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Abstract: Summary
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Methods: A systematic literature search was used to identify relevant trials with ≥100 sample size and to extract the drop-out data. Meta-analyses of proportions were used to calculate the rates of drop-out from the experimental intervention and study. Meta-regression was applied to explore the association between the study and sample characteristics and the drop-out rates.
Findings: 43 RCTs were found, with drop-out from intervention ranging from 0% to 63% and study drop-out ranging from 4% to 71%. Meta-analyses of proportions showed an overall drop-out rate of 19% (95% CI: 15-24%) at the experimental intervention level and 19% (95% CI: 16-24%) at the study level. Meta-regression showed that the drop-out rates were not predicted by any of the study and sample characteristics.
Interpretation: In trials on non-pharmacological interventions for patients with schizophrenia, drop-out rates of less than 20% can be expected for both the study and the experimental intervention. A high heterogeneity of drop-out rates across studies shows that even lower rates are achievable, but current data do not allow to identify helpful study characteristics.
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Drop-out rates in trials evaluating non-pharmacological interventions for schizophrenia – systematic review and meta-analysis

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Summary

Background: Essential criteria for the methodological quality and validity of randomised controlled trials are the drop-out rates from both the experimental intervention and the study as a whole. This systematic review and meta-analysis assessed these drop-out rates in trials evaluating non-pharmacological interventions for schizophrenia.

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Interpretation: In trials on non-pharmacological interventions for patients with schizophrenia, drop-out rates of less than 20% can be expected for both the study and the experimental intervention. A high heterogeneity of drop-out rates across studies shows that even lower rates are achievable, but current data do not allow to identify helpful study characteristics.

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Introduction

Two major challenges in randomised controlled trials (RCTs) include treatment noncompliance and missing outcome data. These complications are caused by participants not receiving or discontinuing the allocated intervention and loss to follow-up. Although some attrition can be expected in clinical trials, ensuring retention of participants is crucial to achieve sufficient statistical power to detect the effect of treatment. There is no standard for acceptable drop-out rates but some evidence suggests that the rate exceeding 20% can introduce a risk of bias[1].

Loss of data can occur at different levels within a trial. In non-pharmacological trials non-adherence refers to the failure to attend a required number of appointments or sessions[2]. In contrast, drop-out from intervention refers to a complete discontinuation of an intervention and it has been estimated to be 13% in RCTs testing psychosocial treatments for people with schizophrenia[3]. Discontinuing an intervention usually does not automatically exclude the participant from the follow-up, so outcome data can be collected if the participant is willing to provide them. Drop-out at the study level is defined as a failure to complete follow-up assessments, usually due to withdrawal from the study, and can occur following completing an intervention. To our knowledge there have been no systematic studies establishing the scale of drop-out from RCTs evaluating non-pharmacological interventions for schizophrenia at both the experimental intervention and the study level.

Complete outcome data from all randomised participants is necessary for a full application of the intention-to-treat (ITT) approach[4], which is the 'gold standard' for analysing the results from trials evaluating the effectiveness of a treatment in a pragmatic setting[5,6]. ITT analysis includes all randomised participants, regardless of whether they adhered to or received the allocated intervention. The purpose of the ITT approach is to reflect a real-life effect of an intervention in clinical practice, taking into account the deviations from protocol that would occur in routine practice. Thus, every effort should be made to obtain complete outcome data for all randomised participants, including those who did not complete the intervention but continued to complete follow-up assessments.

Developing effective and efficient retention strategies for clinical trials requires an understanding of what factors affect the likelihood of premature discontinuation of intervention or loss to follow-up. The vast majority of the literature on the determinants of attrition in psychiatric treatment has focused on pharmacological trials and identified factors negatively correlated with treatment adherence, such as substance misuse[2,7], unemployment[2], unpleasant side effects of medication[7], negative attitude towards medication[7]. In one available study analysing drop-out from psychosocial treatment specifically for schizophrenia the following variables were found to be associated with higher drop-out rates: being male, higher age, longer illness duration, longer treatment duration[3]. Whereas study quality and inpatient setting were associated with lower drop-out rates[3]. These findings suggest that both study and sample characteristics can affect drop-out from clinical trials. Understanding what factors influence discontinuation of intervention and loss to follow-up can guide the development of strategies to limit these. Investigating relationships between specific study and sample characteristics and drop-out rates allows for examining if the data missing from those who dropped out is missing at random or whether individuals dropping out have any characteristics in common that make them more likely to prematurely discontinue participation in trials.

The aims of this study were firstly to systematically identify relevant large-scale RCTs evaluating non-pharmacological interventions for individuals with schizophrenia; secondly to perform meta-analyses to establish the proportion of participants who drop-out of a) experimental intervention and b) study; and thirdly to perform a meta-regression to examine the predictors of drop-out rates.

Methods

Literature search

A protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[8]. Five bibliographic databases (Medline, PsycINFO, Embase, CINAHL, Cochrane Central Database) were searched in January 2016 for papers reporting results from RCTs evaluating non-pharmacological interventions for adults with schizophrenia published

between January 1996 and January 2016. As this review was interested in the reported drop-out rates, the lower time limit was set based on the publication date of the first Consolidated Standards of Reporting Trials (CONSORT) statement[6]. Additional hand searches of six key journals (Schizophrenia Bulletin, The British Journal of Psychiatry, The American Journal of Psychiatry, JAMA Psychiatry, Acta Psychiatrica Scandinavica, and Trials) and reference lists of relevant systematic reviews were carried out to identify other eligible papers.

A comprehensive search strategy of titles and abstracts used MeSH headings including 'SCHIZOPHRENIA' OR 'PSYCHOSIS' OR 'PSYCHOTIC DISORDERS' AND 'CLINICAL TRIALS' OR 'RANDOMISED CONTROLLED TRIAL/S' and text words including 'psychos*s' OR 'psychotic' OR 'schizo*' OR 'therapy' OR 'intervent*' OR 'nonpharmacological' AND 'RCT' OR 'randomi*ed controlled trial' OR 'clinical trial'. Search terms were modified for each database.

A two-step screening process was performed. The first screening of all titles and abstract was performed by the primary reviewer (PS) followed by the second reviewer (SW) independently screening a random selection of 20% of the citations. The same process was followed for the second screening including full texts. Any discrepancies were resolved through discussion between the reviewers.

Study selection

The following eligibility criteria had to be met for papers to be included in the review: 1) RCT design, 2) the sample size of at least 100, 3) evaluated a non-pharmacological intervention delivered either individually or in a group, 4) the sample comprised only adults above the age of 18 with a diagnosis of schizophrenia, schizophreniform, schizoaffective or delusional disorder, 5) written in English.

The decision to include RCTs with a sample size of at least 100 was made as larger sample sizes provide narrower confidence intervals and therefore more precise estimates of the value. This increased the precision of the summary measure of the drop-out rates produced in the meta-analyses.

Interventions requiring involvement of a support person (e.g. family therapy) were excluded as they were thought to potentially influence decisions about participation made by people receiving the intervention. Interventions considered to be invasive (e.g. brain stimulation) were also excluded as they present a different type of risk to be considered by participants and are therefore likely to affect attrition rates. Details of the excluded studies and reasons for exclusions are available the authors on request.

Definition of drop-out

The primary outcomes for two meta-analyses were a) drop-out from experimental intervention and b) drop-out from study. Intervention drop-out rate was defined as the proportion of participants reported as not completing the intervention (according to authors' definition) who were randomised to an arm involving a non-pharmacological intervention for schizophrenia and who began the intervention. Study drop-out rate was defined for the purposes of this study as the proportion of participants who did not complete the last follow-up assessment in all study arms. Participants who were lost prior to randomisation were not considered dropouts and were not included in the calculations.

Data extraction

Drop-out rates were extracted either from the CONSORT diagrams (if provided) or from the text of the article. The authors of 19 studies were contacted with a request for clarification or for information not available in the paper. Twelve responses were received.

Data on study- and sample-level characteristics used as potential predictors of drop-out rates in the meta-regression were extracted on: year of publication, geographical location (Europe, USA, Asia), study setting (inpatient vs. outpatient), intervention delivery (individual vs. group), type of control intervention (active vs. treatment as usual), intervention duration, study duration, number of intervention sessions, number of evaluations, and quality score (see below). Sample-level variables included: age, gender, and illness duration. These included all randomised participants for the meta-

regression of study drop-out and only the participants who were allocated to intervention for the meta-regression of intervention drop-out.

Quality assessment

Quality of studies was appraised by giving a score from 0 to 3 using the following set of criteria developed specifically for the purposes of this study as the data were different from those for clinical effectiveness: i) CONSORT diagram provided (1 point), ii) Clear definition of intervention completion (1 point), iii) Clear information on sample size calculation (1 point). These were selected on the basis of being the most relevant indicators of quality for the aim of this study.

Statistical analysis

The primary outcome was the proportion of participants who dropped out of a) experimental intervention and b) study. This was calculated in Stata using *metaprop* command as the number of individuals who discontinued intervention (a) or were lost to follow-up (b) divided by the total number of individuals who began intervention (a) or were randomised to study (b). The Freeman-Tukey double arcsine transformation was enabled to include studies with estimated proportion at 0 or 1. Otherwise, they would be automatically excluded from the analysis leading to a biased pooled estimate.

For meta-regression a random-effects model was used as it is based on the assumption that the study, intervention and sample characteristics are not identical across studies and that the observed difference between the drop-out rates and the mean cannot entirely be attributed to the sampling error and other factors. The potential predictors used in meta-regressions included both study- and sample-level variables.

The level of between-study heterogeneity was assessed by calculating the Q-statistic and the I^2 statistic. Egger's test of the intercept with the Freeman-Tukey double arcsine transformation and a funnel plot of standard error against study drop-out rate were computed to assess the evidence for publication bias.

Results

Study Characteristics

The database search identified 5,450 studies (see Figure 1 for the PRISMA flow diagram). After screening, 49 papers based on 43 studies were included in this review. Because studies were reported in multiple papers data was extracted per study, not per paper. Details of the 49 papers can be found in Table 1. Two out of the 43 studies did not adequately report study drop-out information to be included in the analysis; therefore they were excluded from the meta-analysis of study drop-out rates. The majority of publications were from European countries (n=29), followed by North America (n=11) and Asian countries (n=3).

The 43 studies evaluated 59 non-pharmacological interventions (Table 1), but only 34 studies reported intervention completion for 50 interventions and these were included in the meta-analysis of intervention drop-out.

Figure 1. PRISMA Diagram for Paper Selection

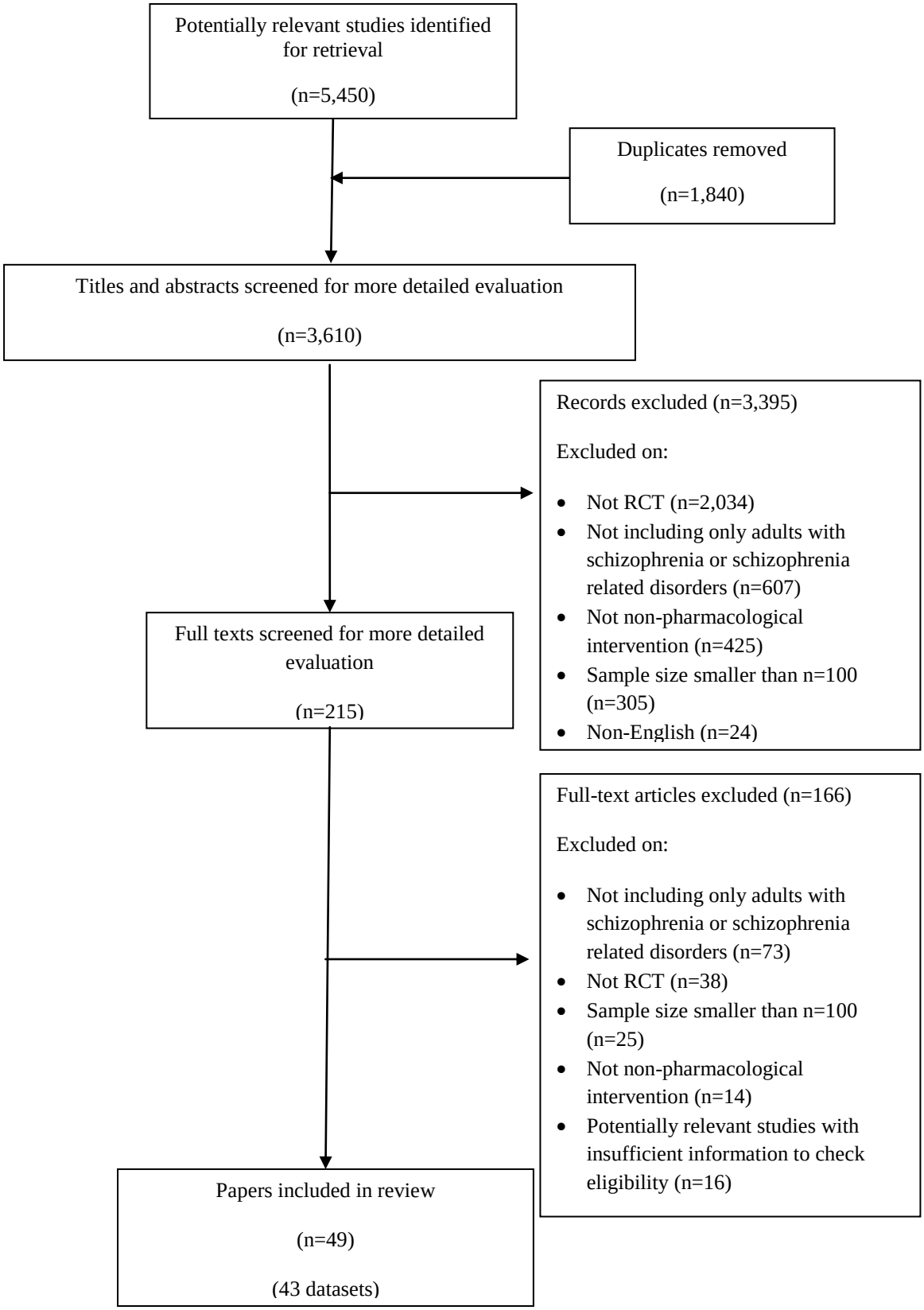


Table 1. Description of studies

Study reference	Region	Intervention evaluated	Participants randomised to study (n)	Intervention delivery	Setting	Length of follow-up (m)	Intervention duration (m)	Quality score
Barkhof 2013 [9]	Europe	Motivational interviewing	114	Individual	In- and out-patient	12	6·5	3
Barrowclough 2006 [10]	Europe	Cognitive Behavioural Therapy (CBT)	113	Group	Out-patient	12	6	3
Bell 1997 [11]	USA	Work program	150	Individual	Out-patient	12	6	1
Bell 2003 [12]	USA	Neurocognitive Enhancement Therapy (NET) with Work Therapy (WT)	131	Individual	Out-patient	12	6	0
[Bell 2005] [13]								
[Bell 2007] [14]								
Bowie 2012 [15]	USA	Cognitive remediation	114	Group	Out-patient	3	6	2
Chien 2015 [16]	Asia	Adherence therapy	114	Individual	Out-patient	6	4	2
Crawford 2012 [17]	Europe	Group art therapy	417	Group	Out-patient	24	12	2
Franck 2013 [18]	Europe	Individualized therapy and Cognitive Remediation Therapy (CRT)	138	Individual	Out-patient	9	3	1
Freeman 2015 [19]	Europe	CBT	150	Individual	In- and out-patient	6	2	3
Gomar [20]	Europe	Computerized Cognitive Remediation	130	Group	In- and out-patient	6	6	1
Gouzoulis-Mayfrank 2015 [21]	Europe	Implemented integrated treatment	100	Group	In-patient	12	NR	1
Granholm 2014 [22]	USA	Cognitive Behavioural Social Skills Training (CBSST)	149	Group	Out-patient	21	9	1
Gray 2006 [23]	Europe	Adherence therapy	409	Individual	In- and out-patient	13	18	3
Gumley 2003 [24]	Europe	CBT	144	Individual	NR	13	3	2
[Gumley 2006] [25]								
Hamann 2006 [26]	Europe	Shared decision aid	113	Individual	In- and out-patient	18	0·03	1
Hansson 2008 [27]	Europe	DIALOG (computer-mediated structured patient-=key worker communication)	507	Individual	Out-patient	12	12	0
Hogarty 2004 [28]	USA	Cognitive Enhancement Therapy (CET)	121	Group	Out-patient	24	NR	0
Jahn 2011 [29]	Europe	Neurocognitive training (COGPIP trial)	122	Group	In-patient	9	1	1
Jones 2001 [30]	Europe	Personalized computer-based information	112	Individual	NR	3	NR	3
Klingberg 2010 [31]	Europe	CBOS (cognitive behaviourally oriented service)	169	Group	In-patient	6	2	3
Klingberg 2011 [32]	Europe	CBT	198	Individual	Out-patient	12	9	3

[Klingberg 2012] [33]		CBT							
Li 2015 [34]	Asia	CBT	192	Group	In- and out-patient	21	6	2	
Montes 2010 [35]	Europe	Telephone-based nursing strategy to improve adherence to antipsychotic treatment	928	Individual	Out-patient	4	3	1	
Montes 2012 [36]	Europe	Short message service (SMS)-based strategy for enhancing adherence to antipsychotic treatment	340	Individual	Out-patient	6	3	3	
Moritz 2013 [37]	Europe	Complementary Metacognitive Training (MCT)	150	Group	In- and out-patient	6	NR	2	
[Moritz 2014] [38]									
Mueller 2015 [39]	Europe	Integrated Neurocognitive Therapy	156	Group	Out-patient	9	3·75	1	
Patterson 2006 [40]	USA	Functional Adaptation Skills Training (FAST)	240	Group	Out-patient	18	6	1	
[Mausbach 2008] [41]									
Pitkanen 2011 [42]	Europe	Patient education	311	Group	In-patient	12	1	1	
Salyers 2014 [43]	USA	Illness Management and Recovery (IMR)	118	Group	NR	18	9	0	
Schirmer 2015 [44]	Europe	Medication training program	141	Individual	Out-patient	NR	1·64		
Schulz 2013 [45]	Europe	Adherence therapy	161	Group	In- and out-patient	3	NR	3	
Sibitz 2007 [46]	Europe	Low intensity booster sessions of psychoeducation	103	Group	Out-patient	11.25	2.25	1	
Silverstein 2014 [47]	USA	Attention shaping	105	Group	In-patient	5·5	5·5	1	
Staring 2010 [48]	Europe	Treatment adherence therapy (TAT)	109	Individual	Out-patient	12	6	1	
Terzian 2013 [49]	Europe	Social Network intervention	357	NR	Out-patient	24	24	1	
Van der Gaag 2011 [50]	Europe	CBT	216	Group	NR	18	6	1	
Van der Krieke 2013 [51]	Europe	Web-based information and decision tool	250	Individual	Out-patient	12	12	2	
Van Oosterhout 2014 [52]	Europe	Metacognitive group training (MCT)	154	Group	In- and out-patient	6	2	2	
Van Os 2004 [53]	Europe	Two-way Communication Checklist (2-COM)	134	Individual	Out-patient	2	1·5	1	
Velligan 2013 [54]	USA	Interventions for improving adherence to oral medications	142	Group	Out-patient	9	6	1	
Velligan 2015 [55]	USA	CBT and Cognitive Adaptation Training (CAT) and a combination of CBT and CAT	166	Individual	Out-patient	15	9	1	
Williams 2003 [56]	USA	Enhanced guideline implementation strategy	349	Individual	In- and out-patient	20	NR	0	
Xiang 2007 [57]	Asia	Community Re-Entry Module (CRM)	103	Group	In-patient	24	4	2	

Note: n = number, m = months, NR = not reported

Quality analysis

Study quality ranged from 0 to 3, with 5 studies scoring 0, 17 studies scoring 1, 10 studies scoring 2 and 9 studies scoring 3. Twenty-nine out of 43 studies (69%) provided a CONSORT diagram.

Drop-out rates

The overall estimate of the proportion of participants who dropped out of intervention was 19% (95% CI: 15-24%), with a range of 0-63% and a median of 19·4%. Heterogeneity was high at I^2=92·14%. Subgroup analysis by intervention delivery (individual vs. group) showed overall estimates of intervention drop-out of 17% (95% CI: 12-23%) for individually delivered interventions (n=24) and 21% (95% CI: 15-28%) for group interventions (n=26). (Table 3)

The overall estimate of the proportion of participants who dropped out of studies was 19% (95% CI: 16-24%), with a range of 4-71% and a median of 16%. Heterogeneity was high at I^2=95·34% Subgroup analysis by intervention delivery (individual vs. group) showed overall estimates of study drop-out of 18% (95% CI: 12-25%) for studies evaluating individually delivered interventions (n=20) and 21% (95% CI: 16-25%) for studies evaluating group interventions (n=21) (Table 2).

Table 2. Meta-analysis of Study Drop-out Rates

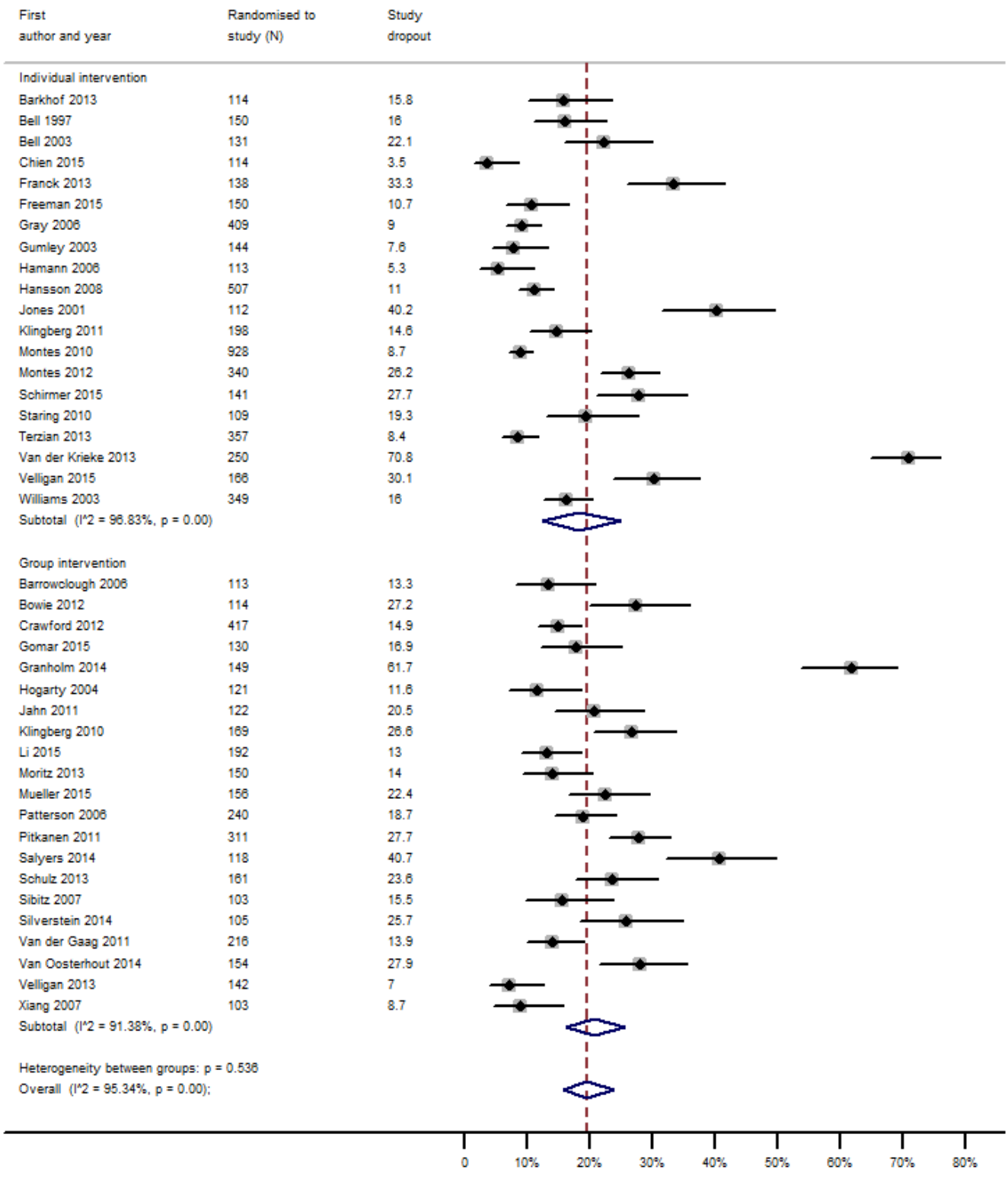
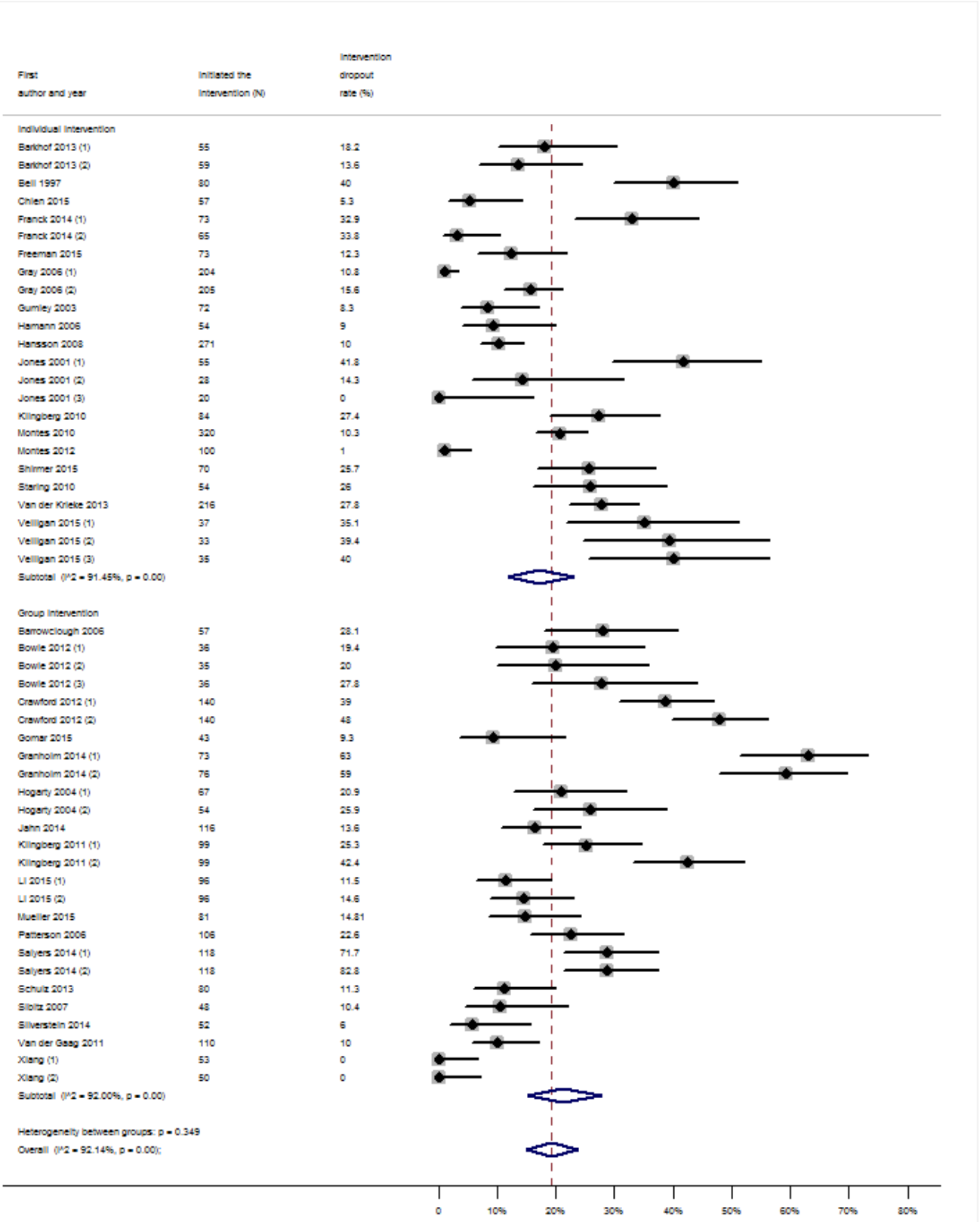


Table 3. Meta-analysis of Intervention Drop-out Rates



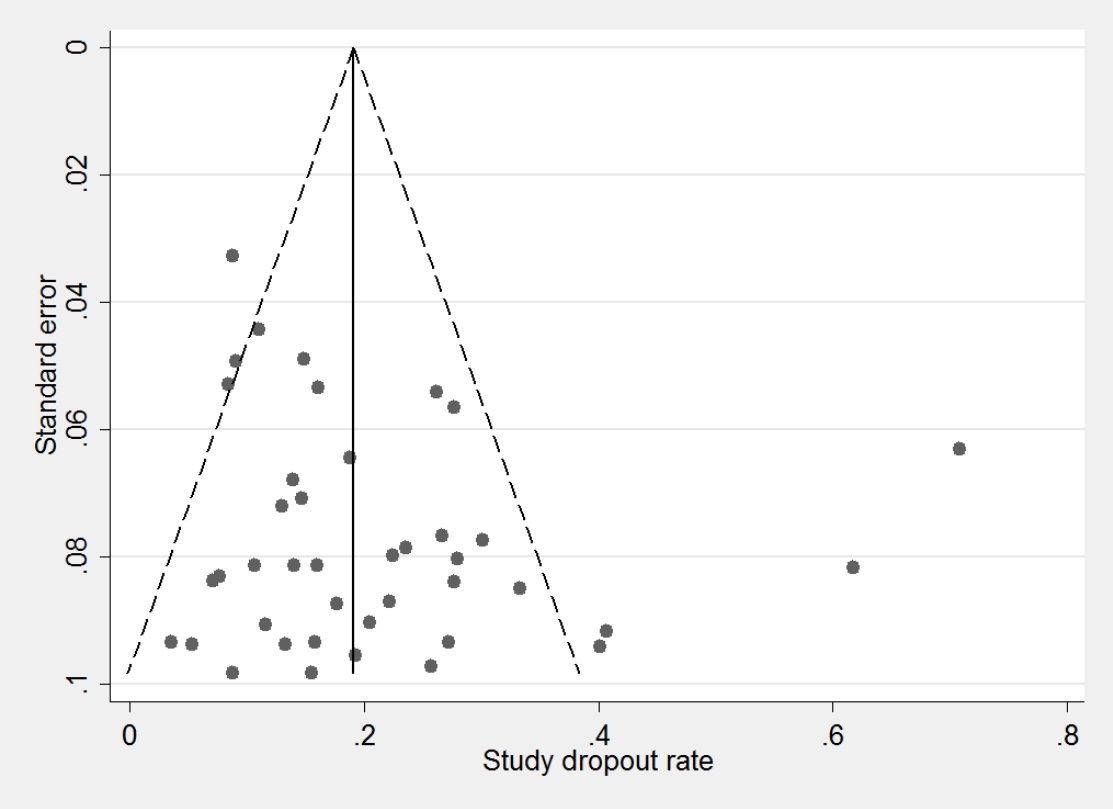
A random effects meta-regression of the effects of the predictors (study and sample characteristics) did not find a significant effect on drop-out either at the intervention- or study- level.

Publication bias

Egger's test of the intercept showed no presence of publication bias: $t(41) = 1{\cdot}67$, p=0.103.

The funnel plot is presented in Figure 2 and could be interpreted as showing no evidence of publication bias with a few outliers. The lack of publication bias could be explained by this review considering only large RCTs with a sample size ≥ 100. This finding suggests that large studies are likely to be published in spite of how high the drop-out rate was.

Figure 2. Funnel Plot of Standard Error by Study Drop-out Rate



Discussion

This study used a systematic literature search and meta-analysis to provide estimates for the proportion of individuals with schizophrenia who participate in non-pharmacological RCTs who discontinue intervention and who are lost to follow up.

Previous meta-analysis of rates of drop-out from psychosocial treatment among people with schizophrenia found that 13% of participants dropped out prior to or during treatment[3]. The study has also identified an association between specific study and sample characteristics and drop-out rates[3]. In contrast to this previous study, this systematic review included any non-pharmacological intervention for schizophrenia and considers the drop-out rates at both experimental intervention and study levels.

Two separate meta-analyses showed the same drop-out rate of 19% at the experimental intervention- and study- level. Meta-regressions of study and sample characteristics as predictors of drop-out did not show any significant association with either intervention or study drop-out rates. This lack of association suggests that, based on the variables reported in the publications, it is difficult to identify potential predictors of drop-out.

Estimating study drop-out rates is an important element of planning a clinical trial as it affects the time and cost of the study. Deciding on a statistically appropriate sample size requires information about the expected participation rates. If there is a reason to assume that a proportion of participants will fail to provide data, the sample size should be proportionately increased. Traditionally information about the expected number of participants to drop out is obtained either from a pilot study or previous studies in the same population. Results obtained in this systematic review and meta-analysis provide evidence about the reported drop-out rates in large non-pharmacological RCTs involving people with schizophrenia, at both study and intervention level. This can guide sample size planning in studies falling into this category. This review also provides details about the included studies, including the specific intervention, how it was delivered and in what setting, as well as the length of follow-up and intervention. These context details together with the reported drop-out rates provide information necessary for sample size calculations.

Strengths and Limitations of the Study

This study has a number of strengths. To our knowledge, this is the first systematic review and meta-analysis to establish the experimental intervention and study drop-out rates in non-pharmacological RCTs involving people with schizophrenia. We followed a rigorous process and a comprehensive search strategy encompassing a broad range of non-pharmacological interventions for schizophrenia. Many of the authors were contacted to clarify ambiguities and to obtain information not provided in the papers.

Several limitations should be considered when interpreting findings from this study. First, almost a third of the studies did not provide information about participant flow in the form of the CONSORT flow diagram, which reflects the quality of reporting data essential for this type of meta-analysis. However, some of the papers missing the CONSORT reported relevant information in the body of the paper and were therefore included in the analysis. Second, the interpretation of intervention drop-out was based on the definitions developed by authors of each reviewed study, which differed across the sample and thus limited the comparability. The lack of a universal threshold for intervention completion can also mean that the rates of participants who completed interventions can be under- or over- estimated by authors. The third limitation is the restricted scope for extracting and testing other potential predictors of drop-out such as incentives or assessment mode due to the lack of these details in many reviewed publications. Finally, it is possible that relevant studies may have been omitted, particularly as studies published not in English were excluded for resource reasons. However, this study adds to the thus far limited literature on drop-out rates in schizophrenia trials and provides suggestions for future studies.

Implications

The findings of this study suggest that drop-out rates below 20% in non-pharmacological RCTs involving people with schizophrenia are possible to achieve as shown by majority of the studies

included in the meta-analysis. Losing more than 20% of participants with schizophrenia can and should be avoided as it creates a risk of bias and can compromise validity[1,58].

Drop-out rates lower than 20% are achievable although the available evidence does not show which study or sample characteristics can help with achieving this. None of the tested study and sample variables that were available for extraction for the purposes of meta-analysis had an effect on either the intervention or study drop-out rates. Extracting variables was impeded by inconsistent reporting of information about study procedures, e.g. incentives, outcome collection method (i.e. remote or in person), and place of assessment. The findings suggest that the characteristics currently reported in publications cannot be used to predict drop-out rates in this context. Different factors may need to be taken into account, such as research processes, researcher characteristics, specific recruitment and retention strategies, psychological processes. Some literature suggests that assertive engagement strategies employed by the research team, involving home visits, flexibility in scheduling appointments, persistence in following up and collaborating with mental health services can have positive impact on retention rates[59] but this has not been systematically tested.

Furthermore, the study shows that there is no need to consider vast differences between drop-out from study and intervention. Trial participants with schizophrenia are just as likely to discontinue the experimental intervention as they are to be lost to follow-up.

Future research could focus on building in-depth understanding of how individuals with schizophrenia make decisions about participating in RCTs, especially about discontinuing their participation, as well as the challenges and barriers researchers experience in engaging this population in clinical trials. This evidence could inform development and implementation of effective retention strategies in trials.

Contributors

PS developed the protocol with all authors. PS did the literature search, assessed the eligibility of the studies for inclusion, extracted data, and did the analysis. SW assessed the eligibility of the studies for inclusion. All authors contributed to the interpretation of the findings. PS drafted the manuscript, to which all authors contributed.

Declaration of interests

We declare no competing interests.

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References:

1 Polit D, Hungler B. Nursing Research: Principles and Methods, 5th edn. Philadelphia: Lippincott, 1995.

2 Nosé M, Barbui C, Tansella M. How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. *Psychol Med* 2003; **33**: 1149–60.

3 Villeneuve K, Potvin S, Lesage a., Nicole L. Meta-analysis of rates of drop-out from psychosocial treatment among persons with schizophrenia spectrum disorder. *Schizophr Res* 2010; **121**: 266–70.

4 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011; **2**: 109–12.

5 Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ* 1996; **313**: 570–1.

6 Begg C, Cho M, Eastwood S, *et al.* Improving the Quality of Randomised Controlled Trials The CONSORT Statement. 1996; **8**: 637–9.

7 Kampman, 0. & Lethinen K. Review article Compliance in psychoses. 1999; : 167–75.

8 Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med Intern Med* 2009; **151**: 264–9.

9 Barkhof E, Meijer CJ, De Sonneville LMJ, Linszen DH, De Haan L. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. *Schizophr Bull* 2013; **39**: 1242–51.

10 Barrowclough C, Haddock G, Lobban F, *et al.* Group cognitive − behavioural therapy for schizophrenia : Randomised controlled trial. *Br J Psychiatry* 2006; **189**: 527–32.

11 Bell M, Lysaker P. Clinical Benefits of Paid Work Activity in Schizophrenia: 1-Year Followup. *Schizophr bull* 1997; **23**: 317–28.

12 Bell M, Bryson G, Wexler BE. Cognitive remediation of working memory deficits: durability of training effects in severely impaired and less severely impaired schizophrenia. *Acta Psychiatr Scand* 2003; **108**: 101–9.

13 Bell MD, Bryson GJ, Greig TC, Fiszdon JM, Wexler BE. Neurocognitive enhancement therapy with work therapy: Productivity outcomes at 6- and 12-month follow-ups. *J Rehabil Res Dev* 2005; **42**: 829–38.

14 Bell M, Fiszdon J, Greig T, Wexler B, Bryson G. Neurocognitive enhancement therapy with work therapy in schizophrenia: 6-month follow-up of neuropsychological performance. *J Rehabil Res Dev* 2007; **44**: 761–70.

15 Bowie CR, McGurk SR, Mausbach B, Patterson TL, Harvey PD. Combined cognitive remediation and functional skills training for schizophrenia: Effects on cognition, functional competence, and real-world behavior. *Am J Psychiatry* 2012; **169**: 710–8.

16 Chien W, Mui J, Cheung E, Gray R. Effects of motivational interviewing-based adherence therapy for schizophrenia spectrum disorders: a randomised controlled trial. *Trials* 2015; **16**: 270–84.

17 Crawford MJ, Killaspy H, Barnes TRE, *et al.* Group art therapy as an adjunctive treatment for people with schizophrenia: multicentre pragmatic randomised trial. *BMJ* 2012; **344**: e846.

18 Franck N, Duboc C, Sundby C, *et al.* Specific vs general cognitive remediation for executive functioning in schizophrenia: A multicenter randomised trial. *Schizophr Res* 2013; **147**: 68–74.

19 Freeman D., Dunn G., Startup H., Pugh K., Cordwell J., Mander H., Cernis E., Wingham G., Shirvell K. KD. Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis. *The Lancet Psychiatry* 2015; **2**: 305–13.

20 Gomar JJ, Valls E, Radua J, *et al.* A Multisite, Randomised Controlled Clinical Trial of Computerized Cognitive Remediation Therapy for Schizophrenia. *Schizophr Bull* 2015; **41**: 1387–96.

21 Gouzoulis-Mayfrank E, König S, Koebke S, Schnell T, Schmitz-buhl M, Daumann J. Trans-Sector Integrated Treatment in Psychosis and Addiction. *Dtsch Arztebl Int* 2015; **112**: 683–91.

22 Granholm E, Holden J, Link PC, McQuaid JR. Randomised Clinical Trial of Cognitive Behavioral Social Skills Training for Schizophrenia: Improvement in Functioning and Experiential Negative Symptoms. *J Consult Clin Psychol* 2014; **82**: 1173–85.

23 Gray R, Leese M, Bindman J, *et al.* Adherence therapy for people with schizophrenia. European multicentre randomised controlled trial. *Br J Psychiatry* 2006; **189**: 508–14.

24 Gumley a, O'Grady M, McNay L, Reilly J, Power K, Norrie J. Early intervention for relapse in schizophrenia: results of a 12-month randomised controlled trial of cognitive behavioural therapy. *Psychol Med* 2003; **33**: 419–31.

25 Gumley A, Karatzias A, Power K, Reilly J, McNay L, O'Grady M. Early intervention for relapse in schizophrenia: impact of cognitive behavioural therapy on negative beliefs about psychosis and self-esteem. *Br J Clin Psychol* 2006; **45**: 247–60.

26 Hamann J, Langer B, Winkler V, *et al.* Shared decision making for in-patients with schizophrenia. *Acta Psychiatr Scand* 2006; **114**: 265–73.

27 Hansson L, Svensson B, Bj??rkman T, *et al.* What works for whom in a computer-mediated communication intervention in community psychiatry? Moderators of outcome in a cluster randomised trial. *Acta Psychiatr Scand* 2008; **118**: 404–9.

28 Hogarty GE, Flesher S, Ulrich R, *et al.* Cognitive enhancement therapy for schizophrenia. *Archives* 2004; **61**: 866–76.

29 Jahn T, Pitschel-Walz G, Gsottschneider A, Froböse T, Kraemer S, Bäuml J. Neurocognitive prediction of illness knowledge after psychoeducation in schizophrenia: results from the Munich COGPIP study. *Psychol Med* 2011; **41**: 533–44.

30 Jones RB, Atkinson JM, Coia DA, *et al.* Randomised trial of personalised computer based information for patients with schizophrenia. *BMJ* 2001; **322**: 835–40.

31 Klingberg S, Wittorf A, Fischer A, Jakob-Deters K, Buchkremer G, Wiedemann G. Evaluation of a cognitive behaviourally oriented service for relapse prevention in schizophrenia. *Acta Psychiatr Scand* 2010; **121**: 340–50.

32 Klingberg S, Wölwer W, Engel C, *et al.* Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: Results of the randomised clinical TONES study. *Schizophr Bull* 2011; **37**. DOI:10.1093/schbul/sbr073.

33 Klingberg S, Herrlich J, Wiedemann G, *et al.* Adverse effects of cognitive behavioral therapy and cognitive remediation in schizophrenia: results of the treatment. *J Nerv Ment Dis* 2012; **200**: 569–76.

34 Li Z, Guo Z, Wang N, *et al.* Cognitive-behavioural therapy for patients with schizophrenia: a multicentre randomised controlled trial in Beijing, China. *Psychol Med* 2015; **45**: 1893–905.

35 Montes J.M., Maurino J., Diez T. S-RJ. Telephone-based nursing strategy to improve adherence to antipsychotic treatment in schizophrenia: A controlled trial. *Int J Psychiatry Clin Pract* 2010; **14**: 274–81.

36 Montes JM, Medina E, Gomez-Beneyto M, Maurino J. A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. *Psychiatry Res* 2012; **200**: 89–95.

37 Moritz S, Veckenstedt R, Bohn F, *et al.* Complementary group Metacognitive Training (MCT) reduces delusional ideation in schizophrenia. *Schizophr Res* 2013; **151**: 61–9.

38 Moritz S, Veckenstedt R, Andreou C, *et al.* Sustained and 'sleeper' effects of group metacognitive training for schizophrenia: A randomised clinical trial. *JAMA Psychiatry* 2014; **71**: 1103–11.

39 Mueller DR, Schmidt SJ, Roder V. One-Year Randomised Controlled Trial and Follow-Up of Integrated Neurocognitive Therapy for Schizophrenia Outpatients. *Schizophr Bull* 2015; **41**: 604–16.

40 Patterson TL, Mausbach BT, McKibbin C, Goldman S, Bucardo J, Jeste D V. Functional Adaptation Skills Training (FAST): A randomised trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. *Schizophr Res* 2006; **86**: 291–9.

41 Mausbach BT, Cardenas V, McKibbin CL, Jeste D V., Patterson TL. Reducing Emergency Medical Service Use in Patients with Chronic Psychotic Disorders: Results from the FAST Intervention Study. *Behav Res Ther* 2008; **46**: 145–53.

42 Pitkanen A, Valimaki M, Kuosmanen L, *et al.* Patient education methods to support quality of life and functional ability among patients with schizophrenia: A randomised clinical trial. *Qual Life Res* 2012; **21**: 247–56.

43 Salyers MP, McGuire AB, Kukla M, Fukui S, Lysaker PH, Mueser KT. A randomised controlled trial of illness management and recovery with an active control group. *Psychiatr Serv* 2014; **65**: 1–7.

44 Schirmer UB, Steinert T, Flammer E, Borbé R. Skills-based medication training program for patients with schizophrenic disorders: a rater-blind randomised controlled trial. *Patient Prefer Adherence* 2015; **9**: 541–9.

45 Schulz M, Gray R, Spiekermann A, Abderhalden C, Behrens J, Driessen M. Adherence therapy following an acute episode of schizophrenia: A multi-centre randomised controlled trial. *Schizophr Res* 2013; **146**: 59–63.

46 Sibitz I, Amering M, G??ssler R, Unger A, Katschnig H. One-year outcome of low-intensity booster sessions versus care as usual in psychosis patients after a short-term psychoeducational intervention. *Eur Psychiatry* 2007; **22**: 203–10.

47 Silverstein SM., Roché MW., Khan Z., *et al.* Enhancing and promoting recovery in attentionally impaired people diagnosed with schizophrenia: Results from a randomised controlled trial of attention shaping in a partial hospital program. *Am J Psychiatr Rehabil* 2014; **17**: 272–305.

48 Staring ABP, Van Der Gaag M, Koopmans GT, *et al.* Treatment adherence therapy in people with psychotic disorders: Randomised controlled trial. *Br J Psychiatry* 2010; **197**: 448–55.

49 Terzian, E., Tognoni, G., Bracco, R., De Ruggieri, E., Ficociello, R. A., Mezzina, R., & Pillo G. Social Network Intervention in Patients With Schizophrenia and Marked ... 2013; **58**: 622–31.

50 Van Der Gaag M, Stant AD, Wolters KJK, Buskens E, Wiersma D. Cognitive-behavioural therapy for persistent and recurrent psychosis in people with schizophrenia-spectrum disorder: Cost-effectiveness analysis. *Br J Psychiatry* 2011; **198**: 59–65.

51 van der Krieke L, Emerencia AC, Boonstra N, Wunderink L, de Jonge P, Sytema S. A Web-Based Tool to Support Shared Decision Making for People With a Psychotic Disorder: Randomised Controlled Trial and Process Evaluationq. *J Med Interent Res* 2013; **15**: e216.

52 van Oosterhout B, Krabbendam L, de Boer K, *et al.* Metacognitive group training for schizophrenia spectrum patients with delusions: a randomised controlled trial. *Psychol Med* 2014; **44**: 3025–35.

53 Van Os J, Altamura AC, Bobes J, *et al.* Evaluation of the Two-Way Communication Checklist as a clinical intervention : Results of a multinational , randomised controlled trial Evaluation of theTwo-Way Communication Checklist as a clinical intervention Results of a multinational , randomised con. 2004; **184**: 79–83.

54 Velligan D, Mintz J, Maples N, *et al.* A randomised trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. *Schizophr Bull* 2013; **39**: 999–1007.

55 Velligan DI, Tai S, Roberts DL, *et al.* A Randomised Controlled Trial Comparing Cognitive Behavior Therapy, Cognitive Adaptation Training, Their Combination and Treatment as Usual in Chronic Schizophrenia. *Schizophr Bull* 2015; **41**: 597–603.

56 Williams DK, Thrush CR, Armitage TL, Owen RR, Hudson TJ, Thapa P. The Effect of Guideline Implementation Strategies on Akathisia Outcomes in Schizophrenia. *J Appl Res* 2003; **3**: 470–82.

57 Xiang YT, Weng YZ, Li WY, *et al.* Efficacy of the community re-entry module for patients with schizophrenia in Beijing, China: Outcome at 2-year follow-up. *Br J Psychiatry* 2007; **190**: 49–56.

58 Gul RB, Ali P a. Clinical trials: the challenge of recruitment and retention of participants. *J Cinical Nurs* 2010; **19**: 227–33.

59 Barrowclough C, Haddock G, Beardmore R, *et al.* Evaluating integrated MI and CBT for people with psychosis and substance misuse: recruitment, retention and sample characteristics of the MIDAS trial. *Addict Behav* 2009; **34**: 859–66.