Author contributions

PS and SP developed the conceptual idea of the paper. PS conducted the main literature search and meta-analyses, and wrote the first draft of the paper. SW assisted with the literature review and editing the paper. PS and LG conducted statistical analyses. LG, SP and SW contributed to the data interpretation. All authors approved the final version of the manuscript.

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We thank all the authors who kindly replied to the requests for more information about their studies.

Conflict of interest

Authors report no potential conflicts of interest.

Introduction

Two major challenges in randomized 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 attrition levels as low as 5% may introduce risk of bias and the rate exceeding 20% can threaten trial validity(Polit and Hungler, 1995; Schulz and Grimes, 2002). The credibility of a trial also depends on the attrition rates. A survey involving patients, caregivers, statisticians and clinicians found drop-out out rates exceeding 25-30% can affect whether pharmacological trials in schizophrenia are judged as credible(Xia et al., 2009).

Loss of data can occur at different levels within a trial. Treatment noncompliance refers to issues with following the recommendations for prescribed treatments. In non-pharmacological trials it can be the failure to attend a required number of appointments or sessions(Nosé et al., 2003). Patients can also choose to completely discontinue an intervention. Treatment drop-out been estimated to be 13% in RCTs testing psychosocial treatments for people with schizophrenia(Villeneuve et al., 2010). In contrast to pharmacological trials, discontinuing a non-pharmacological 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. Most research investigating drop-out of people with schizophrenia at a study level have focused on pharmacological trials, reporting 35% study drop-out in a meta-analysis of RCTs of antipsychotic drugs(Leucht et al., 2013). This contrast in the drop-out rates between pharmacological and non-pharmacological trials can be expected due to the differences in procedures (e.g. single- vs. double-blinding)(Huhn et al., 2014) and non-pharmacological trials not usually prohibiting taking already prescribed medication. Receiving pharmacotherapy on top of the experimental trial

intervention might reduce the likelihood of dropping out even in case of the intervention not being efficacious for the patient.

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 randomized participants is necessary for a full application of the intention-to-treat (ITT) approach(Gupta, 2011), which is the 'gold standard' for analyzing the results from trials evaluating the effectiveness of a treatment in a pragmatic setting(Altman, 1996; Begg et al., 1996). ITT analysis includes all randomized 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 randomized participants, including those who did not complete the intervention but continued to complete follow-up assessments.

Developing effective and efficient retention strategies for RCTs 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(Kampman and Lethinen, 1999; Nosé et al., 2003), unemployment(Nosé et al., 2003), unpleasant side effects of medication(Kampman and Lethinen, 1999), negative attitude towards medication(Kampman and Lethinen, 1999). In one available study analyzing drop-out from psychosocial treatment 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(Villeneuve et al., 2010). Lower drop-out rates were associated with study quality and inpatient setting(Villeneuve et al., 2010). 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 first: to systematically identify relevant large-scale RCTs evaluating non-pharmacological interventions for individuals with schizophrenia; second: 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.

Materials and methods

1.1 Literature search

A protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)(Moher et al., 2009). 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(Begg et al., 1996). 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 ‘RANDOMIZED 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.

1.2 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.

1.3 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 randomized 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 randomization were not considered dropouts and were not included in the calculations. The distinction between the two types of drop-out (intervention vs study) was drawn in order to investigate the differences in the proportions of participants adhering to treatment and completing follow-up appointments.

1.4 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, study setting (inpatient vs. outpatient), intervention delivery (individual vs. group), type of control intervention (active vs. treatment as usual), sample size, duration of intervention period, 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 randomized 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.

1.5 Quality assessment

A unique set of criteria was developed specifically for the purposes of this study as the data were different from those for clinical effectiveness and did not fit in with the existing tools of assessing risk of bias. The methodological quality of the studies was appraised by giving a score from 0 to 3 using the following criteria: i) CONSORT diagram provided (1 point), ii) Clear definition of intervention completion (1 point), iii) Clear information on sample size calculation (1 point). The score was also

used in the meta-analyses as a measure of study quality in the context of reporting information relevant to study drop-out.

1.6 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 across all active interventions in each study (a) or were lost to follow-up (b) divided by the total number of individuals who began intervention (a) or were randomized to study (b). The Freeman-Tukey double arcsine transformation was used to calculate the 95% confidence interval as it can be used for data restricted to the range of 0 and 100%. Otherwise, studies with an estimated percentage near either extreme would be automatically excluded from the analysis leading to a biased pooled estimate.

For meta-regression a random-effects model was used as it assumes that differences in the drop-out rates are not just attributed to the sampling error but represent real differences between studies. The potential predictors used in meta-regressions included both study-level and sample-level variables. Variables which were associated with drop-out (p-value <0.1) in the univariable models were included in a multivariable model

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

1.1 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 studies 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.

Information about the reasons for study discontinuation was extracted but this was limited by the lack of reporting with absence of CONSORT (n=11), presence of CONSORT but lack of or unclear information about the reasons for discontinuation (n=18). Only 14 out of 43 papers reported the reasons for discontinuation of study.

[Insert Figure 1 here]

[Insert Table 1 here]

1.2 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.

1.3 Drop-out rates

The overall estimate of the proportion of participants who dropped out of intervention was 14% (95% CI: 13-15%), with a range of 0-63% and a median of 19.4%. Heterogeneity was high at I^2=93.13%. Subgroup analysis by intervention type showed overall estimates of intervention drop-out of 25% (95% CI: 14-35%) for CBT interventions (n=8), 24% (95% CI: 16-32%) for cognitive or neurocognitive interventions (n=9), 21% (95% CI: 13-29%) for practical or educational interventions

(n=8), 11% (95% CI: 6-17%) for adherence therapies (n=7), and 34% (95% CI: 23-46%) for other interventions (n=18).

The overall estimate of the proportion of participants who dropped out of studies was 20% (95% CI: 17-24%), with a range of 4-71% and a median of 16%. Heterogeneity was high at I^2=95.69%

The results of the analyses are shown in Tables 2 and 3.

[Insert Table 2]

[Insert Table 3]

1.4 Predictors of drop-out

A random effects meta-regression using both univariable and multivariable models was used. At the intervention level, the univariable models included age, gender, illness duration, study location, study setting, intervention delivery, duration of the intervention period, study duration, number of intervention sessions, and study quality. Findings show that the proportion of drop-out from experimental interventions significantly increased as the number of intervention sessions increased (P-value = 0.011). At the study-level, the models included the following variables: age, gender, illness duration, study location, study setting, type of control intervention, study duration, number of evaluations, and study quality. Findings show that none of these variables have an effect on the drop-out from study.

The results of the analyses are shown in Tables 4, 5, 6.

[Insert Table 4]

[Insert Table 5]

[Insert Table 6]

1.5 Publication bias

Egger's test of the intercept showed no presence of publication bias (P= 0.10) for study drop-out.

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 despite how high the drop-out rate was.

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(Villeneuve et al., 2010). The study has also identified an association between specific study and sample characteristics and drop-out rates(Villeneuve et al., 2010). 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 drop-out rates of 14% at the experimental intervention level and 20% at the study level. Meta-regressions of study and sample characteristics as predictors of drop-out showed only one significant association between the number of intervention sessions and drop-out from the experimental intervention.

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 may provide useful information for sample size calculations.

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. Third, there was a high level of heterogeneity. However this could be explained by the inherent differences in individual studies, especially the wide range of drop-out rates observed across the included trials. The fourth 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.

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. Achieving as little drop-out as possible is important in avoiding a risk of bias, which appears at the attrition level of 5% (Schulz and Grimes, 2002). Losing more than 20% of participants with schizophrenia can and should be avoided as it can compromise validity(Gul and Ali, 2010; Polit and Hungler, 1995).

Drop-out rates lower than 20% are achievable although the available evidence is limited in showing which study or sample characteristics can help with achieving this. Only one of the tested study and sample variables that were available for extraction for the purposes of meta-analysis had an effect on the intervention drop-out rates: number of intervention sessions. This finding suggests that interventions involving a large number of sessions have an increased risk of people dropping out. No other participant or study characteristic has shown an effect on the drop-out rates. However, 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 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(Barrowclough et al., 2009) but this has not been systematically tested.

Furthermore, the study shows that more trial participants with schizophrenia drop out of studies than out of active interventions. This finding has potential implications for planning study procedures, especially follow-up assessments, in the context of minimizing attrition.

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.

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Figure 1. PRISMA Diagram for Paper Selection

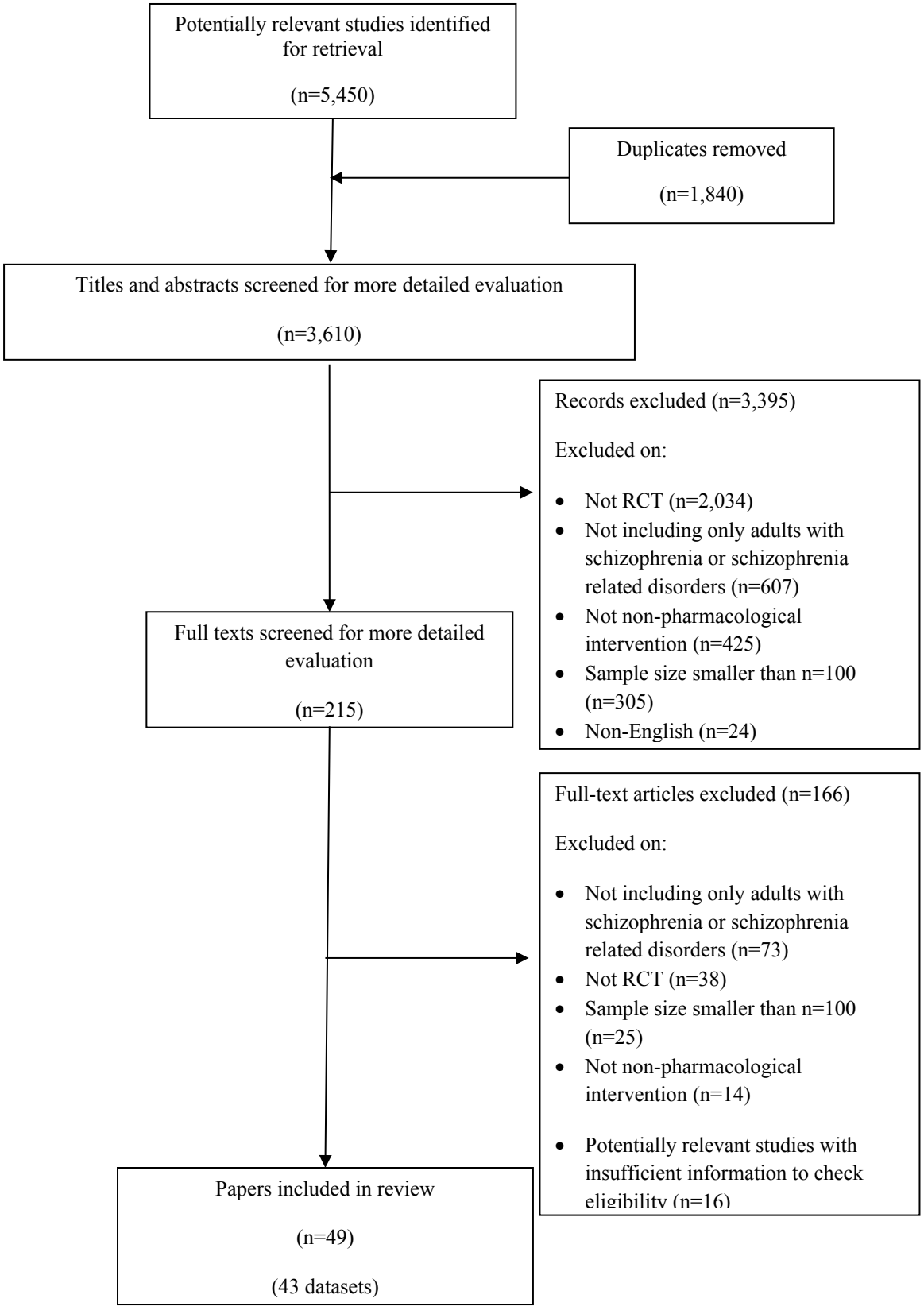

Figure 2. Funnel Plot of Standard Error by Study Drop-out Rate

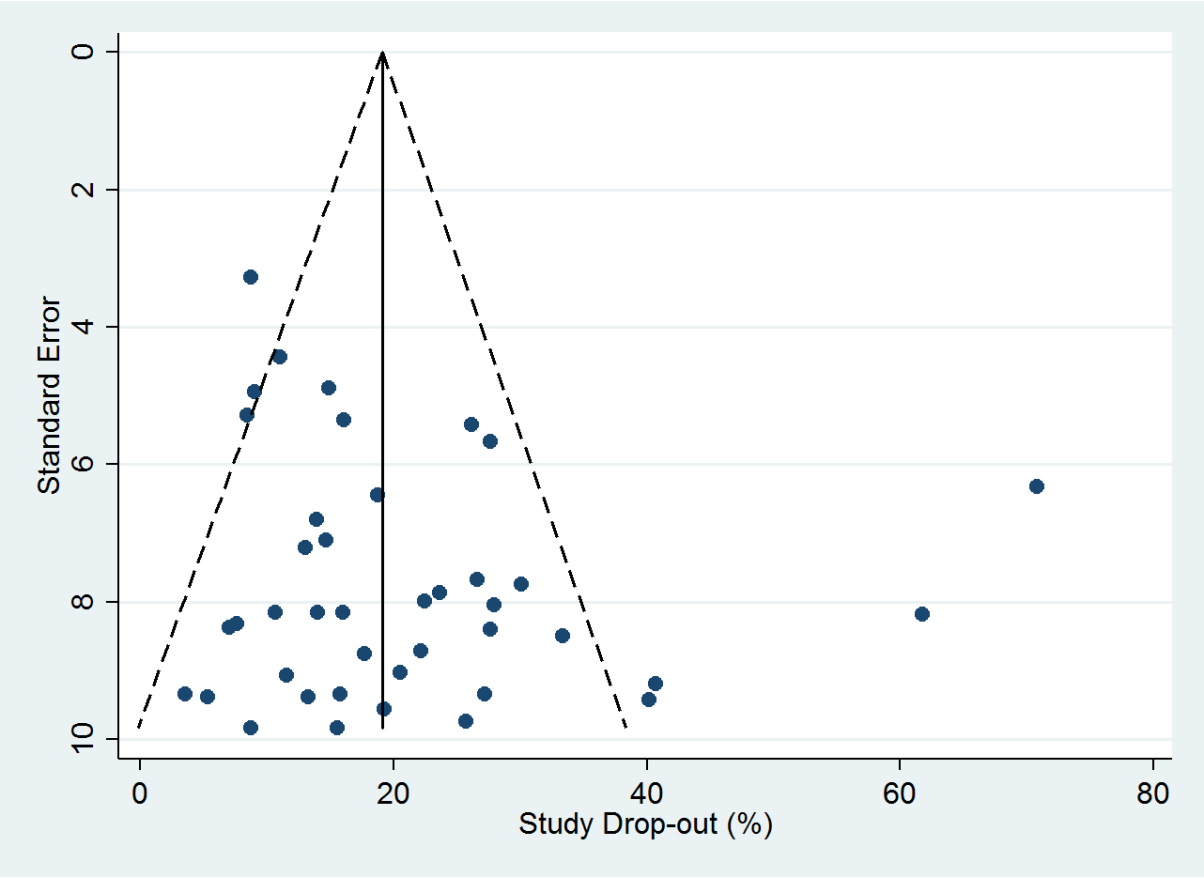

Table 1. Description of studies

Study reference	Region	Intervention(s) evaluated	Participants randomized to study (n)	Intervention delivery	Setting	Length of follow-up (m)	Intervention duration (m)	Quality score
Barkhof 2013 (14)	Europe	Motivational interviewing / Health Education	114	Individual	In- and out-patient	12	6.5	3
Barrowclough 2006 (15)	Europe	Cognitive Behavioral Therapy (CBT)	113	Group	Out-patient	12	6	3
Bell 1997 (16)	USA	Work program	150	Individual	Out-patient	12	6	1
Bell 2003 (17) [Bell 2005] (18) [Bell 2007] (19)	USA	Neurocognitive Enhancement Therapy (NET) with Work Therapy (WT)	131	Individual	Out-patient	12	6	0
Bowie 2012 (20)	USA	Cognitive remediation / Functional Adaptation Skills Training/ Combined Treatment	114	Group	Out-patient	3	6	2
Chien 2015 (21)	Asia	Adherence therapy	114	Individual	Out-patient	6	4	2
Crawford 2012 (22)	Europe	Group art therapy/Activity Groups	417	Group	Out-patient	24	12	2
Franck 2013 (23)	Europe	Individualized therapy / Cognitive Remediation Therapy (CRT)	138	Individual	Out-patient	9	3	1
Freeman 2015 (24)	Europe	CBT	150	Individual	In- and out-patient	6	2	3
Gomar (25)	Europe	Computerized Cognitive Remediation	130	Group	In- and out-patient	6	6	1
Gouzoulis-Mayfrank 2015 (26)	Europe	Implemented integrated treatment	100	Group	In-patient	12	NR	1
Granholm 2014 (27)	USA	Cognitive Behavioral Social Skills Training (CBSST) / Active Goal-Focused Supportive Contact (GFSC)	149	Group	Out-patient	21	9	1
Gray 2006 (28)	Europe	Adherence therapy / Health Education	409	Individual	In- and out-patient	13	18	3
Gumley 2003 (29) [Gumley 2006] (30)	Europe	CBT	144	Individual	NR	13	3	2
Hamann 2006 (31)	Europe	Shared decision aid	113	Individual	In- and out-patient	18	0.03	1
Hansson 2008 (32)	Europe	DIALOG (computer-mediated structured patient-=key worker communication)	507	Individual	Out-patient	12	12	0
Hogarty 2004 (33)	USA	Cognitive Enhancement Therapy (CET) / Enriched Supportive Therapy	121	Group	Out-patient	24	NR	0
Jahn 2011 (34)	Europe	Neurocognitive training (COGPIP trial)	122	Group	In-patient	9	1	1
Jones 2001 (35)	Europe	Personalized computer-based information /	112	Individual	NR	3	NR	3

		Community Psychiatric Nurse / Combined treatment						
Klingberg 2010 (36)	Europe	CBOS (cognitive behaviorally oriented service)	169	Group	In-patient	6	2	3
Klingberg 2011 (37)	Europe	CBT / CR	198	Individual	Out-patient	12	9	3
[Klingberg 2012] (38)		CBT / CR						
Li 2015 (39)	Asia	CBT / Supportive Therapy	192	Group	In- and out-patient	21	6	2
Montes 2010 (40)	Europe	Telephone-based nursing strategy to improve adherence to antipsychotic treatment	928	Individual	Out-patient	4	3	1
Montes 2012 (41)	Europe	Short message service (SMS)-based strategy for enhancing adherence to antipsychotic treatment	340	Individual	Out-patient	6	3	3
Moritz 2013 (42)	Europe	Complementary Metacognitive Training (MCT)	150	Group	In- and out-patient	6	NR	2
[Moritz 2014] (43)								
Mueller 2015 (44)	Europe	Integrated Neurocognitive Therapy	156	Group	Out-patient	9	3.75	1
Patterson 2006 (45)	USA	Functional Adaptation Skills Training (FAST)	240	Group	Out-patient	18	6	1
[Mausbach 2008] (46)								
Pitkanen 2011 (47)	Europe	Patient education	311	Group	In-patient	12	1	1
Salyers 2014 (48)	USA	Illness Management and Recovery (IMR) / Problem-Solving Group	118	Group	NR	18	9	0
Schirmer 2015 (49)	Europe	Medication training program	141	Individual	Out-patient	NR	1.64	
Schulz 2013 (50)	Europe	Adherence therapy	161	Group	In- and out-patient	3	NR	3
Sibitz 2007 (51)	Europe	Low intensity booster sessions of psychoeducation	103	Group	Out-patient	11.25	2.25	1
Silverstein 2014 (52)	USA	Attention shaping	105	Group	In-patient	5.5	5.5	1
Staring 2010 (53)	Europe	Treatment adherence therapy (TAT)	109	Individual	Out-patient	12	6	1
Terzian 2013 (54)	Europe	Social Network intervention	357	NR	Out-patient	24	24	1
Van der Gaag 2011 (55)	Europe	CBT	216	Group	NR	18	6	1
Van der Krieke 2013 (56)	Europe	Web-based information and decision tool	250	Individual	Out-patient	12	12	2
Van Oosterhout 2014 (57)	Europe	Metacognitive group training (MCT)	154	Group	In- and out-patient	6	2	2
Van Os 2004 (58)	Europe	Two-way Communication Checklist (2-COM)	134	Individual	Out-patient	2	1.5	1
Velligan 2013 (59)	USA	Interventions for improving adherence to oral medications	142	Group	Out-patient	9	6	1

Velligan 2015 (60)	USA	CBT / Cognitive Adaptation Training (CAT) / CBT and CAT	166	Individual	Out-patient	15	9	1
Williams 2003 (61)	USA	Enhanced guideline implementation strategy	349	Individual	In- and out-patient	20	NR	0
Xiang 2007 (62)	Asia	Community Re-Entry Module (CRM)	103	Group	In-patient	24	4	2

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

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

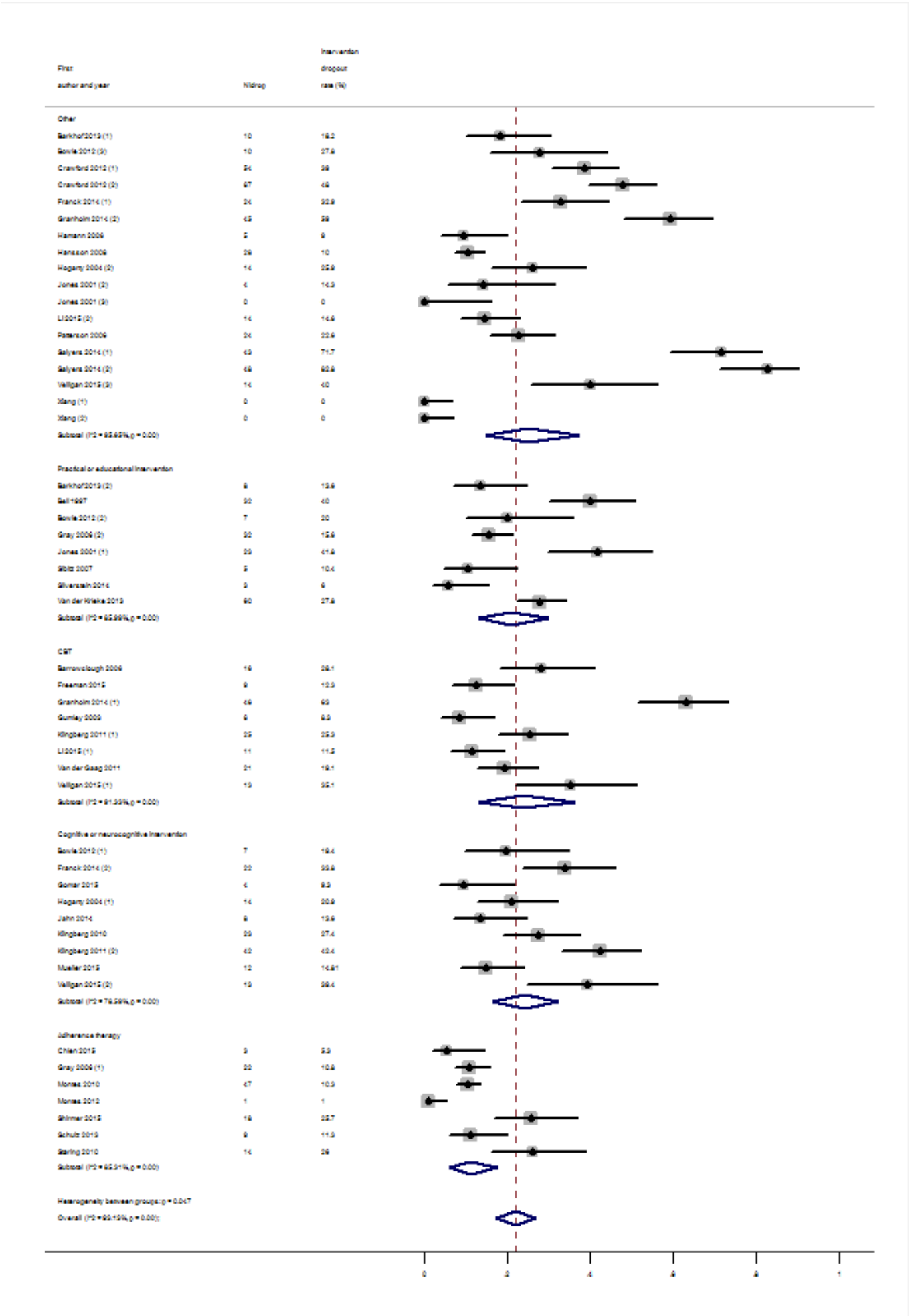

Table 3. Meta-analysis of Study Drop-out Rates

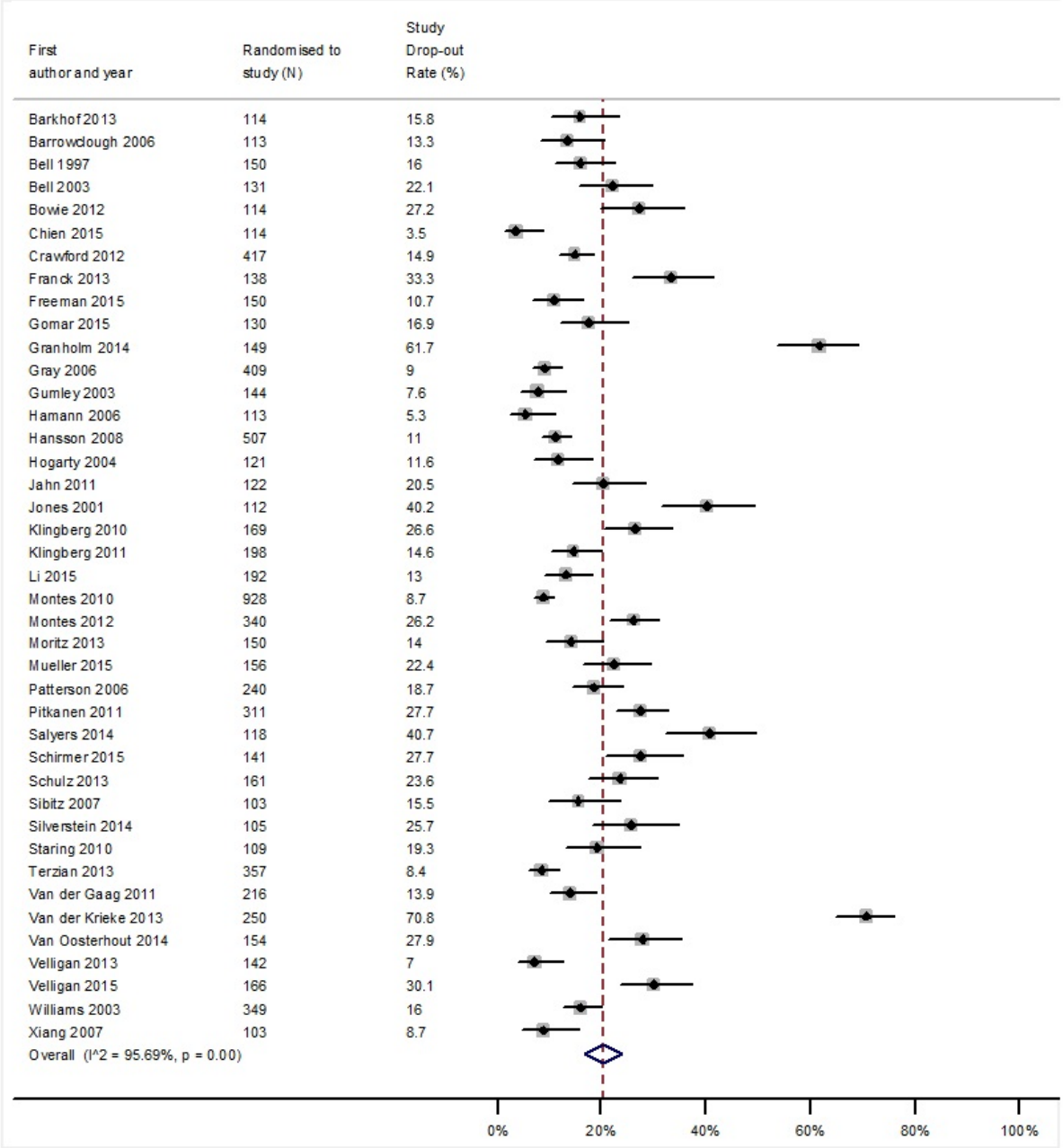

Table 4: Univariable meta-regression for intervention dropout

Factor	**Coefficient**	**95% Lower**	**95% Upper**	***P*-Value**
Age	0.53	-0.77	1.83	0.410
Gender	0.53	-0.03	1.11	**0.065**
Illness duration	1.12	-0.12	2.37	**0.075**
Study location	-9.93	-22.49	2.63	0.117
Study setting (inpatient vs outpatient)	-6.38	-18.30	5.54	0.284
Intervention delivery (individual vs group)	-6.37	-18.30	5.54	0.284
Duration of intervention period	2.37	0.51	4.23	**0.014**
Study duration	0.83	-0.11	1.77	**0.082**
Number of intervention sessions	0.66	0.26	1.05	**0.002**
Study quality	-2.27	-6.64	2.09	0.300

Table 6: Univariable meta-regression for study dropout

Factor	**Coefficient**	**95% Lower**	**95% Upper**	***P*-Value**
Age	0.10	-0.70	0.90	0.803
Gender	0.09	-0.27	0.46	0.606
Illness duration	0.43	-0.37	1.23	0.279
Study location	6.62	-1.56	14.81	0.110
Study setting (inpatient vs outpatient)	1.29	-2.74	5.33	0.521
Study duration	-0.20	-0.95	0.54	0.579
Number follow-up assessments	-0.23	-3.84	3.38	0.897
Type of control (active vs treatment as usual)	1.25	-4.31	6.82	0.651
Study quality	0.05	-4.76	4.86	0.984

Table 5: Multivariable meta-regression for intervention dropout

Factor	**Coefficient**	**95% Lower**	**95% Upper**	***P*-Value**
Gender	0.23	-0.53	1.00	0.235
Illness duration	0.10	-1.44	1.65	0.884
Duration of intervention period	0.09	-2.29	2.48	0.931
Number of intervention sessions	0.97	0.28	1.67	**0.011**
Study duration	-0.38	-1.81	1.05	0.570

Abstract

Essential criteria for the methodological quality and validity of randomized 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 non-pharmacological schizophrenia trials. A systematic literature search was used to identify relevant trials with ≥100 sample size and to extract the drop-out data**.** The rates of drop-out from the experimental intervention and study were calculated with meta-analysis of proportions. Meta-regression was applied to explore the association between the study and sample characteristics and the drop-out rates. 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 14% (95% CI: 13-15%) at the experimental intervention level and 20% (95% CI: 17-24%) at the study level. Meta-regression showed that the active intervention drop-out rates were predicted by the number of intervention sessions. In non-pharmacological schizophrenia trials, drop-out rates of less than 20% can be achieved for both the study and the experimental intervention. A high heterogeneity of drop-out rates across studies shows that even lower rates are achievable.

Keywords: psychosis; schizophrenia; treatment; attrition; retention; review

Attrition in trials evaluating complex interventions for schizophrenia: Systematic review and meta-analysis

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