A network meta-analysis of psychological interventions for schizophrenia and psychosis: impact on symptoms

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Abstract

Background: Evidence for the effectiveness of psychological interventions for schizophrenia/psychosis is growing, however there is no consensus on the psychological intervention most likely to reduce symptoms.

Methods: A network meta-analysis was conducted to identify all randomised controlled trials (RCTs) of psychological interventions for adults with schizophrenia/psychosis. A systematic review of the literature using MEDLINE, PsycINFO, EMBASE and CENTRAL led to an analysis of 90 RCTs with 8,440 randomised participants across 24 psychological intervention, and control groups. Psychological interventions were categorised and rated for treatment fidelity and risk of bias. Data for total symptoms were extracted and network meta-analysis, using a frequentist approach, was undertaken using Stata SE v15 to compare the direct and indirect evidence for the effectiveness of each psychological intervention.

Findings: Psychological interventions were more likely to reduce symptoms than control groups, and one intervention, mindfulness-based psychoeducation, was consistently ranked as most likely to reduce total symptoms. Subgroup analyses identified differential effectiveness in different settings and for different subgroups.

Interpretation: Mindfulness-based psychoeducation was consistently ranked as most likely to reduce symptoms; however all studies were based in China. More RCTs in a variety of cultural contexts would help to elucidate whether these findings generalise internationally. A number of psychological interventions could potentially be more effective than interventions recommended by NICE guidelines, such as CBT and family therapy, and additional RCTs and meta-analyses are needed to generate more conclusive evidence in this regard. Cognitive remediation and social skills training were differentially effective in different subgroup analyses.

Keywords; psychological intervention, network meta-analysis, treatment, psychotherapy

Putting Research into Context

Evidence before this study

Intervention specific meta-analyses of psychological interventions for psychosis and schizophrenia have been published however a systematic review and comprehensive statistical analysis of all available evidence was needed to identify the psychological interventions that are most likely to be effective for total symptoms. A previously published network meta-analysis reported that CBT may be most effective for positive symptoms of psychosis.

Added value of this study

This network meta-analysis synthesises the current evidence base to inform patient choice and clinical decision-making and accounted for variance in treatment as usual across the globe. Interventions not included in current clinical guidelines (such as mindfulness-based psychoeducation, cognitive behaviour therapy combined with social skills training, and cognitive remediation focussed on social cognition) were consistently ranked as more likely to reduce symptoms, than interventions that are currently recommended, however more RCTs are needed in a variety of contexts to support/refute these findings. Intervention setting and time since onset of 'illness' affected which interventions were ranked as more effective. This informs hypothesis generation about the effectiveness of different interventions across different settings and samples.

1 Introduction

Schizophrenia is a major psychiatric syndrome with a diverse array of potential symptoms. Antipsychotic medication has been the primary treatment option however this carries the risk of adverse effects which require extensive, and expensive, monitoring. Patient choice, whether for or against medication, has been recognised as crucial in clinical decision-making, as it impacts both adherence to, and efficacy of, interventions (1). Evidence based information is essential to support this (2).

There is evidence to support psychological models of the mechanisms that contribute to the emergence and maintenance of distress and disability associated with schizophrenia. These include the mediating impacts of attachment style and negative cognitive schema on the likelihood of developing psychotic symptoms after experiencing childhood trauma (3, 4) as well as emerging evidence supporting cognitive and emotion based models of schizophrenia (5). UK National Institute for Clinical Excellence (NICE) (6) guidelines indicate that psychological intervention should be included at all stages of intervention for schizophrenia or psychosis as follows: family intervention and cognitive behaviour therapy (CBT) alongside antipsychotic medication as part of early intervention for first episode psychosis, for acute exacerbation, or reoccurrence. Art therapy is recommended for people with primarily negative symptoms, whereas counselling, supportive psychotherapy and social skills training are contraindicated (6). However, it has been recognised that social skills training may be beneficial for negative symptoms (7). Psychoanalytic and psychodynamic principles are cited as useful in understanding experiences in the early post-acute period, while CBT and family therapy are both recommended for people with active symptoms, persistent symptoms, and when people are 'in remission' (6).

Intervention-specific meta-analyses are available (for example (8)) and a few direct comparisons have been carried out (9,10). Since registration of the protocol of this review, a network meta-analysis of psychological interventions has been published that identifies that CBT may be effective in reducing positive symptoms (11). A comprehensive statistical analysis of all available evidence is needed however to identify the interventions that are most likely to be effective for total symptoms- and this is not currently available. Network meta-analysis allows for comparison across a whole network of psychological interventions that have not been compared in real-life, using both direct and indirect evidence from randomised controlled trials (RCTs) (12).

In a resource-scarce environment, it is essential that evidence about the most appropriate and effective interventions be available to guide service-provision and clinical decision-making. This

study aimed to provide this evidence synthesis, starting with total symptoms. It is acknowledged however that symptom reduction is often not the primary aim of psychological interventions. Interventions include those considered beneficial by NICE (6) and British Psychological Society (BPS) guidelines (13). This network meta-analysis aimed to address two questions: "What is the effect of psychological interventions on total symptoms scores in psychosis?" and "Which psychological interventions are most likely to reduce symptoms?"

2 Materials and methods

A systematic review of the literature was followed by a network meta-analysis of psychological interventions for schizophrenia/psychosis. The protocol was initially based on Leucht et al's complementary network meta-analysis for antipsychotics (14), and adjusted where necessary.

2.1 Study Pre-registration

This project was pre-registered in 2016 on Prospero (see Appendix 1 or https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=32806). Changes made subsequent to protocol registration are identified in Appendix 2.

2.2 Search and Selection

Searches of MEDLINE, PsycINFO, EMBASE and CENTRAL were conducted using search terms presented in Appendix 3, and briefly summarised below. Initial title screening was completed by one author (EMG) using EndNote Web. Two authors (EMG & GD) independently completed the abstract and full text screening using Covidence software, and discrepancies were resolved through discussion with arbitration performed by a 3rd author (PH). There were no language or time period restrictions for the initial search as per the protocol; however only RCTs published in English up to the end of 2016 were included in this analysis.

Network meta-analysis depends on an assumption of transitivity- all participants could in theory have been randomised to any of the intervention arms, and potential effect modifiers, such as differences in participant samples, are balanced across the range of psychological interventions (12,15). The pre-specified systematic review protocol therefore included a caveat that any RCT that contained a highly specified population, unlikely to be generalisable to the whole, would be deemed ineligible. Full details of adaptations to, and clarifications of, the initial protocol are included in Appendix 2.

The systematic review focused on adults with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder). Exclusion criteria were: co-morbid serious medical illness or psychiatric disorder (except anxiety or depression), 'at-risk' populations or prodromal symptoms, and primary negative symptoms. The registered protocol specified 'stable at baseline' as an exclusion criteria to replicate Leucht et al (14), however early in the systematic review it became apparent that a large proportion of otherwise relevant RCTs specified 'stable medication' or ‘clinically stable’. The criteria were updated and a sensitivity analysis was planned to identify whether this decision impacted the results.

Psychological intervention was defined as theory-driven, goal-oriented intervention designed to reduce symptoms of psychosis and/or improve psychological wellbeing and functioning. Psychological therapies of specific interest included, but were not limited to, CBTpsychosis, social skills training, family therapy, and cognitive remediation. All control groups were acceptable including treatment as usual, befriending, and supportive counselling. Treatment as usual (TAU) was categorised according to the standard of care; medication only, medication with ongoing case management, access to a multi-disciplinary team and/or receipt of a range of multi-disciplinary interventions including psychological interventions. Where information about TAU was not provided, the country and year of the RCT was used to categorise the likely TAU (see Appendix 2 for further details). Psychological interventions and control groups were defined according to an adapted definition list from Turner et al (10) (see Appendix 4 for full details). Psychological interventions were aggregated into theoretically similar categories after data extraction was complete, but before analysis (see Table 2). This sorting was completed by three authors including two Clinical Psychologists (PH and WP) who were blind to the results of the RCTs. Combined interventions, such as cognitive remediation with social skills training, were considered as discrete interventions because the mechanism of change is assumed to be an interaction between the interventions.

Total symptom data were extracted from the Positive and Negative Syndrome Scale (PANSS) if available; scores from the Brief Psychiatric Rating Scale (BPRS) were considered next. If neither scale was used, the clinician-identified total symptoms outcome was extracted.

2.3 Data Extraction

Similar to Leucht et al (14) the total symptom outcome data extracted were within-group mean change score with standard deviation, or if unavailable, post intervention mean score with standard deviation. Unreported standard deviations were calculated from other information or

requested from authors, as were missing data for total symptom outcomes. Unreported total PANSS scores were calculated if PANSS positive, negative, and general scales were available, using the correlations reported in Kay et al (16). Data from two meta-analyses that had previously been extracted by study authors were included where appropriate. This data had been double-entered and checked for consistency. All remaining study characteristics and data were extracted by one author (EMG) with a random 10% sample of the full dataset independently extracted by another author (GD) and checked for consistency. There was 100% match for mean and standard deviation extractions.

2.4 Quality Assessment

Bias 'due to deviation from intended interventions' is of specific importance to RCTs of psychological interventions (17,18). This is arguably more important to account for in a network meta-analysis, as inconsistent treatment implementation across different RCTs in the same treatment category could undermine its validity (15). Nine factors adapted from the Clinical Trial Assessment Measure (CTAM:(19)) and the treatment fidelity framework reported by Borrelli et al (20) were used to assess implementation issues in this network meta-analysis (see Appendix 5 for definition and results). This included intervention integrity, fidelity (adherence to the therapeutic model within the RCT), and dose.

The Cochrane Risk of Bias (RoB) tool was used to assess study quality (17). All data were rated by one author (EMG) and compared with ratings from previously collected data. A random sample of 10% of all included RCTs was also rated independently and discrepancies were discussed. Full results are provided in Appendix 6. Sensitivity analyses were completed in two stages; first, the RoB 2.0 cut off for high/low risk was adapted (17). Performance bias was likely to be rated as high in all RCTs of psychological interventions and so all RCTs were expected to fail the RoB 2.0 criteria. Thus RCTs were considered high risk if one *other* RoB item was rated as high risk, or if more than one other item was rated as unclear risk (17). Few studies met this adapted criteria, and so a second sensitivity (post hoc) analysis was completed based on the Leucht et al definition (14); studies that reported high risk of bias for randomisation or allocation concealment were considered high risk and excluded. A third sensitivity analysis was also planned post hoc; excluding RCT with samples described as 'clinically stable', to account for the change in protocol.

2.5 Statistical Analysis

Network meta-analysis was carried out using Stata SE v15. A random effects model was conducted using a frequentist approach to pool direct and indirect evidence while preserving randomisation, using the Stata "mvmeta", "mvmeta-make" and "network" packages. Direct evidence refers to the pooled effect based on RCTs (similar to traditional meta-analysis), whereas indirect is calculated from the network, for example, difference between B and C, as extrapolated from A -v- B and A -v- C. The protocol followed the method from the University of Bristol manual (21), summarised in Appendix 7. The analysis plan below was repeated for the three sensitivity and eight subgroup analyses.

A map of the network was generated for each network. Network meta-analysis provides between-group standardised mean difference (SMD) effect sizes based on direct and indirect evidence between each intervention, as well as confidence intervals and p values (calculated as 95% confidence intervals that exclude 0). Cohen's d interpretations were used to describe the effect sizes; small 0.2, medium 0.5 and large 0.8.

Consistency checks (providing statistical evidence about the transitivity assumption) were then completed using three methods: the chi-squared statistic of the complete model, p values from a comparison of the direct and indirect SMD for each connecting 'arm' of the network, and visual inspection of the diamond plot. Where evidence of inconsistency was identified the source was explored in sequence; 1. investigation of errors in data entry and intervention categorisation, 2. inconsistencies in population/study quality that could explain the discrepancy, and 3. reassessing the intervention categorisation.

The analysis also generated information about the probability of each intervention being 'most effective' using SUCRA (surface under the cumulative rankings curve) values for each intervention. This SUCRA value compares each intervention against a hypothetical 'best' intervention (with a score of 100%), and so a score lower than 50 indicates approximately half of the effectiveness.

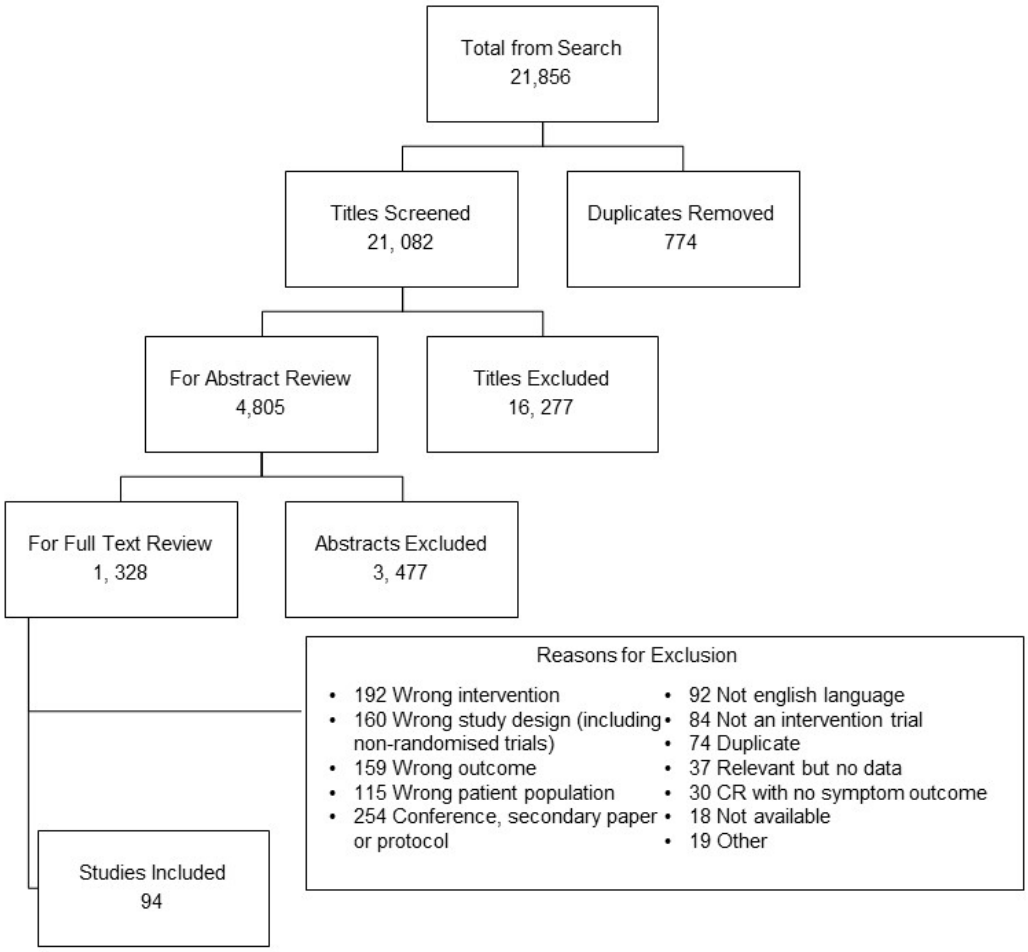

Figure1: PRISMA diagram of systematic review

3 Results

3.1 Description of Included RCTs

The systematic review identified 94 relevant RCTs with available total symptom outcome data. There were 42 psychological interventions, control groups, and 'combined' interventions which were grouped into 24 categories for analysis, with 10 psychological interventions, 6 control groups (3 active, 4 treatment as usual), and 7 'combined' interventions (see Table 2). Two RCTs had interventions that were subsumed in the same category (family therapy) and could not be included in the analysis as the interventions were not unique. Two published studies (were identified as containing data from the same trial and just one was included. Lastly, one study was removed due to evidence of inconsistency (see Appendix 8 for rationale). Ninety studies

remained, with 195 trial arms (see Appendix 9 for a table detailing the characteristics of the included RCTs).

The 90 RCTs included 8,440 randomised participants, (approximately 39% of whom were female, n = 3,320), with data for 7,410 participants (87%). The median year of publication was 2011 (range 1986-2017- articles dated 2017 were published online in 2016). The RCTs took place in various countries, including the UK (20: 22%), the US (14: 15%) and China (13: 14%).

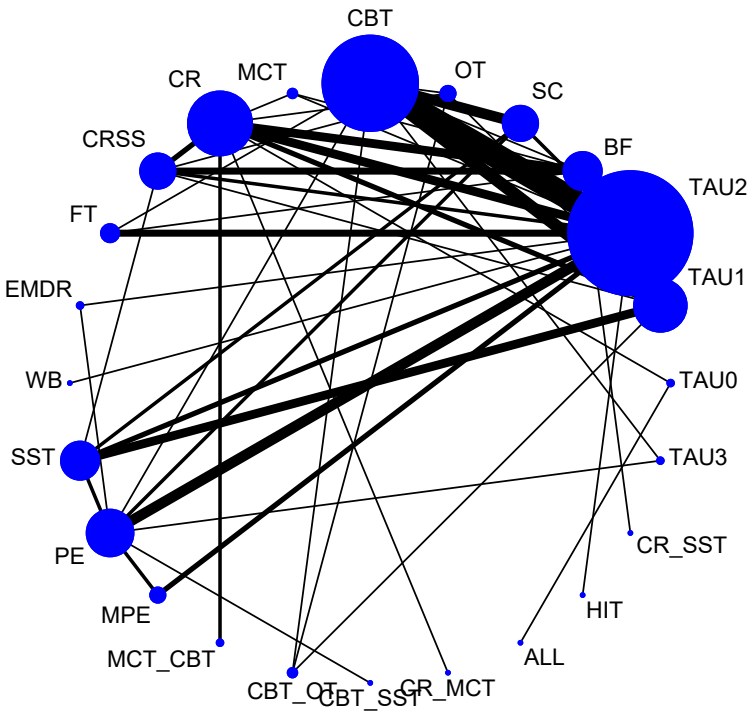

Figure 2: Network of psychological interventions

Note: The circles represent intervention arms in an RCT- larger circles represent presence in more RCTS. The lines connect interventions that were compared in an RCT and thicker connecting lines indicate more direct RCT comparisons. Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy**;** CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy**;** HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation**;** SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Fifty-six (62%) RCTs were based in outpatient settings, 15 (16%) were inpatient settings, and 10 (11%) recruited participants from both settings. Regarding the interventions, 65 (intervention or control) arms from 29 RCTs were delivered individually, whereas 91 arms across 43 RCTs were delivered in a group format. Thirteen arms across 11 studies were computer-based. The average intervention length was 20 sessions (median 16, range 4-52). Seventeen RCTs included people

with ‘recent onset’ schizophrenia, defined as <5 years since diagnosis. Few RCTs reported specific adverse effects; some reported aspects of patient satisfaction, or serious adverse events, and none reported measuring adverse effects using a standardised measure. Intervention integrity was rated on a scale of 0 to 6, with 0 being high integrity; 92% of intervention arms scored 0. There was more variance for fidelity, with 35% scoring in middle of a scale from -1 to 8, with -1 being high likelihood of adherence to the therapy model (full results are reported in Appendix 5). Fourteen RCTs (15%) met the adapted Cochrane RoB 2.0 criteria for low risk of bias (see Appendix 6 for full results). Six RCTs met the post hoc RoB criteria for high risk of bias. Thirty-three RCTs (36%) specified their sample as clinically stable, and/or on stable medication and 4 specified acute, or post-acute symptoms. Five RCTs specified a treatment resistant sample.

3.2 Total Symptom Analysis

A detailed map of the network was created which depicts the 189 treatment RCT arms from 90 RCTs (see Figure 2). Table 2 describes the characteristics of the intervention categories. There was no evidence of inconsistency in the model $\chi 2$ (27, N = 90) = 22.86, p = .583 and there was no evidence of loop inconsistency, that is, when the effect sizes for the direct and in a pairwise comparison do not align (22).

The results of the network meta-analysis comparisons (that is, SMD effect sizes, confidence intervals and statistical significance) can be seen in Table 3 and are briefly summarised here. Table 1 clarifies all intervention abbreviations. Most interventions were found to be statistically significantly more likely to reduce symptoms compared to control groups. Two interventions, CBT with social skills training, and mindfulness-based psychoeducation were also found to be statistically significantly different to other psychological interventions, with medium and large effect sizes respectively, and large confidence intervals. These interventions were also ranked as having the highest probability of being most effective according to the SUCRA values (see Table 4 for scores and Appendix 7 for more detail on SUCRA values). Psychoeducation, family therapy, social skills training and cognitive remediation with social skills training were statistically significantly different compared with TAU2 and had a SUCRA score above the 50 level-indicating that they are likely to provide approximately 50% of the level of effectiveness of a hypothetical best intervention. CBT was ranked below befriending and most intervention categories (with a SUCRA of 39.7), however it was identified as statistically significant, with a small effect size and narrow confidence intervals.

Table 1: List of psychological intervention abbreviations

ALL	Protocol with 4 psychotherapies combined
BF	Befriending
BFT	Behavioural family therapy
CAT	Cognitive adaptation therapy (an OT intervention)
CBT	Cognitive behaviour therapy
CBTp	Cognitive behaviour therapy; psychosis
CC	Computerised control group
CCBF	Computerised control with befriending
CPS	Coping skills training
CR	Cognitive remediation
CR_meta	Cognitive remediation targeting metacognitive processes
CRSS	Cognitive remediation focussed on social cognition
EMDR	Eye movement desensitisation and reprocessing
FPE	Family psychoeducation
FSG	Family support groups
FSIT	Family assisted social cognition training
FT	Family therapy
HIT	Hallucinations focused integrative therapy
MCT	Metacognitive therapy
MPE	Mindfulness-based psychoeducation
OT	Occupational therapy
PE	Psychoeducation
PESC	Psychoeducation with supportive counselling
PMR	Progressive muscle relaxation
PST	Problem solving training
SC	Supportive counselling
SE	Self esteem training
SST	Social skills training
SST_FPE	Social skills training with family psychoeducation
TAU	Treatment as usual
WB	Wellbeing

Table 2: Characteristics of psychological intervention categories

	Number of studies		Presentation				Setting			Delivery					Outcome Measure			Implementation		Risk of Bias	
		total n	Early (<5 years) n/%	Clinical Stable n /%	Acute n/%	Other	Inpatient	Outpatient	Both	Individual	Group	Both Individual and Group	Computer	Average no of weeks (range)	PANSS	BPRS	Other	Reported Integrity (High 0 to Low 6)*	Reported Fidelity (High -1 to Low 8)	High ROB (Leucht)	Low ROB (Cochrane)
TAU0	2	380	1	1	0	1 FGA only	0	1	0												
TAU1	16	634	3	8	0	1 Treatment resistant 1 Insomnia	2	13	1												
TAU2	35	1336	7	11	3	1 No med 1 Suicide attempt 2 Auditory hallucinations 1 Relapse prone	3	28	6												
BF	11	410	2	8	0	1 Treatment resistant	3	9	0	2	8	2	0	18 (4-39)	10	1	1 CPRS	n/a	n/a	1	2
SC	9	464	3	2	1	1 Auditory Hallucination 1 Treatment resistant	4	4	2	6	4	0	0	15 (8-39)	5	5		1 scored 1 1 scored 2 1 scored 6	5 scored 1 1 scored 3	1	0
OT	3	103	0	1	0	1 Treatment resistant	1	2	0	2	1	0	0	22 (13-39)	1	2		n/a	n/a	0	1
CBT	25	1477	4	6	2	3 Treatment Resistant 1 No med 1 Suicide attempt 1 Persecutory delusions 1 Insomnia 1 Relapse prone 1 Auditory hallucinations	2	18	8	23	5	0	0	26 (5-52)	20	5	3 CPRS	3 scored 1 2 scored 2 1 scored 3	5 scored 1 2 scored 2 3 scored 4	3	8
MCT	3	100	1	0	0		2	0	1	0	3	0	0	4 (4-4)	3			0	1 scored 2 1 scored 3 1 scored 4	0	0

CR	19	740	1	12	0	1 delusional	6	10	4	4	5	1	11	12 (4-26)	18	3		2 scored 1 1 scored 2	3 scored 1 1 scored 2 4 scored 3 12 scored 4	2	4
CRSS	11	263	3	6	0	1 Treatment resistant	3	7	1	0	9	0	2	18 (6-52)	10	1		1 scored 1	6 scored 2 1 scored 3 4 scored 4	0	0
FT	4	312	0	1	1		0	9	0	3	6	0	0	32 (13-52)	3	4	2 PAS	1 scored 1	2 scored 4 2 scored 3 1 scored 1	1	1
EMDR	1	15	1	0	1		1	0	0	1	0	0	0	4	1			0	1 scored 4	0	0
WB	1	47	0	0	0		0	0	1	0	1	0	0	11		1		0	0	0	0
SST	13	638	2	8	0		2	12	0	1	13	0	0	28 (8-52)	10	3	1 PAS	3 scored 1	4 scored 1 3 scored 2 1 scored 3 2 scored 4	0	0
PE	13	482	7	0	2		3	9	2	6	8	0	0	17 (4-39)	6	6	1 PAS 1PECC	2 scored 1 1 scored 2 1 scored 3	3 scored 1 4 scored 2 2 scored 3 2 scored 4	0	2
MPE	3	130	3	0	0		0	3	0	0	3	0	0	21 (13-25)	1	2		0	1 scored 2 1 scored 5	0	2
MCT_CBT	1	70	0	0	0		1	0	1	1	1	0	0	5 (4-6)	2			0	2 scored 2	1	0
CBT_OT	1	40	0	0	0		0	1	0	1	0	0	0	39		1		0	0	0	1
CBT_SST	1	20	0	0	0		0	0	1	1	0	0	0	26		1		1 scored 1	1 scored 2	0	0

CR_MCT	1	30	0	1	0	0	1	0	0	0	1	0	16	1	0	1 scored 3	0	0
ALL	1	633	1	1	0	0	1	0	0	1	0	0	52	1	1 scored 1	1 scored -1	0	0
HIT	1	37	0	0	0	0	1	0	1	0	0	0	39	1	0	0	0	0
CR_SST	1	27	0	1	0	0	1	0	0	1	0	0	12	1	0	1 scored 2	0	0
TAU3	1	52	1	0	0	0	1	1										

Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Table 3: Total symptoms SMD effect sizes and confidence intervervals between each category

	TAU 0	TAU 1	TAU 2	BF	SC	OT	CBT	MCT	CR	CRSS	FT	EMDR	WB	SST	PE	MPE	MCT_CBT	CBT_OT	CBT_SST	CR_MCT	ALL	HIT	CR_SST
TAU1	0.29 (-0.42 to 1.00)																						
TAU2	0.15 (-0.54 to 0.85)	-0.14 (-0.37 to 0.09)																					
BF	0.16 (-0.53 to 0.86)	-0.13 (-0.45 to 0.20)	0.01 (-0.28 to 0.30)																				
SC	-0.03 (-0.76 to 0.70)	**-0.32 (-0.61 to -0.03)**	-0.19 (-0.43 to 0.06)	0.20 (-0.56 to 0.17)																			
OT	-0.35 (-1.14 to 0.44)	**-0.64 (-1.09 to -0.19)**	**-0.50 (-0.95 to -0.05)**	**-0.51 (-0.98 to -0.04)**	-0.32 (-0.81 to 0.18)																		
CBT	-0.17 (-0.87 to 0.53)	**-0.46 (-0.67 to -0.24)**	**-0.32 (-0.48 to -0.16)**	**-0.33 (-0.63 to -0.03)**	-0.13 (-0.37 to 0.10)	0.18 (-0.27 to 0.63)																	
MCT	-0.09 (-0.89 to 0.70)	-0.38 (-0.90 to 0.13)	-0.25 (-0.74 to 0.25)	-0.26 (-0.74 to 0.23)	-0.06 (-0.60 to 0.48)	0.26 (-0.37 to 0.88)	0.07 (-0.43 to 0.58)																
CR	-0.07 (-0.72 to 0.59)	**-0.36 (-0.63 to -0.08)**	-0.22 (-0.46 to 0.02)	-0.23 (-0.48 to 0.02)	-0.03 (-0.36 to 0.29)	0.28 (-0.16 to 0.73)	0.10 (-0.16 to 0.36)	0.03 (-0.43 to 0.49)															

CRSS	-0.24 (-0.95 to 0.47)	**-0.53 (-0.86 to -0.19)**	**-0.39 (-0.70 to -0.08)**	**-0.40 (-0.69 to -0.11)**	-0.20 (-0.58 to 0.17)	0.11 (-0.33 to 0.56)	-0.07 (-0.39 to 0.25)	-0.14 (-0.66 to 0.37)	-0.17 (-0.45 to 0.11)														
FT	-0.19 (-0.95 to 0.56)	**-0.48 (-0.86 to -0.10)**	**-0.35 (-0.66 to -0.03)**	-0.36 (-0.75 to 0.04)	-0.16 (-0.55 to 0.24)	0.16 (-0.38 to 0.70)	-0.03 (-0.37 to 0.32)	-0.10 (-0.67 to 0.47)	-0.13 (-0.51 to 0.26)	-0.04 (-0.38 to 0.47)													
EMDR	-0.25 (-1.30 to 0.81)	-0.53 (-1.36 to 0.29)	-0.40 (-1.20 to 0.40)	-0.41 (-1.26 to 0.44)	-0.21 (-1.04 to 0.61)	0.10 (-0.81 to 1.02)	-0.08 (-0.89 to 0.73)	-0.15 (-1.09 to 0.78)	-0.18 (-1.01 to 0.65)	0.01 (-0.86 to 0.85)	-0.05 (-0.91 to 0.81)												
WB	-0.30 (-1.26 to 0.66)	-0.59 (-1.29 to 0.11)	-0.45 (-1.11 to 0.21)	-0.46 (-1.18 to 0.26)	-0.26 (-0.97 to 0.44)	0.05 (-0.75 to 0.85)	-0.13 (-0.81 to 0.55)	-0.20 (-1.03 to 0.62)	-0.23 (-0.94 to 0.47)	-0.06 (-0.79 to 0.67)	-0.10 (-0.84 to 0.63)	-0.05 (-1.09 to 0.99)											
SST	-0.17 (-0.89 to 0.55)	**-0.46 (-0.68 to -0.23)**	**-0.32 (-0.56 to -0.08)**	-0.33 (-0.68 to 0.01)	-0.14 (-0.43 to 0.16)	0.18 (-0.30 to 0.66)	0.00 (-0.25 to 0.24)	-0.08 (-0.60 to 0.45)	-0.10 (-0.41 to 0.20)	0.07 (-0.28 to 0.42)	0.02 (-0.37 to 0.41)	0.08 (-0.75 to 0.90)	0.13 (-0.58 to 0.83)										
PE	-0.41 (-1.13 to 0.32)	**-0.70 (-0.99 to -0.41)**	**-0.56 (-0.79 to -0.34)**	**-0.57 (-0.93 to -0.22)**	**-0.38 (-0.66 to -0.10)**	-0.06 (-0.55 to 0.43)	**-0.24 (-0.48 to 0.00)**	-0.32 (-0.85 to 0.22)	-0.34 (-0.66 to 0.03)	-0.17 (-0.54 to 0.20)	-0.22 (-0.60 to 0.17)	-0.16 (-0.96 to 0.64)	-0.11 (-0.81 to 0.59)	-0.24 (-0.53 to 0.05)									
MPE	-0.70 (-1.48 to 0.08)	**-0.98 (-1.40 to -0.57)**	**-0.85 (-1.21 to -0.49)**	**-0.86 (-1.32 to -0.40)**	**-0.66 (-1.08 to -0.24)**	-0.35 (-0.92 to 0.22)	**-0.53 (-0.91 to -0.15)**	**-0.60 (-1.21 to 0.00)**	**-0.63 (-1.06 to -0.20)**	-0.46 (-0.93 to 0.01)	**-0.50 (-0.98 to -0.03)**	-0.45 (-1.32 to 0.42)	-0.40 (-1.15 to 0.35)	**-0.53 (-0.95 to -0.11)**	-0.29 (-0.66 to 0.09)								
MCT_CBT	-0.37 (-1.19 to 0.44)	**-0.66 (-1.23 to -0.10)**	-0.53 (-1.08 to 0.02)	-0.54 (-1.09 to 0.01)	-0.34 (-0.93 to 0.25)	-0.03 (-0.69 to 0.64)	-0.21 (-0.76 to 0.35)	-0.28 (-0.95 to 0.39)	-0.31 (-0.80 to 0.18)	-0.14 (-0.71 to 0.43)	-0.18 (-0.81 to 0.44)	-0.13 (-1.10 to 0.84)	-0.08 (-0.94 to 0.78)	-0.21 (-0.78 to 0.37)	0.03 (-0.55 to 0.62)	0.32 (-0.33 to 0.97)						
CBT_OT	0.08 (-0.84 to 0.99)	0.21 (-0.83 to 0.41)	-0.08 (-0.71 to 0.55)	-0.09 (-0.75 to 0.58)	0.11 (-0.55 to 0.77)	0.42 (-0.25 to 1.09)	0.24 (-0.38 to 0.86)	0.17 (-0.61 to 0.95)	0.14 (-0.50 to 0.79)	0.31 (-0.35 to 0.98)	0.27 (-0.43 to 0.97)	0.32 (-0.69 to 1.34)	0.37 (-0.54 to 1.29)	0.24 (-0.40 to 0.89)	0.48 (-0.17 to 1.14)	***0.77 (0.05 to 1.49)***	0.45 (-0.36 to 1.26)					

CBT_SST	**-1.13 (-2.23 to -0.02)**	**-1.42 (-2.30 to -0.53)**	**-1.28 (-2.14 to -0.42)**	**-1.29 (-2.20 to -0.38)**	**-1.09 (-1.97 to -0.21)**	-0.78 (-1.75 to 0.19)	**-0.96 (-1.83 to -0.09)**	**-1.03 (-2.02 to -0.04)**	**-1.06 (-1.95 to -0.17)**	-0.89 (-1.80 to 0.02)	**-0.93 (-1.85 to -0.02)**	-0.88 (-2.04 to 0.27)	-0.83 (-1.92 to 0.26)	**-0.96 (-1.84 to -0.07)**	-0.72 (-1.55 to 0.12)	-0.43 (-1.35 to 0.48)	-0.75 (-1.77 to 0.27)	**-1.20 (-2.26 to -0.14)**	-			
CR_MCT	-0.16 (-1.15 to 0.84)	-0.45 (-1.24 to 0.35)	-0.31 (-1.10 to 0.48)	-0.32 (-1.11 to 0.47)	-0.12 (-0.94 to 0.70)	0.19 (-0.68 to 1.06)	0.01 (-0.78 to 0.80)	-0.06 (-0.94 to 0.82)	-0.09 (-0.84 to 0.66)	0.08 (-0.72 to 0.88)	0.04 (-0.81 to 0.88)	0.09 (-1.03 to 1.21)	0.14 (-0.89 to 1.17)	0.01 (-0.80 to 0.82)	0.25 (-0.56 to 1.07)	0.54 (-0.33 to 1.40)	0.22 (-0.68 to 1.12)	-0.23 (-1.22 to 0.76)	0.97 (-0.20 to 2.14)			
ALL	-0.29 (-0.81 to 0.23)	-0.58 (-1.46 to 0.30)	-0.45 (-1.31 to 0.42)	-0.46 (-1.33 to 0.41)	-0.26 (-1.16 to 0.64)	0.06 (-0.89 to 1.00)	-0.13 (-1.00 to 0.75)	-0.20 (-1.15 to 0.75)	-0.23 (-1.06 to 0.61)	-0.06 (-0.94 to 0.82)	-0.10 (-1.02 to 0.82)	-0.05 (-1.23 to 1.13)	0.00 (-1.09 to 1.10)	-0.12 (-1.01 to 0.76)	0.12 (-0.78 to 1.01	0.40 (-0.53 to 1.34)	0.08 (-0.89 to 1.05)	-0.37 (-1.42 to 0.69)	0.83 (-0.39 to 2.06)	-0.14 (-1.26 to 0.99)			
HIT	-0.49 (-1.47 to 0.50)	-0.77 (-1.51 to -0.04)	-0.64 (-1.34 to 0.06)	-0.65 (-1.41 to 0.11)	-0.45 (-1.19 to 0.29)	-0.14 (-0.97 to 0.69)	-0.32 (-1.03 to 0.39)	-0.39 (-1.25 to 0.46)	-0.42 (-1.16 to 0.32)	-0.25 (-1.01 to 0.51)	-0.29 (-1.06 to 0.47)	-0.24 (-1.30 to 0.82)	-0.19 (-1.15 to 0.77)	-0.32 (-1.05 to 0.42)	-0.08 (-0.81 to 0.65)	0.21 (-0.57 to 0.99)	-0.11 (-1.00 to 0.78)	-0.56 (-1.50 to 0.38)	0.64 (-0.47 to 1.75)	-0.33 (-1.38 to 0.72)	-0.19 (-1.31 to 0.92)		
CR_SST	0.09 (-0.94 to 1.12)	-0.20 (-1.03 to 0.63)	-0.06 (-0.88 to 0.75)	-0.07 (-0.84 to 0.69)	0.12 (-0.72 to 0.97)	0.44 (-0.46 to 1.33)	0.26 (-0.56 to 1.07)	0.18 (-0.72 to 1.08)	0.16 (-0.64 to 0.96)	0.33 (-0.49 to 1.14)	0.28 (-0.58 to 1.14)	0.33 (-0.81 to 1.48)	0.39 (-0.66 to 1.44)	0.26 (-0.58 to 1.09)	0.50 (-0.34 to 1.34)	0.78 (-0.10 to 1.67)	0.46 (-0.48 to 1.40)	0.01 (-1.00 to 1.03)	***1.22 (0.03 to 2.40)***	0.25 (-0.85 to 1.34)	0.38 (-0.77 to 1.54)	0.57 (-0.50 to 1.65)	
TAU3	0.25 (-0.64 to 1.14)	-0.04 (-0.63 to 0.55)	0.10 (-0.47 to 0.66)	0.08 (-0.54 to 0.71)	0.28 (-0.31 to 0.87)	0.60 (-0.11 to 1.31)	0.42 (-0.14 to 0.97)	0.34 (-0.40 to 1.08)	0.34 (-0.29 to 0.92)	0.49 (-0.15 to 1.12)	0.44 (-0.20 to 1.08)	0.49 (-0.47 to 1.46)	0.55 (-0.32 to 1.41)	0.42 (-0.18 to 1.01)	***0.66 (0.10 to 1.22)***	***0.94 (0.29 to 1.60)***	0.62 (-0.16 to 1.40)	0.17 (-0.66 to 1.00)	***1.38 (0.37 to 2.38)***	0.41 (-0.56 to 1.37)	0.54 (-0.49 to 1.57)	0.73 (-0.16 to 1.63)	0.16 (-0.82 to 1.14)

Table 3 notes: Vertical compared to the horizontal- minus score indicates greater reduction in symptoms; such that compared to TAU1, CBT reported a reduction in score of 0.46 more than TAU1 (confidence interval -0.67 to -0.24). Score above zero indicates lesser reduction in symptoms, such that compared to MPE, CBT_OT reported 0.77 less of a reduction in score. Statistically significant differences highlighted in bold, and greater reduction vertical/horizontal underlined, lesser reduction vertical/horizontal in italics.

Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Table 4: SUCRA values, probability of being best in rank order and SMD (CI) compared to TAU2 (see Table 1 for abbreviations)

	SUCRA	Prob. Best	SMD (CI)*
MPE	91.8	26.4	**-0.85 (-1.21 to -0.49)**
CBT_SST	86.3	42	**-1.28 (-2.14 to -0.42)**
HIT	73.4	5.3	-0.64 (-1.34 to 0.06)
MCT_CBT	68.3	1	-0.53 (-1.08 to 0.02)
WB	61.8	1.9	-0.45 (-1.11 to 0.21)
ALL	59.9	3.8	-0.45 (-1.31 to 0.42)
MCT	57.2	5.1	-0.25 (-0.74 to 0.25)
PE	56.6	0.1	**-0.56 (-0.79 to -0.34)**
FT	56.2	0	**-0.35 (-0.66 to -0.03)**
SST	54.9	0.3	**-0.32 (-0.56 to -0.08)**
CRSS	54.5	9.3	**-0.39 (-0.70 to -0.08)**
EMDR	51.1	1.1	-0.40 (-1.20 to 0.40)
CR_MCT	50.7	1.2	-0.31 (-1.10 to 0.48)
CR_SST	46.4	1.7	-0.06 (-0.88 to 0.75)
CR	44.4	0	-0.22 (-0.46 to 0.02)
BF	41.1	0	0.01 (-0.28 to 0.30)
CBT	39.7	0	**-0.32 (-0.48 to -0.16)**
TAU0	39.4	0.2	.
SC	38.7	0.3	-0.19 (-0.43 to 0.06)
OT	33.1	0.2	**-0.50 (-0.95 to -0.05)**

CBT_OT	33	0.1	-0.08 (-0.71 to 0.55)
TAU2	28.9	0	.
TAU1	22.5	0	.
TAU3	10.2	0	.

*Compared with TAU2

Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

3.3.1 Sensitivity Analyses

A sensitivity analysis was carried out with the 14 RCTs that met the stringent criteria for low risk of bias RoB 2.0 (17) (see Appendix 6 for full results) to investigate whether study quality affected the results. Eleven intervention types remained across 33 arms (see Figure 3 and Table 5). There was no evidence of inconsistency in the model $\chi 2$ (2, N = 14) = 0.61, p = .736 and no statistically significant differences between the direct and indirect evidence indicating that the model was coherent. As seen in Table 5, the results were similar to the total analysis; mindfulness-based psychoeducation remained highest ranked according to SUCRA values, with psychoeducation also ranked highly and with statistical significance. In contrast to the full analysis befriending had the lowest SUCRA and family therapies were ranked lower.

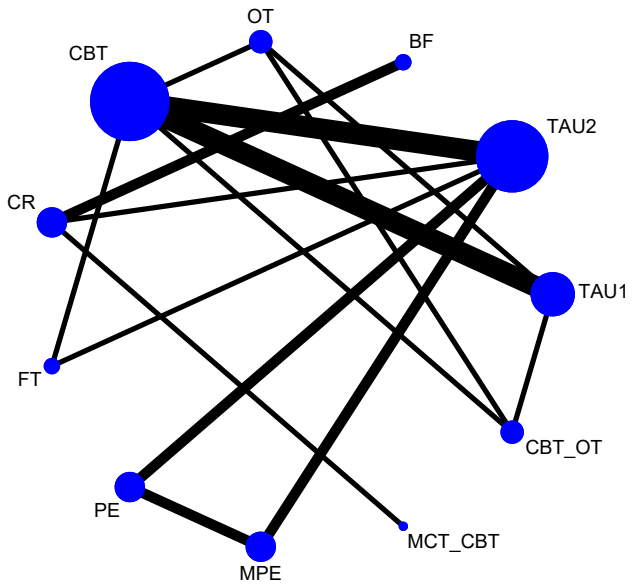

Figure 3: Network of psychological interventions for sensitivity analysis (Cochrane RoB).

Note: The circles represent intervention arms in an RCT- larger circles represent presence in more RCTS. The lines connect interventions that were compared in an RCT and thicker connecting lines indicate more direct RCT comparisons. Intervention Abbreviations: BF – Befriending; CBT -Cognitive behaviour therapy**;** CR -Cognitive remediation; FT - Family therapy**;** MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation**;** TAU - Treatment as usual (levels 0-3). Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

The post hoc RoB sensitivity analysis based on the Leucht et al (14) criteria excluded six studies which had a high risk of allocation concealment and/or randomisation bias. Eighty-four RCTs remained, with 177 arms. All intervention types were included, and there was no evidence of inconsistency in the model $\chi 2$ (25, N = 84) = 20.74, p = .706 and no statistically significant differences between the direct and indirect evidence. Again, the SUCRA hierarchy was similar, with mindfulness-based psychoeducation and CBT with social skills training, reporting the highest SUCRA values. As in the original analysis, the majority of control groups were ranked lower than the intervention groups.

The sensitivity analysis removing RCTs that specified a clinically stable sample involved 48 RCTs with 102 arms across 20 interventions. The results were largely consistent with the full analysis (see Table 6), with most interventions ranked in similar positions in the SUCRA hierarchy compared to the full analysis, except cognitive remediation had a lower SUCRA score, while befriending and meta-cognitive training had a higher SUCRA score than in the full analysis. Figure 4 details the number of RCTs that met the criteria for each level of risk of bias, RCT level details can be found in Appendix 9.

Table 5: Sensitivity analysis (Cochrane RoB): SUCRA values and probability of being best in rank order

	SUCRA	Prob. Best	SMD (CI)*
MPE	97.7	81.7	**-1.02 (-1.42 to -0.62)**
PE	74.7	0.1	**-0.50 (-0.89 to -0.11)**
MCT_CBT	68.2	11.5	-0.43 (-1.29 to 0.43)
OT	61.4	4.6	-0.23 (-0.87 to 0.41)
CBT	54.2	0	-0.23 (-0.50 to 0.05)
CBT_OT	37.3	0.9	0.07 (-0.55 to 0.69)
FT	35.7	0.6	-0.03 (-0.62 to 0.56)
CR	32.7	0	0.02 (-0.54 to 0.57)
TAU1	31.4	0.6	.
TAU2	31.4	0	.
BF	25.4	0	0.11 (-0.60 to 0.82)

*Compared with TAU2

Intervention Abbreviations: BF – Befriending; CBT -Cognitive behaviour therapy; CR -Cognitive remediation; FT - Family therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; TAU - Treatment as usual (levels 0-3). Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

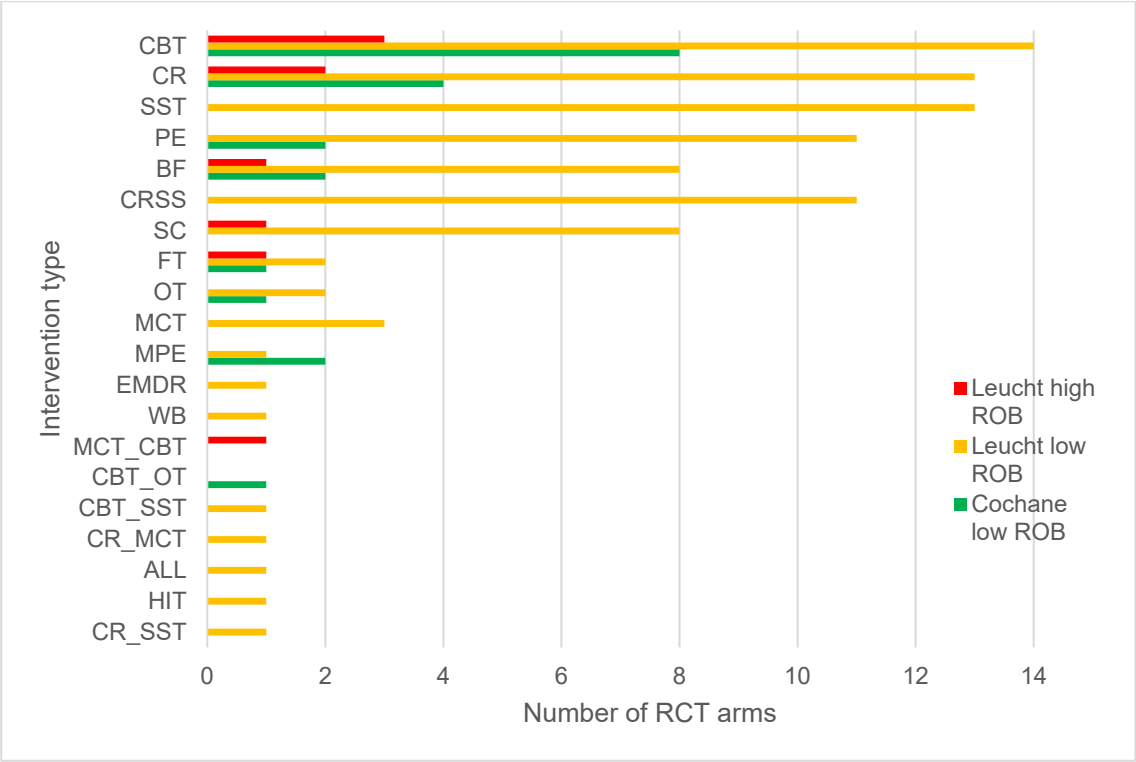

Figure 4: Risk of bias by intervention category

Note Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

3.4 Subgroup Analyses

Eight subgroup analyses were completed with the 84 studies meeting the post hoc RoB sensitivity analysis criteria. The SMD and CI for each, compared with TAU2 is presented in Table 6. Evidence of inconsistency was not found for any of the models except Chronic. Similarly, there was no evidence of inconsistency between the direct and indirect evidence in any analysis, except as detailed for the Chronic analysis- details can be found in Appendix 8.

RCTs that specified treatment resistant symptoms or a sample not taking medication were excluded to identify if these characteristics impacted the results. Seventy-seven RCTs across 22 intervention types remained. Similar to the full analysis, the highest ranked intervention was mindfulness-based psychoeducation and cognitive remediation focussed on social cognition was

ranked second. OT (occupational therapy) and TAU1 had the lowest SUCRA values. Fifteen RCTs were in the inpatient setting across 13 intervention types. OT had the highest SUCRA value, and CBT had the lowest for this setting. Fifty-six RCTs were described as outpatient, with 119 study arms across 17 interventions. Mindfulness-based psychoeducation was ranked highest followed by psychoeducation. Ten RCTs across seven intervention types took place across both in-and outpatient settings CBT with social skills training was ranked highest.

Seventeen RCTs were classified as 'recent onset', with 38 arms. Cognitive remediation focussed on social cognition, mindfulness-based psychoeducation, and cognitive remediation were ranked highest; social skills training and TAU1 ranked lowest. Sixty-six RCTs were classified as 'chronic', however inconsistency was identified between the direct and indirect evidence for OT and CRSS. In this analysis CBT with social skills training and HIT were ranked highest, with TAU1 lowest.

Interventions in 29 RCTs were delivered on an individual basis. Fourteen intervention types were included in the analyses of 65 arms. CBT with social skills training, psychoeducation, and HIT were ranked highest using SUCRA scores, with family therapy and TAU1 lowest. Interventions were delivered in a group format for 15 different intervention types across 91 arms in 43 RCTs. OT, mindfulness-based psychoeducation, and metacognitive therapy with CBT were ranked highest, with befriending ranked lowest.

Table 6: Subgroup analyses: network details and SMD with CI for each intervention compared with TAU2

	Number of studies	Total (Post hoc RoB) SMD (CI)	Without Clinically Stable SMD (CI)	Treatment resistant removed SMD (CI)	Inpatient SMD (CI)	Outpatient SMD (CI)	Both	Chronic SMD (CI)	Recent Onset (<5 yrs) SMD (CI)	Individual SMD (CI)	Group SMD (CI)
Number of RCTs		84	48	77	15	56	10	66	17	29	43
Number of study arms		177	102	163	31	119	19	137	38	65	91
Model consistency: Chi^2 (d.f.) p value		20.74 (25) p = .706	10.42 (17) p = .885	17.10 (23) p = .804	0.67 (3) p = .881	14.08 (19) p = .779	0.61 (2) p = .737	27.94 (20) p = .111	3.42 (6) p = .755	3.17 (7) p = .868	12.41 (13) p =.494
Intervention types		24	20	22	13	17	7	20	13	14	16
TAU0	2	.	.	.	.	.	.	.	.	.	.
TAU1	16	.	.	.	.	.	.	.	.	.	.
TAU2	35	.	.	.	.	.	.	.	.	.	.
BF	11	-0.01 (-0.33 to 0.30)	-0.16 (-0.64 to 0.32)	-0.02 (-0.37 to 0.34)	-0.17 (-0.73 to 0.39)	0.02 (-0.36 to 0.41)	.	0.03 (-0.26 to 0.32)	-0.55 (-1.98 to 0.88)	-0.10 (-0.77 to 0.57)	-0.31 (-0.92 to 0.29)
SC	9	-0.16 (-0.41 to 0.10)	-0.08 (-0.40 to 0.23)	-0.14 (-0.40 to 0.12)	-0.14 (-0.96 to 0.67)	0.09 (-0.32 to 0.50)	-0.21 (-0.46 to 0.04)	0.01 (-0.27 to 0.29)	-0.38 (-0.97 to 0.21)	-0.26 (-0.61 to 0.09)	-.012 (-0.55 to 0.31)
OT	3	**-0.49 (-0.94 to -0.04)**	-0.10 (-0.66 to 0.46)	-0.17 (-0.72 to 0.38)	-0.64 (-1.41 to 0.13)	-0.20 (-0.78 to 0.38)	.	**-0.43 (-0.83 to -0.02)**	.	-0.11 (-0.69 to 0.47)	**-1.30 (-2.15 to -0.45)**
CBT	25	**-0.29 (-0.45 to -0.13)**	**-0.24 (-0.47 to -0.02)**	**-0.27 (-0.45 to -0.10)**	0.42 (-0.79 to 1.64)	**-0.31 (-0.53 to -0.10)**	**-0.21 (-0.40 to -0.02)**	**-0.25 (-0.40 to -0.10)**	-0.17 (-0.77 to 0.42)	**-0.26 (-0.46 to -0.05)**	-0.26 (-0.60 to 0.08)
MCT	3	-0.24 (-0.74 to 0.25)	-0.22 (-0.74 to 0.31)	-0.24 (-0.74 to 0.27)	-0.45 (-1.14 to 0.25)	.	.	-0.18 (-0.65 to 0.30)	-0.78 (-2.55 to 0.99)	.	-0.55 (-1.23 to 0.13)

CR		19	-0.20 (-0.46 to 0.05)	-0.11 (-0.50 to 0.29)	-0.19 (-0.46 to 0.07)	0.00 (-0.47 to 0.47)	-0.26 (-0.59 to 0.07)	.		-0.15 (-0.38 to 0.08)	-1.00 (-2.38 to 0.38)		-0.13 (-0.60 to 0.34)	-0.60 (-1.21 to 0.02)
CRSS		11	**-0.39 (-0.71 to -0.07)**	-0.21 (-0.68 to 0.27)	**-0.46 (-0.81 to -0.12)**	-0.05 (-0.68 to 0.58)	**-0.66 (-1.07 to -0.25)**	.		-0.24 (-0.57 to 0.09)	**-1.11 (-2.15 to -0.08)**		.	**-0.71 (-1.22 to -0.21)**
FT		4	-0.26 (-0.60 to 0.08)	-0.33 (-0.71 to 0.05)	-0.26 (-0.60 to 0.09)	.	-0.26 (-0.62 to 0.10)	.		-0.26 (-0.55 to 0.04)	.		-0.04 (-0.70 to 0.62)	-0.33 (-0.74 to 0.08)
EMDR		1	-0.41 (-1.21 to 0.39)	.	-0.41 (-1.21 to 0.39)	-0.29 (-1.07 to 0.48)	.	.		.	-0.39 (-1.35 to 0.56)		-0.41 (-1.23 to 0.40)	.
WB		1	-0.45 (-1.11 to 0.21)	-0.45 (-1.08 to 0.18)	-0.45 (-1.11 to 0.21)	.	.	**-0.45 (-0.88 to -0.02)**		-0.45 (-1.01 to 0.11)	.		.	-0.45 (-1.13 to 0.24)
SST		13	**-0.31 (-0.55 to -0.07)**	-0.25 (-0.64 to 0.14)	**-0.29 (-0.54 to -0.05)**	-0.34 (-1.27 to 0.59)	-0.27 (-0.55 to 0.01)	.		**-0.34 (-0.57 to -0.11)**	0.48 (-0.72 to 1.69)		.	**-0.37 (-0.69 to -0.05)**
PE		13	**-0.58 (-0.81 to -0.36)**	**-0.61 (-0.86 to -0.37)**	**-0.58 (-0.81 to -0.35)**	-0.36 (-1.12 to 0.40)	**-0.63 (-0.92 to -0.35)**	-0.47 (-0.93 to 0.00)		**-0.63 (-0.95 to -0.30)**	**-0.56 (-0.96 to -0.15)**		**-0.59 (-1.00 to -0.18)**	**-0.51 (-0.82 to -0.20)**
MPE		3	**-0.86 (-1.21 to -0.50)**	**-0.87 (-1.21 to -0.52)**	**-0.85 (-1.21 to -0.50)**	.	**-0.88 (-1.26 to -0.49)**	.		.	**-0.85 (-1.33 to -0.37)**		.	**-0.83 (-1.21 to -0.45)**
MCT_CBT		1	-0.65 (-1.45 to 0.15)	-0.55 (-1.39 to 0.28)	-0.64 (-1.45 to 0.16)	-0.45 (-1.19 to 0.30)	.	.		-0.59 (-1.30 to 0.12)	.		.	**-1.05 (-2.04 to -0.05)**
CBT_OT		1	-0.06 (-0.69 to 0.57)	0.12 (-0.52 to 0.76)	0.06 (-0.58 to 0.70)	.	0.04 (-0.64 to 0.72)	.		-0.01 (-0.57 to 0.54)	.		0.12 (-0.53 to 0.78)	.
CBT_SST		1	**-1.30 (-2.16 to -0.44)**	**-1.33 (-2.18 to -0.49)**	.	.	.	**-1.18 (-2.00 to -0.37)**		**-1.34 (-2.16 to -0.52)**	.		**-1.31 (-2.23 to -0.39)**	.
CR_MCT		1	-0.29 (-1.08 to 0.50)	.	-0.29 (-1.08 to 0.51)	.	-0.35 (-1.20 to 0.50)	.		-0.24 (-0.94 to 0.46)	.		.	.
ALL		1	-0.43 (-1.30 to 0.44)	.	.	.	.	.		.	.		.	.

HIT		1	-0.64 (-1.33 to 0.06)		-0.64 (-1.30 to 0.03)		-0.64 (-1.34 to 0.06)		.		-0.64 (-1.37 to 0.10)		.		**-0.64 (-1.24 to -0.04)**		.		-0.64 (-1.33 to 0.05)		.
CR_SST		1	-0.09 (-0.91 to 0.73)		.		-0.09 (-0.93 to 0.75)		.		-0.05 (-0.94 to 0.83)		.		-0.04 (-0.77 to 0.69)		.		.		-0.39 (-1.38 to 0.60)
TAU3		1	.		.		.		.		.		.		.		.		-0.43 (-1.35 to 0.50)		

SMD (standardised mean difference) and CI (confidence interval) results that are statistically significant are in bold and underlined.
Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

4 Discussion

This network meta-analysis is the first to synthesise the evidence base for psychological interventions impact on total symptoms for schizophrenia and psychosis. The systematic review identified 42 distinct interventions, analysed within 24 categories. Of these, two were consistently identified as being most likely to be most effective at reducing total symptoms; mindfulness-based psychoeducation and CBT with social skills training. Mindfulness-based psychoeducation had the first or second highest SUCRA value in every analysis it was included in, including sensitivity analyses and subgroup analyses. It is important to note that the three RCTs of mindfulness-based psychoeducation were conducted in China. Replication of these RCTs in Western settings is prudent, given the cultural relevance of mindfulness in Buddhist traditions, which are more prevalent in Asia, compared to the West. It is unclear whether cultural familiarity with mindfulness may have contributed to the large effect sizes for mindfulness-based psychoeducation and further RCTs are required. Similarly, more RCTs of CBT with social skills training are required as it was present in just one RCT, which may inflate its effect size, and this study did not meet the stringent Cochrane low risk of bias criteria.

There is a lack of direct comparisons of the interventions currently recommended (6, 13) against the available alternatives, and this network meta-analysis allows these comparisons to be inferred. Specifically, CBT alone and family therapy consistently had SUCRA values in the mid-range or bottom compared to all other interventions, including in the stringent RoB analysis. CBT was ranked as least likely intervention to reduce symptoms for inpatient settings. Despite the comparatively low ranking, CBT was consistently identified as having a statistically significant reduction in total symptoms. This may in be due to a function of the greater number of studies with CBT- as the evidence base is more robust, and inversely, there is the potential for an inflation of effects for interventions with few RCTs. A third of the CBT interventions included other specific criteria such as insomnia and suicide attempts (see Table 2). Similarly, there was a wide variety of family therapy interventions.

Social skills training and cognitive remediation had differential ranking depending on setting, and both had differential rankings depending on stage of illness. Social skills training had a higher SUCRA score (that is, greater than 50) for group delivered interventions, and for samples with >5 years with schizophrenia, and lowest for recent onset. Cognitive remediation had a low SUCRA score for most analyses; however it was ranked highly for recent onset and group delivered interventions. It is important to note that most RCTs of cognitive remediation do not target, or measure, clinical symptoms, and the bulk of evidence is not represented in this analysis. Indeed, total symptoms is often not the primary goal and/or outcome for psychological interventions for psychosis- distress and quality of life are more common treatment targets. RCTs that included total symptoms as a secondary outcome were designed with other outcomes in mind which may have affected participant sampling and be

underpowered to detect a change in total symptoms. While meta-analysis addresses the issue of underpowered studies, it is acknowledged that consideration of other outcomes may be more appropriate to understanding the effectiveness of psychological interventions. As per the pre-registered protocol, these outcomes will be considered in later analyses.

Supportive counselling, included as a control group, was ranked in the mid and bottom ranges for most analyses. Similarly, befriending was ranked in the mid to low range- it was last in the analysis of group interventions. Its ranking above TAU1 in most analyses provides some support to the argument that manualised befriending merits investigation as an intervention (23). Occupational therapy as a control group was ranked highest for inpatient settings and group delivered interventions, but second to last in the analysis that excluded treatment resistant samples, indicating that the large effects may be associated with this group in particular. Art therapy was not included in the definition of psychological intervention for this network meta-analysis, and no RCTs were found for psychoanalytic and/or psychodynamic interventions, and thus no inferences can be made about their inclusion in NICE guidelines.

Overall, three interventions were consistently identified as being most likely to reduce total symptoms across analyses: mindfulness-based psychoeducation, CBT with social skills training, and cognitive remediation focussed on social cognition. However not all of these were included in the stringent RoB analysis and high quality RCTs are required to confirm/refute these findings. The categorisation of cognitive remediation focussed on social cognition also provides insight into the differential effects compared with traditional cognitive remediation. TAU0, unsurprisingly was in the bottom third for all analyses.

4.1 Limitations

This analysis did not include non-English articles, and while the grey literature was retained in the systematic review, it was not possible to investigate whether there were unpublished RCTs associated with conference proceedings or search clinical trial registries. This may lead to publication bias especially for intervention categories with few RCTs. Similarly, there are a number of psychological interventions currently under investigation which, as of December 2016 had not been included in a complete evaluation using a randomised design and were not included in this analysis (24).

This network meta-analysis was based on the initial design of Leucht et al (2013) which excluded RCTs from China, citing concerns about study quality; however, no evidence was found to assume this concern also applied to RCTs of psychological interventions. All three RCTs of mindfulness-based psychoeducation, conducted in China and ranked as having a low RoB using the stringent Cochrane

criteria, were conducted in medically affiliated university hospitals, and published in prestigious peer reviewed journals- meeting the criteria suggested by Wu et al (25).

A random effects model was chosen in the first instance to account for heterogeneity across RCTs (22). The subgroup analyses overall suggest differential effectiveness in different settings and with different samples however this is in part due to the lack of RCTs across multiple settings, for example, mindfulness-based psychoeducation was not delivered in an inpatient setting and therefore effectiveness cannot be assumed in this setting. As there were differences in potential confounding variables, such as location, sample and delivery, across intervention types (see Table 2) it is possible that overall findings may be impacted by such confounders, however it is important to note that there was little evidence of loop inconsistency (22). Future analyses, including meta-regression, may identify the impact of potential confounding variables. It recommended that the subgroup results be given precedence in clinical decision-making and could support research strategies.

This network meta-analysis excluded people with substance-induced psychosis or substance abuse, bipolar disorder, veterans, and RCTs conducted in forensic settings, and is therefore not generalisable to these populations. First episode psychosis (FEP) is included in the recent onset subgroup analysis, however RCTs that had an age restriction of less than 40 years old were excluded, therefore the majority of evidence relevant to FEP is missing from this analysis.

This analysis focused on total symptoms however symptom reduction is not always the goal of psychological therapy. Alternative measures of recovery, and patient identified outcomes are increasingly being used in RCTs (e.g. Choice of outcome in CBT for psychoses (26)). Indeed, many psychological interventions are recovery focused, an outcome which encapsulates aspects of subjective improvement which are not correlated with symptom change (30). Further analysis of the effectiveness for different outcomes is required, particularly as some interventions target specific outcomes (7) - effectiveness may be obscured within the total symptoms analysis.

There is no consensus on the number of RCTs required in each intervention type (aka node) for network meta-analysis (27) however it is important to note that intervention nodes containing single RCTs are arguably less accurate as they do not represent a robust evidence base, and may be susceptible to overestimation of effects (28). This issue may be compounded by the inclusion of single RCTs that did not meet the Cochrane low risk of bias criteria. In this review, this is of particular relevance to CBT with social skills training. In contrast, nodes with numerous RCTs are likely to have a lower effect size but also more likely to report statistical significance (29). This pattern may be observed with CBT.

4.2 Conclusions

This analysis indicates that several treatments not currently included in NICE guidelines (for example, mindfulness-based psychoeducation and CBT with social skills training) could potentially be more effective than currently included treatments, though this finding is based on few studies and additional RCTs and meta-analyses are needed to generate more conclusive evidence in this regard.

This analysis also highlights the importance of including evidence from combined interventions which may have different mechanisms of change and efficacy, compared with either intervention alone. As seen in the subgroup analysis, recommendations should take treatment setting and time since onset into account- this analysis may inform hypothesis generation about the effectiveness of different interventions across different settings and samples. More high quality RCTs based on these results would be prudent, particularly as many intervention categories in this study contained just one RCT. Meta-analysis of recovery-based outcomes would also provide further evidence to support personalised patient and clinician decision-making about psychological interventions for psychosis and schizophrenia.

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Funding body

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Contributors

EMG and PH designed the study. EMG registered the protocol and managed the literature search, analysis and writing of the draft. GD contributed to the systematic review of the literature, categorisation of interventions, and data extraction. DT and CW provided pre-collected data. PH, ND, PM, WP and HS provided ongoing supervision and advice, and in-depth feedback on drafts of the article.

Declaration of interest: None.

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[Reference list for included studies is provided in Appendix 10]

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Appendices for

A network meta-analysis of psychological interventions for schizophrenia and psychosis

NMA Appendix 1- Prospero registered protocol

-as copied from Prospero: International prospective register of systematic reviews- last update June 2017.

A network meta-analysis of psychological interventions for schizophrenia and psychosis

Edel Mc Glanaghy, Paul Hutton, David Turner, Georgina Davis

Citation

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Review question

What is the effect of psychological interventions for psychosis?

Which psychological interventions are most effective?

For which outcomes are psychological interventions most effective?

Searches

Searches of MEDLINE, PsycINFO, EMBASE and CENTRAL will be conducted using search terms for 'psychosis and schizophrenia' from relevant Cochrane Reviews, psychological interventions as listed in Turner et al 2014, and RCT filters where available. Unpublished trials will be identified through contacting investigators listed in grey literature (such as conference abstracts) and a search of clinicaltrials.gov.

Abstracts and full text will be screened by 2 authors using Covidence software and discrepancies will be resolved through discussion.

There will be no language or time period restrictions, however trials published after 31st December 2017 will not be included.

Reference:

Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry.

Types of study to be included

Ideally blinded randomised controlled trials will be included, however, due to the nature of psychological intervention it is anticipated that there will be minimal blinded trials. Thus 'open label' randomised trials will be included. Single intervention within group studies and case studies will be excluded. So too will studies that allow for switching of treatments between groups (crossover trials).

Condition or domain being studied

People with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder) as defined by diagnostic or clinical criteria.

Participants/population

People aged 18-65 years old of both sexes with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder) as defined by diagnostic or clinical criteria.

This includes first episode psychosis, people with drug-resistant symptoms, people receiving concurrent treatment as usual and/or pharmacological intervention.

Exclusion criteria are as follows: Trials that specify a co morbid serious medical illness or other psychiatric disorder (except anxiety or depression), trials of people deemed to be 'at-risk' or who have not yet developed symptoms, trials that specify primary negative symptoms or in which all participants were stable at baseline. Exclusion criteria also include trials that focus on conditions such as bipolar disorder, substance-induced psychosis, post-partum psychosis specifically or dementia.

To protect the assumption of transitivity, it is important that all participants in all trials could, theoretically, be recruited into all trials. Thus any trial that meets the inclusion criteria yet has further rigid inclusion criteria may be excluded.

Intervention(s), exposure(s)

Psychological intervention is defined as theory driven, goal oriented intervention designed to reduce symptoms and improve functioning, taking place in the community or inpatient setting. Therapies of specific interest include, but are not limited to, CBTp, social skills training, family therapy and cognitive remediation- however cognitive remediation trials must include a clinical outcome, such as PANNS, to be included. Group and individual trials will be included.

Art, music and exercise therapy will be excluded, along with occupational therapy and interventions targeting physical health (such as weight gain), or adherence to medication schedules. Self help, online and trials of environmental interventions (such as community versus inpatient setting) will be excluded, as will trials that are drug only or preventative.

Comparator(s)/control

All psychological interventions will be compared against each other, and against the 'non- interventions', that is, the treatment as usual, waitlist, befriending and psychological placebo groups. Alternative groups may be included to facilitate loops in the Network Meta Analysis network if required. This will be stated explicitly.

Primary outcome(s)

Overall efficacy will be primarily measured as the mean change in total score of the Positive and Negative Syndrome Scale (PANNS) from baseline to endpoint. If PANNS results are not available, the scores from the Brief Psychiatric Rating Scale (BPRS) will be used. If neither scale is used, the clinician identified primary outcome will be used and noted.

Timing and effect measures

All pre and post data will be gathered along with follow up data for up to 12 months post trial, where available.

Secondary outcome(s)

1. Positive Symptoms (derived from PANNS, BPRS or author defined).

2. Negative Symptoms (derived from PANNS, BPRS or author defined).

3. Relapse (as measured by authors)

4. Hospital (re) admission rates

5. General Functioning (General Assessment Functioning preferred then as measured)

6. Quality of Life (as measured by authors).

Finally, data on stakeholder defined improvement/recovery (outcomes defined by person receiving intervention, such as QPR (Questionnaire about the Process of Recovery) or as described by authors) and adverse outcomes will be collected where available however it is anticipated that there will be insufficient studies to allow for analysis.

Timing and effect measures

All pre- and post data will be gathered along with follow up data for up to 12 months post trial, where available.

Data extraction (selection and coding)

Independent data extraction will be completed by EMG and GD and discrepancies will be resolved by discussion. Previously extracted data for comparative outcome studies included in Turner et al (2014) will be included in the dataset, updated with extra outcomes where relevant.

Reference: Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry

Risk of bias (quality) assessment

Risk of bias assessed by Cochrane Risk of Bias tool.

Strategy for data synthesis

Aggregate trial data will be collected and a Network Meta-Analysis will be carried out using STATA 14. A detailed diagram of the network will be presented with a brief narrative table to describe the trials and categorisation of interventions. Similar to Leucht et al (2013) the primary outcome will be based on mean scores, using LOCF for dropouts where possible. Unreported standard deviations will be calculated from other information or requested from authors. Standardised mean difference will be calculated with a 95% CI, with a random effects model in the first instance. Dichotomous outcomes will be based on ITT, and odds ratio will be calculated with a 95% CI. Statistical heterogeneity will be investigated through visual inspection of the forest plots, the I-squared statistic and p value from a standard test for heterogeneity.

A mutli-treatment meta-analysis will be carried out, following the statistical protocol of Leucht et al (2013). To ensure the validity of the underlying assumptions of the analysis the network will be assessed for coherence. Incoherence within a closed loop will be investigated for material cause, that is clinical and methodological variables that may explain the incoherence, such as differences in therapy, participants, chronicity etc, rather than the nature of the intervention.

Reference: Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., ... & Kissling, W. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet,382(9896), 951-962.

Analysis of subgroups or subsets

A number of exploratory sensitivity analyses will be carried out if there are adequate numbers of studies:

1. Trials that specify first episode/early stage compared with non-specified,

2. Drug resistant psychosis compared with non-specified,

3. Group -v- individual format interventions.

Sensitivity analysis will include:

1. Blinded -v- non-blinded RCTs and

2. High quality trials -v- low quality (as assessed by Cochrane Risk of Bias tool).

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Conflicts of interest

None known

Language

English

Country

Scotland

Stage of review

Review_Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans; Psychotic Disorders; Schizophrenia

Date of registration in PROSPERO

22 May 2016

Date of publication of this version

27 June 2017

Revision note for this version

After recent training on Network Meta Analysis the population criteria has been specified more clearly; for example, older adults will be excluded. Similarly, the interventions of interest have been identified with a more concise definition of a psychological therapy. The Systematic review is not complete and will be updated to reflect these criteria moving forwards.

Details of any existing review of the same topic by the same authors

While a full search will be carried out, it is anticipated that there will be some overlap in trials from Turner et al, 2014, and data already extracted will be incorporated into this analysis.

Reference: Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry.

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

----- End-----

NMA Appendix 2- Clarifications of, and adaptations to, registered protocol.

General RCT characteristics

- Only RCTs that were randomised were included- and this was conservatively judged. Cluster randomisation and crossover trials were excluded.
- Cochrane RoB 2.0 (17) was used in first instance, however was too stringent, so a post hoc analysis was completed using Leucht criteria which considered RCTs to be at high risk of bias if there was high risk of randomisation or allocation concealment bias.
- There was only one double-blind RCT (involving computerised intervention), and so the blind -v- non-blind subgroup was not possible.
- RCTs published up to end of 2016 were included. Some RCTs, dated 2017 were included if the article was published online in 2016.
- RCTs that specified 'clinically stable' or 'on stable medication' were included, as a large proportion of RCTs included this in their inclusion criteria. A sensitivity analysis was carried out to account for the impact of this.

Participant Characteristics

- RCTs that included people with characteristics cited as exclusion criteria for this protocol (that is, people with bipolar disorder, substance-induced psychosis, post-partum psychosis specifically or dementia) were considered for inclusion if the number meeting that criteria was 10% or less of the RCT total sample. Where RCTs included people from specific populations not listed as exclusion criteria in the protocol, such as veterans and people in forensic settings; these were included if no more than 50% of the RCT sample met the specific criteria.
- RCTs that took place in forensic and VA (Veteran's Administration health centres in the US) settings only were excluded.
- RCTs that included extra inclusion criteria that were unlikely to be commonly present in other samples, for example, history of violence, or history of compliance with command hallucinations, were excluded. Clinical judgements were made about other criteria such as PTSD, worry, and auditory hallucinations, and these were considered symptoms likely to be commonly present in non-specified samples.
- RCTs that specified primarily, or predominantly, negative symptoms as inclusion criteria were excluded. In contrast, RCTs that involved an intervention targeting negative symptoms, but did not specify negative symptoms as inclusion criteria, were included.
- Age 18 and above was specified in the protocol, however a number of RCTs included people age 16 and 17 up to age 60, and the criteria was adapted as follows; RCTs targeting young

people or older people specifically were excluded, such that RCTs with an upper age limit of less than age 40, or RCTs with a lower age limit of more than 40 years old were excluded.

Intervention/Control Characteristics

- Interventions lasting longer than 12 months were not included in the analysis.
- Psychoeducation interventions were only included if they were judged by both reviewers (EMG & GD) to have psychological aspects beyond medication adherence, except as a control group for other relevant interventions.
- Family based interventions were only included if the person with psychosis was included in the intervention sessions as standard; RCTs targeted at family members alone were not included, except as a control group for other relevant interventions.
- RCTs that included 2 variations of the same psychological intervention were excluded as they could not be included in the analysis; for example, psychotherapy administered in group and individual format, or two forms of cognitive remediation targeting broad and specific functions respectively.
- RCTs that included medication were included unless medication dose was an element under investigation. Similarly, RCTs with an uncommon medication under investigation were excluded.
- RCTs of psychological intervention alongside vocational programmes were excluded, as were psychological intervention that were provided within a service wide intervention- for example, CBT included as part of a global early intervention service which included enhanced case management, psychoeducation etc. compared with a TAU service. The exception to this rule was if both randomised groups received the enhanced service (TAU3) and the specific psychological interventions were the only difference.
- Treatment as usual was categorised according to the level of standard treatment; medication only (TAU0), medication with ongoing case management (TAU1), access to a multi-disciplinary team (TAU2) and receipt of a range of multi-disciplinary interventions including psychological interventions (TAU3). Where information about TAU was not provided, the country and year of the RCT was used to categorise the likely TAU as follows.
    - Country of RCT was used to identify the number of psychiatrists per 100,000 for that population (according to WHO global health observatory data; http://www.who.int/gho/mental_health/human_resources/en/)
        - If the country had 10+ psychiatrists per 100,000 AND was published in the past 10 years it was assigned TAU2.
        - If the country had 10+ psychiatrists per 100,000 AND was published in more than 10 years ago it was assigned TAU1.

        - Countries with between 4-10 psychiatrists per 100,000 were assigned TAU1.
        - Countries with less than 4 psychiatrists per 100,000, were assigned TAU0.
- Behavioural interventions which would now be considered unethical (such as self-shock) were excluded.

Outcome Measure Characteristics

- A range of outcomes were listed in the protocol; this study reports on total symptoms outcome only.

NMA Appendix 3- Search terms

Simultaneous search of Medline R, Embase and Pychinfo using Ovid

1. psychotherapy.mp OR exp Psychotherapy, Rational-Emotive/ or exp Psychotherapy/ or exp Psychotherapy, Multiple/ or exp Psychotherapy, Group/ or exp Psychotherapy, Brief/ or exp Psychotherapy, Psychodynamic/ OR psychological intervention.mp OR exp Cognitive Therapy/ OR exp Behavior Therapy/ OR behavio*r therapy.mp OR cognitive therapy.mp Or CBT.mp OR exp Family Therapy/ OR family therapy.mp OR cognitive remediation.mp OR social skills training.mp OR sensory art therapies.mp OR exp sensory art therapies/ OR art therapy.mp OR exp Art therapy/ OR psychoeducation*.mp OR exp Patient Education as Topic/ OR psychoanalytic therapy.mp OR exp Psychoanalytic Therapy/ OR counse*ling.mp OR Directive Counselling OR exp Counselling/ OR Distance Counselling/ OR supportive therapy.mp Or befriending.mp or psychosocial intervention.mp
2. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/ or Disorders with Psychotic Features/ or exp Psychotic Disorders/ or exp Paranoid Disorders/ or schizo*.mp or psychotic*.mp or psychos*.mp or psychoses.mp
3. randomi$ed controlled trial.pt OR controlled clinical trial .pt OR randomi$ed.tw OR randomly.tw OR trial.tw OR groups.tw
4. animals/ NOT humans/
5. 3 NOT 4
6. 1 AND 2 AND 5

CENTRAL database

1. Psychotherapy OR psychological intervention OR behavio*r therapy OR cognitive therapy Or CBT OR family therapy OR cognitive remediation OR social skills training OR sensory art therapies OR art therapy OR psychoeducation* OR psychoanalytic therapy OR counse*ling OR Directive Counselling OR Distance Counselling OR supportive therapy Or befriending or psychosocial intervention
2. MeSH descriptor: [Psychotherapy] explode all trees
3. #1 or #2
4. MeSH descriptor: [Schizophrenia] explode all trees
5. Schizo* or Psychotic or psychos* or psychoses
6. #4 or #5
7. #3 and #6 Publication Year from 1860 to 2016, in Trials

NMA Appendix 4- Classification of psychological interventions

-See Table 1 in main text for list of abbreviations

Category & Code	Description	Intervention Code
Control Groups		
Treatment as Usual TAU0 TAUA TAUB	Treatment as usual is a control condition where participants continue to receive routine services and/or interventions. This includes wait list control groups that continued to receive TAU. As standard intervention may vary across time and geography, a number of distinct categories were listed as follows; • TAU0- Minimal contact and/or intervention- for example, medication only with no follow up. • TAU1- Medication with routine check-up appointments/follow up. • TAU2: Case management and/or access to MDT services such as social work, OT and psychosocial interventions. • TAU3- TAU2 plus specified delivered psychological interventions, for example, CBT or motivational interviewing. • Details on classification of TAU that was not specified can be found in Appendix 1.	TAU0 TAU TAU1 TAU2 TAU3
Befriending BF	Often included as a control group. Intervention contact time and format is matched, but the content involves leisure activities and/or socialising with peers and supportive 'therapist'. Content is not related to mental health difficulty. This category also included computerised controls- control groups for computerised interventions to match contact time and format.	BF CCBF CC
Supportive counselling SC	Supportive counselling is often included as a control condition to account for contact time and the non-specific factors of a face-to-face talking therapy, without specific techniques or agenda. This usually involves an empathetic, person-centred approach focused on mental health difficulty but there is no focus on developing new skills or perspective.	SC
Occupational Therapy OT	Occupational therapy is often included as a control group. It included guided activities to develop daily living skills and cognitive adaptive therapy, which involved adaptation to the home environment to support daily functioning.	OT CAT
Intervention Groups		
Cognitive behaviour therapy CBT	CBT is a goal focused intervention based on the links between thoughts, feelings, behaviours and bodily sensations. CBT typically includes formulation, psychoeducation about the CBT model, thought challenging, progressive muscle relaxation and relaxation strategies,	CBT CBTp

	regular 'homework' and behavioural experiments. In this systematic review CBT has also been used to target insomnia and worry specifically. CBTp specifically focused on theoretical models of psychosis.	
Metacognitive therapy MCT	A form of CBT, metacognitive therapy focuses on meta-cognitions specifically. It aims to bring cognitive distortions to awareness of patient, and highlight alternative responses (Agothor et al, 2010). It is commonly delivered in a group using power-point presentation.	MCT
Cognitive remediation CR	Cognitive remediation targets the cognitive difficulties associated with psychosis, and typically involves strategies to promote basic cognitive processes, such as working memory, attention, and executive function. The intervention may be delivered in group or in a one-to-one setting, may be computerised or include pen and paper tasks. Therapist/trainer involvement is common. Some CR interventions focus primarily on attention or auditory hallucinations. Only included if a trainer/therapist was involved- so no self help.	CR CR_BF CR_meta
Cognitive remediation; social cognition CRSS	Interventions classed as CRSS are similar to CR but specifically target social cognitive difficulties, such as theory of mind and emotional processing.	CRSS CR_CRSS
Family therapy FT	Family therapy includes all interventions that aimed to improve functioning by involving and supporting family members. To meet the systematic review criteria family based interventions had to include the person with psychosis, and not only target carer needs. Behavioural family therapy, family psychoeducation, family social groups (which may involve psychoeducation, but not only psychoeducation), family therapy and family assisted social cognitive training were all included in this category.	BFT FPE FSG FT FSIT
Eye Movement Desensitisation and Reprocessing EMDR	EMDR is a one-to-one therapy that targets traumatic memories and aims to ameliorate these using eye movements and/or other bilateral stimulation.	EMDR
Wellbeing WB	WELLFOCUS (Schrank, 2016), a wellbeing intervention, focuses on positive psychology and uses exercises to promote positive experiences and self-narrative.	WB
Social skills training SST	Behavioural intervention based on social learning theory in which participants' social functioning is targeted in order to improve their ability to perform in social situations, manage daily life tasks, and reduce social distress. Importance is typically placed on verbal and nonverbal communication alongside learning appropriate perception and responses to	SST SST_FPE

	social cues. The intervention may also include training in independent living skills and is often provided in a group setting.	
Psychoeducation& Coping PE	Psychoeducation interventions are diverse yet most aim to share information about psychosis and/or helpful coping strategies. Psychoeducation for medication adherence alone did not meet the systematic review criteria. This category included coping skills sessions, progressive muscle relaxation, problem-solving therapy and a self-esteem intervention (Lecomte, 1999).	PE CPS PMR PST PESC SE
Mindfulness-based psychoeducation MPE	Mindfulness-based psychoeducation aims to enhance understanding of schizophrenia, and to increase awareness, acceptance and management of symptoms such as hallucinations and delusions.	MPE
Combined Others		
MCT_CBT CBT_OT CBT_SST CR_MCT CR_SST	Combined interventions are identified as X_Y; Intervention X combined with intervention Y.	
ALL	ALL refers to an intervention protocol which included 4 distinct therapies delivered simultaneously (Guo, 2010); psychoeducation, family intervention, skills training and CBT.	ALL
HIT	HIT included cognitive behavioural interventions, coping training, family therapy and rehabilitative efforts- case management was not mentioned and so HIT was included, whereas other MDT based interventions are not.	HIT
This table is adapted from the descriptive table in Turner et al (2014)		

NMA Appendix 5- Evaluation of Intervention Implementation

	Rating item	Scoring system
1	Is the treatment described?	0 In Detail/Yes 2 No
2	Is the treatment manualised/protocol referenced?	0 Yes includes adapted/developed for this intervention 1 Unclear/flexible 2 No
3	Was the theoretical model articulated/appropriate?	0 Yes 1 Unclear. 2 No
	Integrity of Intervention total	**0 High Integrity- 6 Low Integrity**
4	Was therapy practice supervised?	0 Yes, with detail. 1 Unclear/not mentioned 2 No
5	Was adherence to manual assessed?	0 Yes 1 Not mentioned/unclear/using therapist's own notes 2 No
6	Was the training received by therapists described?	0 Yes with some detail 1 Unclear/not mentioned/'was trained' 2 No
7	What was the qualification of therapist?	-1 Clinical Psychologist, Psychiatrist, other therapist above MSc level 0 Other mental health professional (includes nurses, therapists, OTs) 1 Unspecified 2 Inappropriate
	Reported fidelity total	**-1 to 0 High likelihood of fidelity- 8 Low likelihood of fidelity**
8	Was dose captured?	0 Yes with enough detail to calculate total contact time 1 Unclear 2 Not mentioned
9	Was attendance captured?	0 Yes 1 Unclear 2 No
	Dose total	**0 Dose well reported- 4 Dose not reported**

Ratings of intervention arms of RCTs

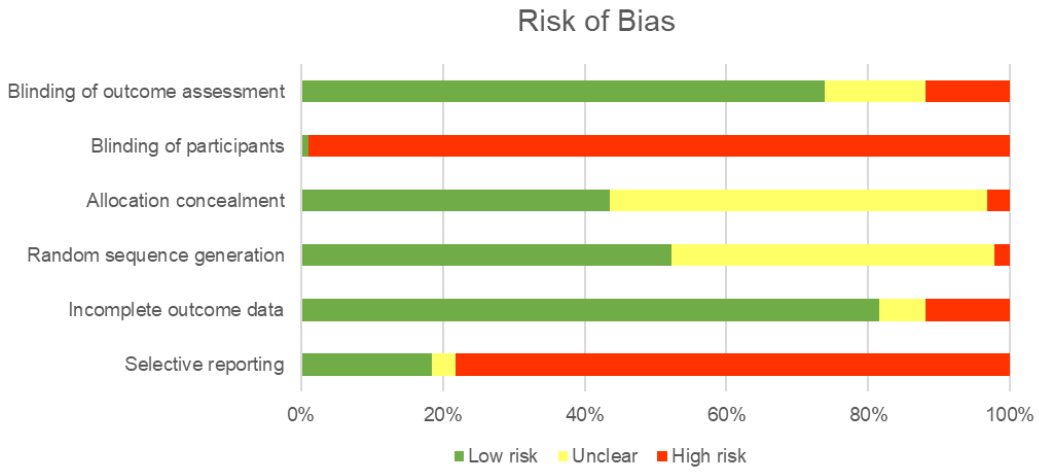
	Rating	Intervention arms N (%)	Score interpretation
Integrity of intervention	0	92 (81%)	0 High Integrity
	1	15 (13%)	6 Low Integrity
	2	5 (4%)	
	3	2 (2%)	
	4	0 (0%)	
	5	0 (0%)	
	6	0 (0%)	
Fidelity to intervention	-1	15 (13%)	-1 to 0 High likelihood of adherence
	0	20 (18%)	
	1	16 (14%)	8 Low likelihood of adherence
	2	23 (20%)	
	3	12 (11%)	
	4	27 (24%)	
	5	1 (1%)	
	6	0 (0%)	
	7	0 (0%)	
	8	0 (0%)	
All 20 (18%) arms where the fidelity rating outcome was reported it was at least 'good' or distinct from control			
Dose	0	2 (2%)	0 Dose well reported
	1	31 (27%)	4 Dose not reported
	2	57 (50%)	
	3	24 (21%)	
	4	0 (0%)	
Dose 83 (73% arms)			
Session length		Mean: 77 minutes Median: 60 (range: 25-210)	
Number of sessions		Mean: 20 sessions Median: 16 sessions (range: 1-52)	
Total contact time		Mean: 24 hours Median: 20 hours (range: 3.5- 65)	
Results based on 114 of 197 intervention arms. Excluded: TAU (58), BF (12), SC (10) and OT (3).			

NMA Appendix 6- Risk of bias assessment

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Aghotor 2010	✓	!	✗	✓	✗	✓
Andreou 2017	!	✓	✗	✓	✗	✓
Bark 2003	!	!	✗	!	✗	✓
Barrowclough 2006	✓	✓	✗	✓	✗	✓
Bechdolf 2004	✓	!	✗	✓	✗	!
Bradley 2006	✓	✓	✗	✓	✗	✓
Buonocore 2015	✓	!	✗	✓	✗	!
Byrne 2013	✓	✓	✗	✗	✗	✗
Cai 2015	✓	✓	✗	✓	✗	✓
Chan 2009	✓	✓	✗	✓	✗	✓
Chien 2013a	!	!	✗	✓	✗	✓
Chien 2013b	✓	!	✗	✓	✗	✓
Chien 2014	✓	✓	✓	✓	✗	✓
d'Amato 2011	!	!	✗	✓	✗	✓
Dickinson 2010	!	✓	✗	✓	✓	✓
Durham 2003	✓	✓	✗	✓	✗	✓
England 2007	✓	!	✗	✓	✗	✓
Fardig 2011	✓	!	✗	✓	✗	✓
Farreny 2012	✓	!	✓	✓	✗	✓
Fernandez-Gonzalo 2015	✓	✓	✗	✓	✗	✓
Fiszdon 2016	!	!	✗	✓	✗	✗
Freeman 2015a	✓	✓	✓	✓	✗	✓
Freeman 2015b	✓	✓	✓	✓	✗	✓
Garcia 2003	!	!	✗	✗	✗	!
Garety 2008 (i)	!	✓	✓	✓	✗	✓
Garety 2008 (ii)	!	✓	✓	✓	✗	✓
GilSanz 2009	!	!	✗	!	✗	!
Gohar 2013	!	!	✗	✓	✗	✗
Gumley 2003	✗	✗	✗	✓	✗	✗
Guo 2010	!	!	✗	✗	✗	✓

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Haddock 1999	?	?	-	+	-	+
Hayes 1995	?	?	-	-	-	+
Jenner 2004	?	+	-	+	-	-
Jorgensen 2015	+	+	+	+	-	-
Kang 2016	+	+	-	+	-	+
Kantrowitz 2016	+	+	+	-	-	+
Keefe 2012	?	?	-	+	-	+
Kim 2010	?	?	-	+	-	+
Kuipers 1997	+	+	-	+	-	?
Kumar 2010	?	?	-	?	-	?
Leclerc 2000	?	?	-	+	-	+
Lee 2013	+	?	-	+	-	+
Lewis 2002	?	+	?	+	-	+
Li 2015	+	+	+	+	-	-
Liberman 2009	?	?	-	+	-	+
Lincoln 2012	+	+	+	+	-	+
Lindenmayer 2013	?	?	-	+	-	-
Lopez-Luengo 2016	+	+	-	-	-	+
Lukoff 1986	?	?	-	+	-	?
Moritz 2011	+	+	+	+	-	+
Mortiz 2013	?	+	?	+	-	+
Morrison 2014	+	+	+	-	-	+
Naeem 2015	+	+	+	+	-	+
Naeem 2016	+	+	-	+	-	+
Ng 2006	+	+	-	+	-	+
Ojeda 2012	?	?	-	+	-	+
Omiya 2016	-	?	-	+	-	?
Penn 2009	+	+	-	+	-	+
Penn 2011	+	?	-	+	-	+
Peters 2010	+	?	-	-	-	+

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Pinto 1999	?	?	-	+	-	?
Rakitzi 2016	?	+	-	+	-	+
Rathod 2013	+	+	+	+	-	+
Rector 2003	?	?	-	+	-	+
Roberts 2014	?	?	-	+	-	+
Rus-Calafell 2013	?	?	-	+	-	?
Sanchez 2014	+	?	-	+	-	+
Schaub 2016	+	?	-	+	-	+
Schrank 2016	+	+	+	+	-	-
Sensky 2000	?	?	-	+	-	+
Shin 2002	?	?	-	+	-	+
Startup 2004	+	-	-	-	-	-
Tan 2016	+	?	-	+	-	+
Tao 2015	?	?	-	?	-	?
Tarrier 2014	+	+	-	-	-	+
Tas 2012	+	-	-	+	-	+
Turkington 2002	+	+	-	+	-	+
Valencia 2007	?	?	-	+	-	+
Valencia 2010	?	?	-	+	-	+
Valencia 2012	?	?	-	+	-	+
Valencia 2013	?	?	-	+	-	+
Valmaggia 2005	+	?	-	+	-	+
Velligan 2015	+	+	?	+	-	+
Veltro 2011	+	+	-	?	-	?
Vita 2011b	?	?	-	+	-	+
Vita 2011a	+	+	-	+	-	+
Wang 2016	+	+	+	+	-	+
Wolwer 2011	?	?	-	+	-	+
Wykes 1999	?	?	-	+	-	+
Wykes 2007	+	+	+	+	-	+


Risk of Bias
Blinding of outcome assessment
Blinding of participants
Allocation concealment
Random sequence generation
Incomplete outcome data
Selective reporting
0%
20%
40%
60%
80%
100%
Low risk
Unclear
High risk

NMA Appendix 7- Statistical method

This study applied a frequentist approach to network meta-analysis using a random effects model, in Stata SE v15. The first author attended training with the University of Bristol and applied the method as indicated in the course manual (21). The summary below is based on this manual and training, and the accessible review provided by Tonin et al (2017) (12). The mvmeta package in Stata applies multivariate meta-analytical models, similar to regression where estimates of multiple studies are combined while accounting for their correlation (Gasparrini, 2018; White, 2009).

Network meta-analysis is an evidence synthesis method similar to traditional meta-analysis, and it shares many of the same statistical and epistemological assumptions. Where meta-analysis synthesises the evidence for A -v- B using pooled effect sizes, network meta-analysis synthesises the evidence for A -v- B, A -v-C, B -v- D etc, by creating a network of all interventions and calculating the direct and indirect effects. The indirect effect is calculated from the network, for example, difference between B and C, as extrapolated from A -v- B and A -v- C. Direct evidence, the pooled effect based on RCTs (similar to traditional meta-analysis) is therefore not necessarily available for all comparisons within the network; indeed the ability of network meta-analysis to compare interventions which have not been compared in real life RCTs is one of the key attractive features of the analysis. It can support clinical decision-making across a wider range of intervention types.

The principle assumption, transitivity (known as consistency in the statistical analysis) assumes that every participant in every RCT could, *in theory,* have been randomised to any study arm. Again, this is similar to traditional meta-analysis however in network meta-analysis it is important to consider across intervention types as well as across RCTs. Clear inclusion criteria, and a well-defined systematic review protocol can support the preservation of transitivity in the sample (15). Consistency checks statistically compare the indirect and direct evidence (where available) to provide evidence about the consistency of the model as a whole using a chi^2 statistic. P values are reported for comparisons of the direct and indirect SMDs for each connecting 'arm' of the network, and the diamond plot provides a visual depiction of this evidence. Where evidence of inconsistency was identified the source was explored in sequence; 1. investigation of errors in data entry and intervention categorisation, 2. inconsistencies in population/study quality that could explain the discrepancy, and 3. reassessing the intervention categorisation. Decisions about the exclusion of RCTs which contribute to inconsistency are reported in Appendix 8 to preserve transparency of analysis

decision-making. Higgins et al (22) indicate that loop inconsistency across RCTs is usually caused by differences between; participants, intervention delivery and/or setting, context or time period.

Along with direct and indirect effect sizes, network meta-analysis also generates information about the probability of each intervention being 'best' using SUCRAs (surface under the cumulative rankings curve) for each intervention. This SUCRA value compares each intervention against a hypothetical ‘best’ intervention which permits easy comparison across all interventions- by providing a hierarchy of effectiveness. A score of 100 would indicate 100% effectiveness of the hypothetical ‘best’- a score lower than 50 indicates approximately half of the effectiveness.

References specific to Appendix 7:

Gasparrini A, Multivariate and univariate meta-analysis and meta-regression [Package ‘mvmeta’]. March 7, 2018. Retrieved from https://cran.r-project.org/web/packages/mvmeta/mvmeta.pdf.

White, I R. Multivariate random-effects meta-analysis. The Stata Journal, 2009; 9, 1. 40-56.

NMA Appendix 8: Inconsistency Strategy

Total Symptom Analysis

Original model; 91 RCTs with 191 arms. There was no evidence of inconsistency for the model $\chi 2$ (27, N = 91) = 32.45, p = .216 however there was a statistically significant difference between direct and indirect evidence for OT -CRSS (direct 0.58, indirect -0.43, p = .032), and CRSS-SST (direct 1.71, indirect 0.01, p = .001). Review of the diamond plot (see Figure 8.1) identified Study 564 (Mazza, 2010) as the potential source of the inconsistency. Data was checked, and no obvious RCT characteristic was identified as the source of the inconsistency. Mazza (2010) was excluded and the analysis was re-run; no evidence of inconsistency found $\chi 2$ (27, N = 90) = 22.86, p = .583 with no differences between direct and indirect evidence. The full results are presented in the main article.

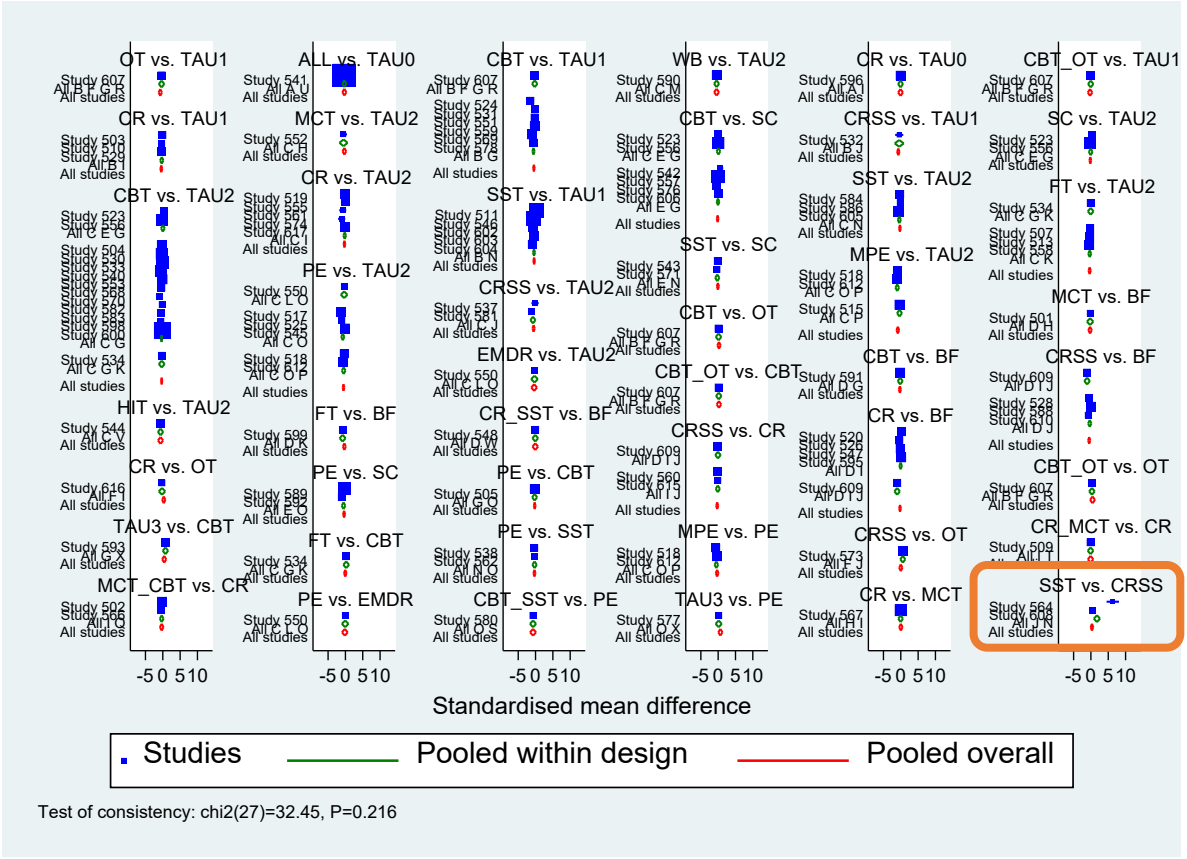


Figure 8.1: Original Analysis diamond plot. Note; blue indicates direct evidence from RCTs, green diamond is combined direct evidence, and red is indirect evidence. Inconsistency can be identified if green and red diamonds are different. Table 1 in the main text contains the full list of abbreviations.

Sub group analysis: Chronic

Original model for chronic included 66 RCTs with 139 arms. There was no evidence of inconsistency $\chi 2$ (20, N = 66) = 27.94.86, p = .111 however comparison of direct and indirect evidence identified one comparisons as being statistically significantly different OT v cognitive remediation focussed on social cognition (see Figure 8.2); Study 609, Vita 2011a (3 arms; cognitive remediation- befriending - cognitive remediation focussed on social cognition) was visibly inconsistent and the analysis was run again without this RCT, however this did not change the results. As the model was not found to be inconsistent the decision was made to keep this RCT in the full analysis, however the discrepancy with direct and indirect evidence indicates that the results should be interpreted with caution.

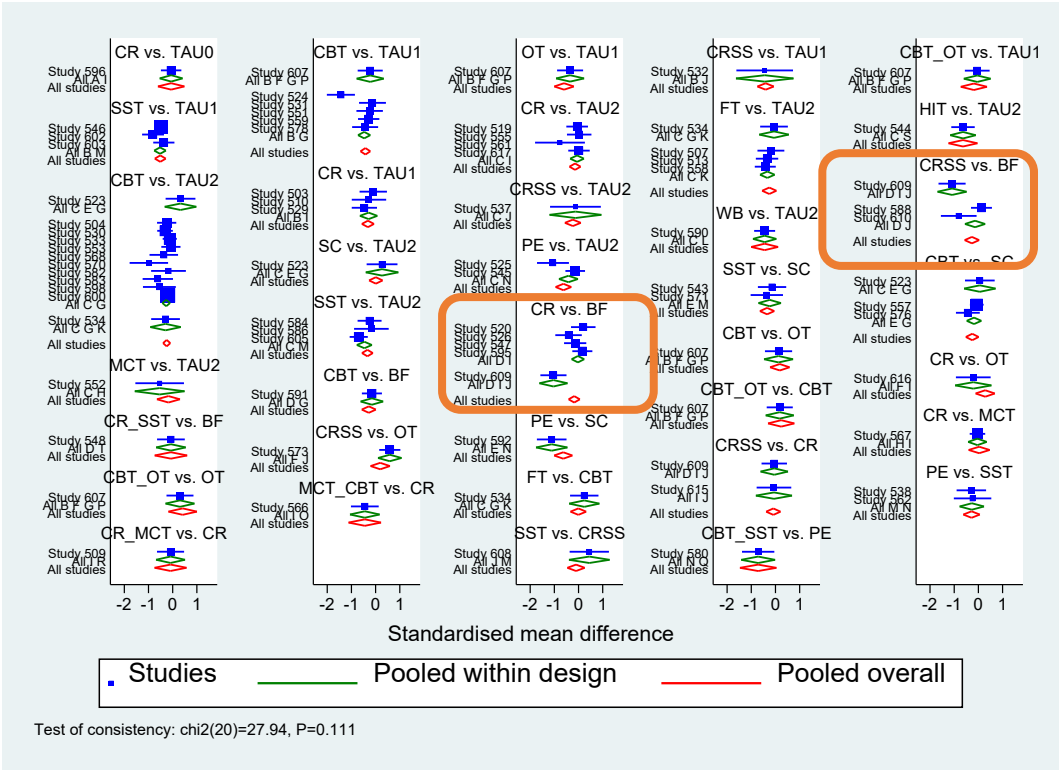


Figure 8.2: Original Chronic sub group analysis diamond plot

NMA Appendix 9- Description of included studies

Reference list is in Appendix 10.

Study, year	Mean Duration of illness (years)	Setting	Mean Age (x.x sd; x-x range)	Stage			Intervention and Control Groups				Outcome Measure			Risk of Bias	
				Early (<5 years duration)	Clinically Stable/ Acute	Other	Group	n	Intervention format	Trial length (weeks)	Total Symptoms	Reported Integrity (High 0 to Low 6)	Reported Fidelity (High -1 to Low 8)	High RoB (Leucht) (1 is yes)	Low RoB (Cochrane) (1 is yes)
Aghotor 2010	3.75	Inpatient	28.9 (18-48)	Early			MCT	16	Group	4	PANSS	0	3	0	0
Aghotor 2010			32.6 (22-62)	Early			BF	14	Group	4		n/a	n/a	0	0
Andreou 2017	.	Both	36.91 (12.5)			Delusional disorder	MCT_CBT	46	Individual	6	PANSS	0	2	1	0
Andreou 2017	.		35.59 (13.1)				CR	46	Computer	6		0	3	1	0
Bark 2003	.	Inpatient	35 (7.07)				CR	36	Computer	10	PANSS	1	2	0	0
Bark 2003			38.55				TAU1	18		10		n/a	n/a	0	0
Barrowclough 2006	13.67 (7.99)	Outpatient	38.83 (8.6)		Stable		CBT	57	Group	26	PANSS	0	0	0	0
Barrowclough 2006					Stable		TAU2	56		26		n/a	n/a	0	0
Bechdolf 2004	4.72 (5.45)	Both	32.2 (9.9)	Early			CBT	40	Group	8	PANSS	0	4	0	0
Bechdolf 2004	4.17 (4.89)		31.4 (10.6)	Early			PE	48	Group	8		0	4	0	0
Bradley 2006	n/a	Outpatient	33.6 (6.68)				FSG	25	Group	52	BPRS	0	3	0	0
Bradley 2006			34.0 (9.6)				TAU2	25		52		n/a	n/a	0	0
Buonocore 2015	13	Outpatient	34.4 (9.9)		Stable		CR_MCT	30	Group & Indiv	16	PANSS	0	3	0	0
Buonocore 2015			38.4 (9.2)		Stable		CR_BF	27	Group & Indiv	16		0	4	0	0

Byrne 2013	19.44 (10.04)	Inpatient	45.15 (9.81)		Stable	CR	27	Computer	6	PANSS	0	3	0	0
Byrne 2013	24.92 (8.82)		46.04 (8.68)		Stable	TAU1	24		6		n/a	n/a	0	0
Cai 2015	3.95 (0.72)	Outpatient	33.92 (9.03)	Early	Stable	SST_FPE	133	Group	10	PANSS	0	4	0	0
Cai 2015	3.69 (1.37)		34.49 (8.92)	Early	Stable	TAU1	123		10		n/a	n/a	0	0
Chan 2009	10.2 (7.6)	Outpatient	34.2 (10.1)			FPE	36	Group	13	BPRS	0	4	0	0
Chan 2009	10.5 (9.5)		36.3 (13.10)			TAU2	37		13		n/a	n/a	0	0
Chien 2013a	3.1	Outpatient	25.8 (8.5)	Early		MPE	48	Group	13	BPRS	0	5	0	0
Chien 2013a				Early		TAU2	48		13		n/a	n/a	0	0
Chien 2013b	0.1	Outpatient	25.7 (6.9)	Early		PE	48	Individual	13	BPRS	0	4	0	0
Chien 2013b	0.1			Early		TAU2	48		13		n/a	n/a	0	0
Chien 2014	2.6 (1.7)	Outpatient	25.1 (6.8)	Early		MPE	36	Group	24	BPRS	0	0	0	1
Chien 2014	2.5 (1.8)		25.8 (7.9)	Early		PE	36	Group	24		0	0	0	1
Chien 2014	2.7 (1.8)		26.0 (8.5)	Early		TAU2	35		24		n/a	n/a	0	1
d'Amato 2011	8.7	Outpatient	33.4 (6.9)		Stable	CR	39	Computer	7	PANSS	0	4	0	0
d'Amato 2011	8.1		32.2 (6.0)		Stable	TAU2	38		7		n/a	n/a	0	0
Dickinson 2010	0	Outpatient	46.9 (6.6)		Stable	CR	35	Computer	15	BPRS	0	1	0	1
Dickinson 2010	0		48.5 (8.8)		Stable	CC	32		15		n/a	n/a	0	1
Durham 2003	15 (2-31)	Outpatient	36 (10)		Stable	CBT	22	Individual	39	PANSS	0	1	0	0
Durham 2003	14 (2-30)		37 (11.2)		Stable	SC	23	Individual	39		0	0	0	0
Durham 2003	10 (2-27)		36 (10.2)		Stable	TAU2	21		39		n/a	n/a	0	0
England 2007		Outpatient	41			CBT	44	Individual	18	BPRS	3	4	0	0
England 2007						TAU1	21		18		n/a	n/a	0	0
Fardig 2011		Outpatient	40.38 (6.76)			PE	21	Group	39	PECC	2	2	0	0
Fardig 2011			40.45 (6.44)			TAU2	20		39		n/a	n/a	0	0
Farreny 2012	17.5 (8.9)	Outpatient	40.6 (7.6)		Stable	CRmeta	34	Group	16	PANSS	0	4	0	1
Farreny 2012					Stable	BF	28	Group			n/a	n/a	0	1
Fernandez-Gonzalo 2015	2.3 (1.7)	Outpatient	30.9 (5.9)	Early	Stable	CR_CRSS	28	Computer	17	PANSS	0	2	0	0

Fernandez-Gonzalo 2015	3.01 (1.8)		30.02 (7.4)	Early	Stable		CC	25	Computer	17		n/a	n/a	0	0
Fiszdon 2016	.	Outpatient	47.22 (9.17)		Stable		CR	50	Individual	8	PANSS	0	4	0	0
Fiszdon 2016			49.00 (9.68)		Stable		TAU1	25		8		n/a	n/a	0	0
Freeman 2015a	Median; >20 years	Both	40.9 (10.5)			Persecutory delusions	CBT	73	Individual	8	PANSS	0	0	0	1
Freeman 2015a	Median: 11-20 years		42.1 (12.2)				TAU2	77				n/a	n/a	0	1
Freeman 2015b	.	Outpatient	39.6 (11.6)			Insomnia	CBT	24	Individual	12	PANSS	0	0	0	1
Freeman 2015b			42.2(13.5)				TAU1	26				n/a	n/a	0	1
Garcia 2003	21	Outpatient	40.45 (7.1)				CRSS	13	Group	13	BPRS	0	4	0	0
Garcia 2003	14.77		36.88 (8.1)				TAU1	10		13		n/a	n/a	0	0
Garety 2008 (i)	10.9 (8.1)	Outpatient	39.1 (10.3)		Acute		CBTp	106	Individual	52	PANSS	0	-1	0	1
Garety 2008 (i)	9.9 (8.7)		37.1 (10.9)		Acute		TAU2	112		52		n/a	n/a	0	1
Garety 2008 (ii)	10.9 (9.7)	Outpatient	38.6 (12.2)		Acute		CBTp	27	Individual	52	PANSS	0	-1	0	1
Garety 2008 (ii)	13.3 (11.8)		35 (12.3)		Acute		FT	28	Individual	52		0	-1	0	1
Garety 2008 (ii)	10.5 (8.6)		35.6 (11.2)		Acute		TAU2	28		52		n/a	n/a	0	1
GilSanz 2009	13.43	Outpatient	33.29 (8.36)				CRSS	7	Group	10	PANSS	0	4	0	0
GilSanz 2009	20.57		41.43 (9.03)				TAU2	7				n/a	n/a	0	0
Gohar 2013	11.77 (10.6)	Outpatient	32.95 (10.86)				SST	22	Group	8	PANSS	0	4	0	0
Gohar 2013	8.40 (7.02)		30.75 (10.58)				PE	20	Group	8		0	3	0	0
Gumley 2003	9.42 (6.75)	Outpatient	35.8 (9.6)			Relapse prone	CBT	72	Individual	52	PANSS	0	2	1	0
Gumley 2003	9.5 (7)		36.7 (10.1)				TAU2	72		52		n/a	n/a	1	0

Guo 2010	.	Outpatient	26.1 (25.5-26.8)	Early	Stable		ALL	633	Group	52	PANSS	1	-1	0	0
Guo 2010			26.4 (25.7-27)	Early	Stable		TAU0	635		52		n/a	n/a	0	0
Haddock 1999	.	Inpatient	28.1 (7.24)	Early			CBT	10	Individual	5	BPRS	0	1	0	0
Haddock 1999	.		30 (7.9)	Early			SC	11	Individual	5		0	1	0	0
Hayes 1995	11	Outpatient	36 (10)		Stable		SST	32	Group	18	BPRS	0	0	0	0
Hayes 1995					Stable		SC	31	Group			0	0	0	0
Jenner 2004	13.4 (12.3)	Outpatient	36.7 (11.4)			Auditory hallucinations	HIT	37	Individual	39	PANSS	0	0	0	0
Jenner 2004	10.3 (8.1)		36 (11.6)				TAU2	39		39		n/a	n/a	0	0
Jorgensen 2015	7.9 (8.4)	Outpatient	35.4 (12.2)				PST	50	Individual	26	PANSS	0	1	0	0
Jorgensen 2015	11.7 (9.3)		39.6 (12.7)				TAU2	51		26		n/a	n/a	0	0
Kang 2016	21.3 (11.7)	Outpatient	46.4 (11.9)		Stable		SST	118	Group	52	PANSS	0	1	0	0
Kang 2016	19.8 (12.1)		45.4 (12.3)		Stable		TAU1	126		52		n/a	n/a	0	0
Kantrowitz 2016	.	Outpatient	37.7 (10.1)		Stable		CR	56	Group	26 (4-6 months)	PANSS	1	4	0	0
Kantrowitz 2016					Stable		CC	64	Group			n/a	n/a	0	0
Keefe 2012	.	Outpatient	37 (10.27)		Stable		CR_SST	27	Group	12	PANSS	0	2	0	0
Keefe 2012					Stable		CCBF	26	Group			n/a	n/a	0	0
Kim 2010	2.81 (2.91)	Inpatient	29.9 (7.4)	Early	Acute		EMDR	15	Individual	4	PANSS	0	4	0	0
Kim 2010	1.76 (2.55)		36.0 (9.5)	Early	Acute		PMR	15	Individual	4		1	0	0	0
Kim 2010	2.3 (3.87)		31.8 (8.4)	Early	Acute		TAU2	15		4		n/a	n/a	0	0
Kuipers 1997	12.1 (range 1-26)	Both	38.5 (19-65)			Treatment resistant	CBTp	28	Individual	39	BPRS	0	2	0	0
Kuipers 1997	14 (range 1-33)		41.8 (18-63)				TAU1	32				n/a	n/a	0	0
Kumar 2010	7.63 (7.74)	Inpatient	31.5 (7.98)			Paranoid Schizophrenia	MCT	8	Group	4	PANSS	0	4	0	0
Kumar 2010	6.5 (5.21)		34.13 (8.2)				TAU2	8		4		n/a	n/a	0	0

Leclerc 2000	.	Both	40.6 (10.7)				CBT	55	Group	12	PANSS	1	4	0	0
Leclerc 2000							TAU2	44		12		n/a	n/a	0	0
Lee 2013	17.75 (4.14)	Inpatient	43.53 (4.87)		Stable		CR	33	Computer	13	PANSS	0	1	0	0
Lee 2013	17.53 (3.03)		43.46 (3.53)		Stable		TAU2	33		13		n/a	n/a	0	0
Lewis 2002	Unclear, but early (1st or 2nd episode)	Both	Median 29.1	Early			CBTp	101	Individual	6	PANSS	0	1	0	0
Lewis 2002			Median 27.2	Early			SC	106	Individual	6		0	1	0	0
Lewis 2002			Median 27.2	Early			TAU2	102		6		n/a	n/a	0	0
Li 2015	7.6 (6.49)	Both	29.27 (8.36)				CBT	96	Individual	24	PANSS	0	-1	0	0
Li 2015	8.82 (8.07)		33.44 (9.51)				SC	96	Individual	24		1	1	0	0
Liberman 2009	.	Outpatient	37.6 (10.8)				FPE	45	Group	13	PANSS	0	3	0	0
Liberman 2009			39.1 (12.3)				TAU2	47		13		n/a	n/a	0	0
Lincoln 2012	11.1 (10)	Outpatient	33.2 (10.4)				CBTp	40	Individual	38	PANSS	1	0	0	1
Lincoln 2012	9.7 (6.8)		33.1 (10.9)				TAU1	40		38		n/a	n/a	0	1
Lindenmayer 2013	Not specified, but <5 years	Both	42.48 (9.09)	Early	Stable		CR	27	Computer	12	PANSS	0	3	0	0
Lindenmayer 2013			43.95 (11.12)	Early	Stable		CRSS	32	Computer	12		0	3	0	0
Lopez-Luengo 2016	6.38 (3.42)	Outpatient	29.25 (7.65)		Stable	Auditory hallucinations	CR	20	Computer	13	BPRS	0	4	0	0
Lopez-Luengo 2016	11.25 (6.63)		34 (11.64)		Stable		TAU2	20		13		n/a	n/a	0	0
Lukoff 1986		Inpatient	.				SST	14	Group	10	PAS	1	2	0	0
Lukoff 1986							PE	14		10		0	2	0	0

Moritz 2011		Inpatient	32.63 (12.48)				MCT_CBT	24	Group	4	PANSS	0	2	0	1
Moritz 2011			35.46 (9.10)				CR	24	Computer	4		0	4	0	1
Moritz 2013	.	Both	36.82 (11.12)			Delusions	MCT	76	Group	4	PANSS	0	2	0	0
Moritz 2013			32.68 (9.54)				CR	74	Computer	4		0	4	0	0
Morrison 2014	.	Outpatient	32.95 (13.11)			No medication	CBT	37	Individual	39	PANSS	0	-1	0	0
Morrison 2014			29.68 (11.95)				TAU2	37		39		n/a	n/a	0	0
Naeem 2015	4.7	Outpatient	31.7 (8.4)	Early			CBTp	59	Individual	17	PANSS	0	0	0	1
Naeem 2015	5.8		31.1 (7.4)	Early			TAU1	57		17		n/a	n/a	0	1
Naeem 2016	.	Outpatient	42.0 (11.53)		Stable		CBT	18	Individual	16	PANSS	1	1	0	0
Naeem 2016			38.6 (12.03)		Stable		TAU2	15		16		n/a	n/a	0	0
Ng 2006	13.3 (7.6)	Inpatient	37.9 (10.6)				SST	18	Group	8	BPRS	1	1	0	0
Ng 2006	14.8 (9.2)		41.3 (11.4)				SC	18	Group	8		2	1	0	0
Ojeda 2012	10.92 (7.6)	Inpatient	33.81 (9.7)		Stable	Treatment resistant	CR_CRSS	47	Group	13	PANSS	0	2	0	0
Ojeda 2012	15.25 (9.4)		37.75 (8.3)		Stable		OT	46		13		n/a	n/a	0	0
Omiya 2016	14.75 (13.53)	Both	43.25 (14.5)				CR	8	Individual	26	PANSS	0	1	1	0
Omiya 2016	11.78 (10.62)		39.00 (11.09)				TAU2	9		26		n/a	n/a	1	0
Penn 2009	.	Outpatient	41.7 (11.8)			Auditory hallucinations	CBT	32	Group	12	PANSS	0	-1	0	0
Penn 2009			39.6 (15.7)				SC	33	Group	12		0	-1	0	0
Penn 2011	.	Outpatient	23.48 (3.89)	Early			PE	23	Individual	36	PANSS	1	-1	0	0
Penn 2011			20.96 (2.14)	Early			TAU3	23		36		n/a	n/a	0	0
Peters 2010	median 6 years	Outpatient	34 (9.8)		Stable		CBTp	36	Individual	26	PANSS	0	0	0	0

Peters 2010	median 7 years		39.6 (10.2)		Stable		TAU1	38		26		n/a	n/a	0	0
Pinto 1999	11.6 (7.9)	Both	33.9 (10.1)			Treatment resistant	CBT_SST	20	Individual	26	BPRS	1	2	0	0
Pinto 1999	11.7 (6.6)		35.8 (11.9)				PE	21	Individual	26		3	2	0	0
Rakitzi 2016	5.4 (1.3)	Outpatient	31.3 (7.2)	Early	Stable		CRSS	24	Group	10	PANSS	0	2	0	0
Rakitzi 2016	5.9 (1.1)		33.8 (6.7)	Early	Stable		TAU2	24		10		n/a	n/a	0	0
Rathod 2013	8.56 (8.24)	Both	31.37 (12.43)				CBTp	17	Group	20	CPRS	2	1	0	1
Rathod 2013	12.33 (8.88)		35.58 (10.72)				TAU2	17		20		n/a	n/a	0	1
Rector 2003	Years on neuroleptics 13.9 (9.4)	Outpatient	37.5 (8.3)		Stable		CBT	29	Individual	26	PANSS	0	-1	0	0
Rector 2003	Years on neuroleptics 17.9 (10.0)		41.2 (10.9)		Stable		TAU2	21		26		n/a	n/a	0	0
Roberts 2014	.	Outpatient	40.0 (12.2)				SST	33	Group	26	PANSS	0	-1	0	0
Roberts 2014	.		39.4 (10.8)				TAU2	33		26		n/a	n/a	0	0
Rus-Calafell 2013	13.15	Outpatient	37.54 (8.05)		Stable		SST	18	Group	8	PANSS	0	3	0	0
Rus-Calafell 2013	13.5		42.39 (8.1)		Stable		TAU2	18		8		n/a	n/a	0	0
Sanchez 2014	.	Inpatient	33.6 (9.4)				CR_CRSS	38	Group	13	PANSS	0	2	0	0
Sanchez 2014			36.92 (10.5)				BF	54	Group	13		n/a	n/a	0	0
Schaub 2016	3.3 (2.7)	Inpatient	33.3 (10.3)	Early	Post Acute		CPS	100	Group	8	BPRS	0	1	0	0
Schaub 2016	3.2 (2.5)		34.0 (12.2)	Early	Post Acute		SC	96	Group	8		0	1	0	0
Schrank 2016	.	Both	43 (11)				WB	47	Group	11	BPRS	0	-1	0	0
Schrank 2016	.		42 (11.5)				TAU2	47		11		n/a	n/a	0	0

Sensky 2000	14 (12-17)	Outpatient	39 (35-42)			Treatment resistant	CBT	46	Individual	39	CPRS	0	0	0	0
Sensky 2000	15 (11-18)		40 (35-45)				BF	44		39		n/a	n/a	0	0
Shin 2002	.	Outpatient	39.50 (7.85)				PESC	24	Group	10	BPRS	0	3	0	0
Shin 2002			34.7 (9.39)				SC	24	Individual	10		6	3	0	0
Startup 2004	.	Both	30.5 (8.7)				CBTp	47	Individual	52	BPRS	2	-1	1	0
Startup 2004			31.3 (9.6)				TAU3	43		52		n/a	n/a	1	0
Tan 2016	23.95 (8.18)	Inpatient	46.77 (7.18)		Stable		CR	52	Group	10	PANSS	0	3	0	0
Tan 2016	21.51 (6.5)		46.09 (5.52)		Stable		BF	52	Group	10		n/a	n/a	0	0
Tao 2015	.		28.95 (7.38)			FGA only	CR	44		12	PANSS	2	4	0	0
Tao 2015	.		29.71 (6.36)				TAU0	42		12		n/a	n/a	0	0
Tarrier 2014	.	Outpatient	34.9 (13.1)			Suicide attempt	CBT	25	Individual	17	PANSS	0	0	0	0
Tarrier 2014							TAU2	24		17		n/a	n/a	0	0
Tas 2012	12.63 (9.99)	Outpatient	33.32 (11.57)		Stable		FSIT	22	Group	16	PANSS	0	0	1	0
Tas 2012	11.85 (8.73)		34.62 (10.06)		Stable		BF	27	Individual	16		n/a	n/a	1	0
Turkington 2002	.	Outpatient	40.47 (CI 39.78-41.88)		Stable		CBT	257	Individual	20	CPRS	0	0	0	0
Turkington 2002					Stable		TAU2	165		20		n/a	n/a	0	0
Valencia 2007	.	Outpatient	29.7 (6.6)		Stable		SST_FPE	49	Group	52	PANSS	0	1	0	0
Valencia 2007			30.1 (7.1)		Stable		TAU1	49		52		n/a	n/a	0	0
Valencia 2010	.	Outpatient	29.9 (7.4)		Stable		SST_FPE	54	Group	52	PANSS	0	0	0	0
Valencia 2010			29.5 (7.2)		Stable		TAU1	53		52		n/a	n/a	0	0
Valencia 2012	.	Outpatient	24.5 (3.0)	Early	Stable		SST_FPE	44	Group	52	PANSS	0	1	0	0

Valencia 2012			24.1 (3.2)	Early	Stable		TAU1	44		52		n/a	n/a	0	0
Valencia 2013	8.2 (5.3)	Outpatient	29.5 (6.8)		Stable		SST	74	Group	26	PANSS	0	-1	0	0
Valencia 2013	8.3 (6.5)		26.4 (4.0)		Stable		TAU2	74		26		n/a	n/a	0	0
Valmaggia 2005	10.4 (6.6)	Inpatient	35.43 (10.53)			Treatment resistant	CBT	36	Individual	22	PANSS	0	-1	1	0
Valmaggia 2005	11.1 (8.8)		35.52 (11.42)				SC	26	Individual	22		0	-1	1	0
Velligan 2015	.	Outpatient	43.47 (10.7)				CAT	41	Individual	39	BPRS	0	-1	0	1
Velligan 2015			39.2 (12.5)				CBT	43	Individual	39		0	0	0	1
Velligan 2015			39.5 (12.8)				CBT_CAT	40	Individual	39		0	0	0	1
Velligan 2015			40.3 (11.1)				TAU1	42		39		n/a	n/a	0	1
Veltro 2011	11.91 (7.9)	Outpatient	37.7 (11.16)				SST	12	Group	52	PANSS	1	2	0	0
Veltro 2011	14.17 (8.3)		38.8 (6.3)				CRSS	12	Group	52		1	2	0	0
Vita 2011a	14.94 (9.76)	Outpatient	37.15 (9.1)		Stable		CRSS	26	Group	24	PANSS	0	4	0	0
Vita 2011a	17.93 (9.68)		43 (7.76)				BF	28	Group	24		0	4	0	0
Vita 2011a	14.8 (9.78)		36.87 (11.4)		Stable		CR	30	Group	24		0	4	0	0
Vita 2011b	12.5 (8.4)	Outpatient	34.6 (7.6)		Stable		CRSS	16	Group	24	PANSS	1	2	0	0
Vita 2011b	14.9 (11.5)		39.9 (8.6)		Stable		BF	16	Group	24		n/a	n/a	0	0
Wang 2016	2 (1)	Outpatient	23.8 (6.8)	Early			MPE	46	Group	25	PANSS	0	2	0	1
Wang 2016	2.1 (0.9)		24.1 (6.3)	Early			PE	46	Group	25		0	1	0	1
Wang 2016	2.0 (0.9)		25.0 (7.0)	Early			TAU2	46		25		n/a	n/a	0	1
Wolwer 2011	.	Inpatient	36.7 (13.1)				CRSS	20	Group	6	PANSS	0	4	0	0
Wolwer 2011	.						CR	18	Group	6		0	4	0	0
Wykes 1999	59% >10 years	Outpatient	36.5 (19-55)				CR	17	Individual	13	BPRS	0	4	0	0
Wykes 1999	81% >10 years		40.6 (24-64)				OT	16		13		n/a	n/a	0	0
Wykes 2007	.	Outpatient	36				CR	43	Individual	12	PANSS	0	0	0	1

Wykes 2007					TAU2	42		12		n/a	n/a	0	1
Mazza 2010*	.	Outpatient	24.37 (2.12)		CRSS	17	Group	12	BPRS	0	2	0	0
Mazza 2010*	.		24.71 (2.17)		PST	16		12		0	2	0	0
Montero 2001*	5.7 (4.5)	Outpatient	27.2 (6.6)		BFT	46	Group	52	PAS	0	0	0	0
Montero 2001*	5.3 (3.6)		26.4 (5.9)		FPE	41	Group	52		0	4	0	0
Weisman de Mamani 2014*	.	Outpatient	42.73 (14.31)		FT	38	Individual	17	BPRS	0	1	0	0
Weisman de Mamani 2014*	.		42.42 (12.7)		FPE	31	Individual	17		1	0	0	0

*Mazza 2010 was not included due to inconsistency in the model (see Appendix 8 for rationale). Montero 2001 & Weisman de Mamani 2014 were not included as the inteventions were classified in the same node.
Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.
Outcome measures: BPRS- Brief psychiatric rating scale, CPRS: Comprehensive psychopathological rating scale, FGA: first generation antipsychotics, PANSS- Positive and negative syndrome scale. PAS- Psychiatric assessment scale, PECC- Psychosis evaluation tool for common use by caregivers (completed by staff in RCTs in this study), RoB; Risk of Bias.

NMA Appendix 10: Reference list of Included Studies

Aghotor J, Pfueller U, Moritz S, Weisbrod M, Roesch-ely D. Metacognitive training for patients with schizophrenia (MCT): Feasibility and preliminary evidence for its efficacy. J Behav Ther Exp Psychiatry [Internet]. Elsevier Ltd; 2010;41(3):207–11. Available from: http://dx.doi.org/10.1016/j.jbtep.2010.01.004

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