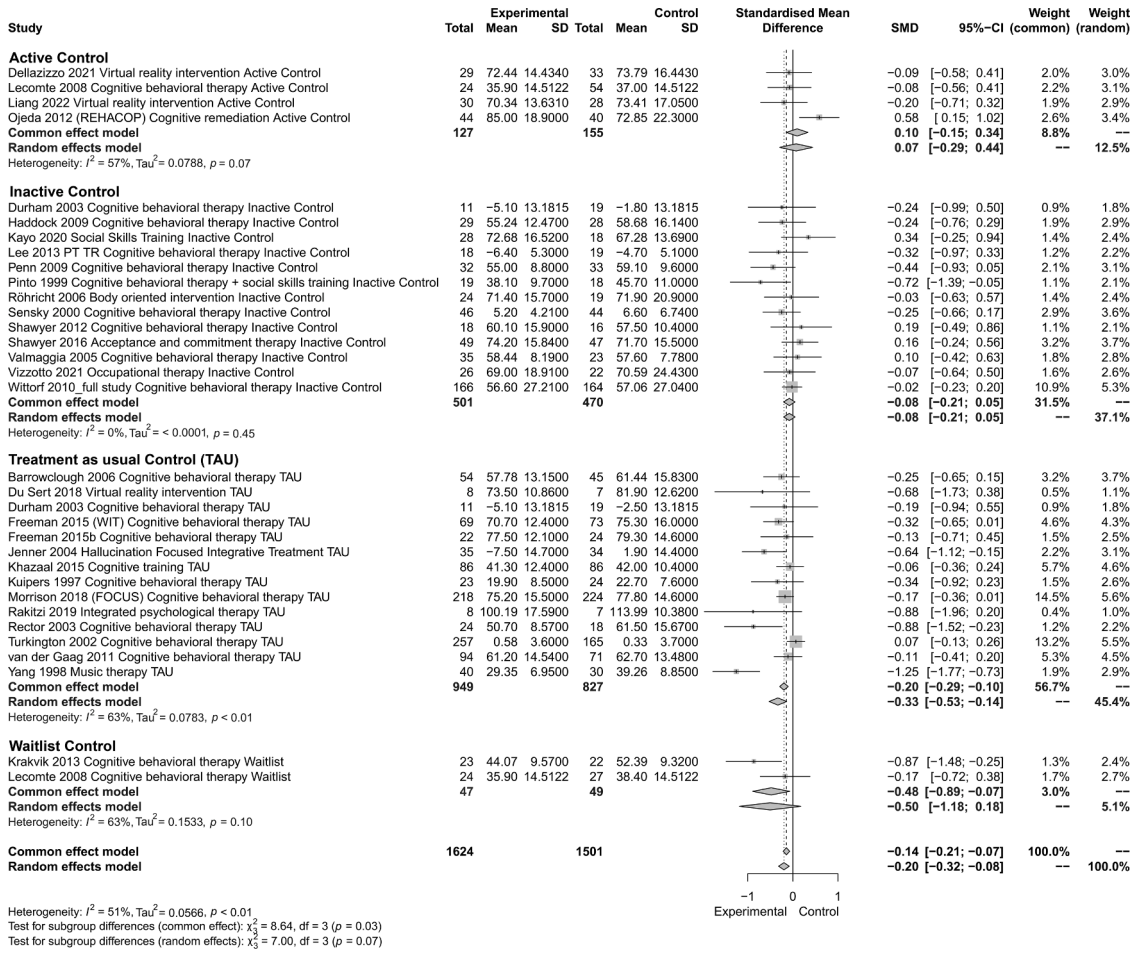

Fig. 2. Forest-plot of psychological interventions versus control groups.
Forest plot displaying the results of the subgroup analysis of the control groups (active CG, inactive CG, TAU-CG, waitlist CG) with the number of participants for the experimental and control condition, standardized mean difference (SMD) with its confidence interval (CI) and the weight of each study.

psychological interventions showing no difference to active CGs (mean SMD 0.07, 95 % CI −0.29;0.44), a very small but not significantly different SMD compared to inactive CGs (−0.08, 95 % CI −0.21;0.05), a small to medium SMD compared to TAU-CGs (−0.33, 95 % CI −0.53;−0.14) and a medium SMD compared to waitlist CGs (−0.50, 95 % CI −1.18;0.18). When separately examining only CBT as psychological intervention the results were similar. The results for all studies met the conventional $p < 0.05$ threshold for statistical significance when a common-effects model was applied.

The analysis of the change in mean values from pre- to post-intervention for the CGs showed that all CGs were associated with a reduction in overall symptoms of schizophrenia. As hypothesized, the smallest reduction was found in the waitlist-CGs followed by TAU-CGs. The magnitude of effects in the other two CGs did not match our expectations, because the effects were larger in the inactive CGs compared with the active CGs. It was assumed that the symptoms of patients in more active CGs, with specific therapy content, improved more than those of patients in inactive CGs, with less specific therapy content.

Thus, our results indicate that there are differences in the effects of various control groups in psychotherapy studies on treatment-resistant schizophrenia. From a methodological point of view, this means that the choice of the control group can have a significant impact on the size of the effect determined for the investigated psychological intervention.

For the active CGs, a meta-analysis on CGs in psychotherapy studies on depression similarly showed that no difference was found between the active comparison groups and the experimental condition (Mohr et al., 2014). Our results on patients with treatment-resistant schizophrenia are in line with these findings but should be treated with caution as only based on four comparisons with a total of 282 participants. Moreover, the active control groups were CBT (versus virtual reality as intervention) in Dellazizzo et al. (2021) and in Liang et al. (2022), social skills training (versus CBT and waitlist) in Lecomte et al. (2008), and occupational therapy (versus cognitive remediation) in Ojeda et al. (2012), thus quite effective CGs.

A similar result was also found for the inactive CGs. The result of the pronounced symptom reduction from pre- to post- measurement, which was greatest within the CGs for the inactive CG (mean SMC –0.46, 95 % CI −0.63;−0.29) may in part explain this finding. This finding is in contrast to a network meta-analysis in patients with positive symptoms in schizophrenia where CBT outperformed inactive CGs (Bighelli et al., 2018).

Only when compared to treatment as usual, the psychological interventions were associated with a significant effect in symptom reduction. The point estimate was even larger when waitlist CGs were used, but there was uncertainty due to low power because only two waitlist CG studies were available. At the same time, the pre- to post-change in symptom severity was again the smallest compared for waitlist CGs and TAU-CGs compared to the other CGs. This is in agreement with other research, particularly for depression (Mohr et al., 2014; Michopoulos et al., 2021). In terms of TAU, it should be noted that it represents a heterogeneous group and can range from minimal treatment to comprehensive treatment (Watts et al., 2015; Cuijpers et al., 2021). This aspect should be considered when interpreting the results and when designing future studies.

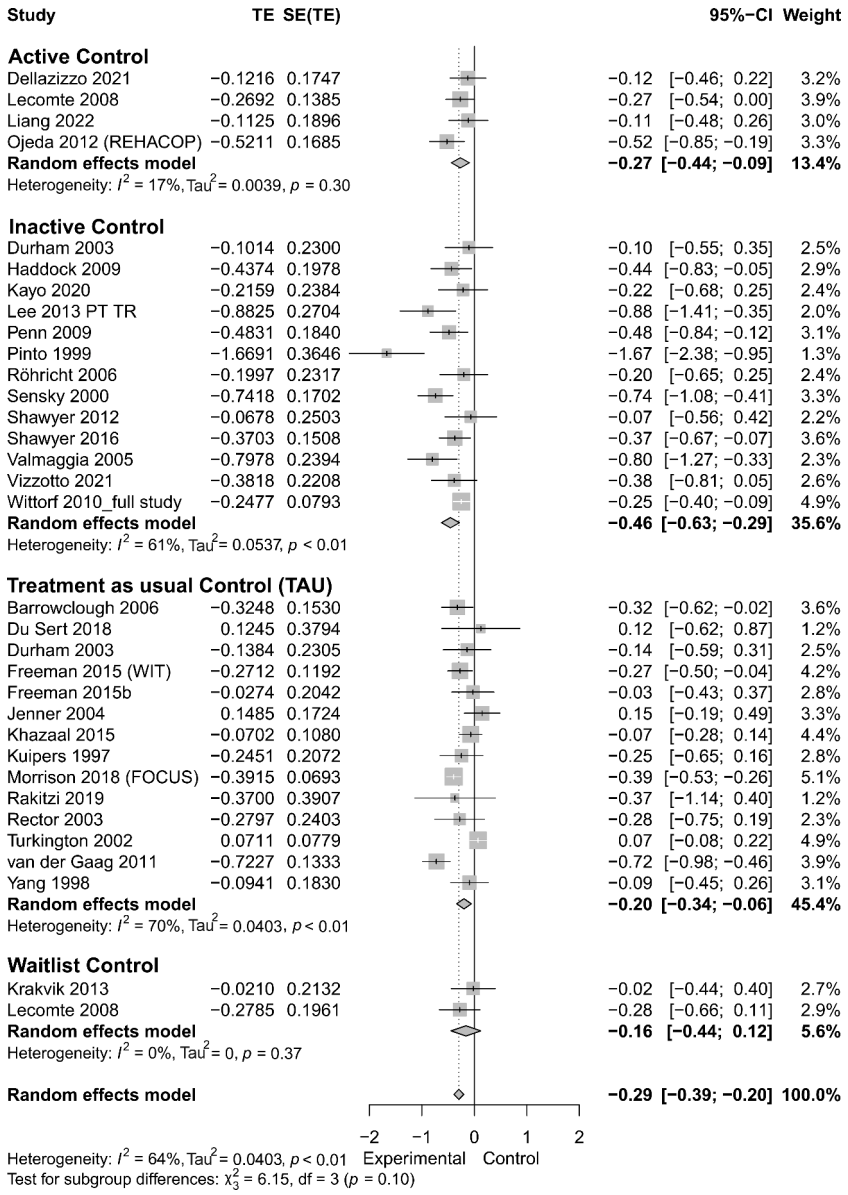

Fig. 3. Forest-plot of change in overall symptoms in control groups.
Forest plot displaying the results of the single group meta-analysis of the control groups (active CG, inactive CG, TAU-CG, waitlist CG) with the treatment effect (TE), standard error (SE), standardized mean change with its confidence interval (CI) and the weight of each study.

4.1. Limitations and strengths

First, the subgroup test of the primary analysis was $p = 0.07$ (0.03 in a post-hoc analysis using a common-effects model) and did thus not meet conventional levels of statistical significance. However, statisticians strongly argue against dichotomising study results as statistically significant or not based on p-value thresholds such as $p < 0.05$ (Wasserstein and Lazar, 2016; Wasserstein et al., 2019). The pattern of magnitude of SMDs was as expected. When waitlist comparisons were used, the superiority of psychotherapeutic interventions was the largest and when active CGs were used it was the lowest. Among others, general patterns in the data and previous knowledge should also be applied. In this regard it was well known from studies in other fields that SMDs depend on the control group (Mohr et al., 2014; Cuijpers et al., 2016; Michopoulos et al., 2021). The number of studies available for these studies was clearly higher (Mohr et al., 2014; Cuijpers et al., 2016; Michopoulos et al., 2021). Thus, our relatively small number of studies might have reduced statistical power.

Another potential limitation was the considerable heterogeneity in some comparisons, which was reduced when limiting the investigation to CBT. Furthermore, except for the sensitivity analysis with CBT, all psychological interventions were considered together in the analysis and thus no precise conclusions about individual psychological interventions can be drawn from our results. Another aspect was the weak description of TRS groups in the included studies. As can be seen in the Supplementary 3 (Table 1), no study could be categorised in the strongest category with the most detailed definition of TRS. Future studies should define TRS more clearly, and at best, using more stringent definition criteria.

An important strength of our study was the homogeneous patient population comprising treatment-resistant schizophrenia, which provides a specific insight into this population. So far, no other detailed investigations of CGs have yet been undertaken in the field of schizophrenia in general. Due to the considerable proportion of about 30 % of patients with schizophrenia that does not respond to treatment (Meltzer, 1997), the more detailed investigation of this subpopulation is of great

importance.

Finally, our study was planned according to the PRISMA guidelines.

5. Conclusion

Our results were preliminary because some uncertainty remained, and the sample was relatively small. Nevertheless, the results suggest that the effect of the investigated intervention varies depending on the control group used as comparator. This finding has implications in the design of future studies trying to measure the efficacy of psychological interventions for treatment-resistant schizophrenia. A comparison with active controls may not be essential as long as these are effective themselves. A good test for efficacy may be a comparison with at least inactive controls. Moreover, future studies could, for example, consider three-arm trials comparing psychotherapeutic interventions with inactive control conditions and treatment as usual, to measure the added effect of specific therapeutic components.

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Availability of data and materials

The code for the analysis can be provided on request.

CRediT authorship contribution statement

Alexandra Schütz: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nurul Husna Salahuddin:** Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Josef Priller:** Writing – review & editing, Supervision, Resources. **Irene Bighelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefan Leucht:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

Stefan Leucht: In the last 3 years SL has received honoraria as advisor and/or for lectures and/or for educational material from Alkermes, Angelini, Apsen, Eisai, Gedeon Richter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Merck Sharp and Dohme, Mitshubishi, Neurotorium, NovoNordisk, Otsuka, Recordati, Roche, Rovi, Sanofi Aventis, and TEVA.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116069.

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