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Review article

Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis

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Background
Negative symptoms observed in patients with psychotic disorders undermine quality of life and functioning. Antipsychotic medications have a limited impact. Psychological and psychosocial interventions, with medication, are recommended. However, evidence for the effectiveness of specific non-biological interventions warrants detailed examination.

Aims
To conduct a meta-analytic and systematic review of the literature on the effectiveness of non-biological treatments for negative symptoms in psychotic disorders.

Method
We searched for randomised controlled studies of psychological and psychosocial interventions in psychotic disorders that reported outcome on negative symptoms. Standardised mean differences (SMDs) in values of negative symptoms at the end of treatment were calculated across study domains as the main outcome measure.

Results
A total of 95 studies met our criteria and 72 had complete quantitative data. Compared with treatment as usual cognitive–behavioural therapy (pooled SMD −0.34, 95% CI −0.55 to −0.12), skills-based training (pooled SMD −0.44, 95% CI −0.77 to −0.10), exercise (pooled SMD −0.36, 95% CI −0.71 to −0.01), and music treatments (pooled SMD −0.58, 95% CI −0.82 to −0.33) provide significant benefit. Integrated treatment models are effective for early psychosis (SMD −0.38, 95% CI −0.53 to −0.22) as long as the patients remain in treatment. Overall quality of evidence was moderate with a high level of heterogeneity.

Conclusions
Specific psychological and psychosocial interventions have utility in ameliorating negative symptoms in psychosis and should be included in the treatment of negative symptoms. However, more effective treatments for negative symptoms need to be developed.

Declaration of interest
None

Negative symptoms, characterised by an absence or reduction of affective, as well as social and behavioural expression, are regarded as an inherent aspect of psychotic disorders and among the most important predictors of quality of life[1] and functional outcome.[1–3] Further, negative symptoms may be transitory and secondary to depression and side-effects from antipsychotic medication,[4] whereas persistent negative symptoms are often regarded as primary to the underlying disease process.[4] Persistent negative symptoms are present in 25% of patients with first-episode psychosis (FEP)[5] and in an even greater proportion of patients with chronic schizophrenia.[6,7] Antipsychotic medications, highly effective for the treatment of positive symptoms, and newer biological treatments such as transcranial magnetic stimulation, have at best a modest impact on negative symptoms.[8] Given the paucity of options available to treat negative symptoms, current best practice suggests the use of psychological and psychosocial interventions in addition to medication.[9,10] The evidence supporting the effectiveness of such interventions for negative symptoms has, however, not been fully explored. Reviews on psychological and psychosocial treatment options have focused largely on positive symptoms and relapse prevention[11–14] with two exceptions[15,16] that presented negative symptom outcomes as their primary objective. In their meta-analysis, Fusar-Poli and colleagues[15] pooled negative symptom outcomes from a broad range of primarily biological and some psychological interventions. They aggregated all negative symptom outcome data from a limited number of psychological interventions into a single effect size, limiting the interpretation for different psychological and psychosocial treatments. In a narrative analysis of results of randomised control trials (RCTs) of psychological interventions with negative symptom outcomes,[16] alternative intervention types such as arts- and exercise-based therapies were excluded and a stringent systematic review of the literature including quality ratings was not performed. Our study extends previous work by providing a systematic review and complete qualitative and quantitative synthesis of the current literature on the effectiveness of all psychological and psychosocial interventions for the treatment of negative symptoms in psychotic disorders.

Method

Search strategy

We searched the following five major databases: MEDLINE via PubMed, Embase, Web of Science, PsycINFO and the Cochrane Library. Articles from inception to 19 October 2015 were included in our search. Database-specific search terms included the key words ‘psychosis’, ‘schizophrenia’, ‘negative symptoms’, ‘therapy’ and ‘intervention’ with diagnosis-specific and symptom-specific subtypes and relevant variations and synonyms (online supplement DS1). We searched only English-language publications and identified additional studies through hand searches of bibliography from primary studies, review articles and key journals, as well as through contacts with experts in the field (Fig. 1).

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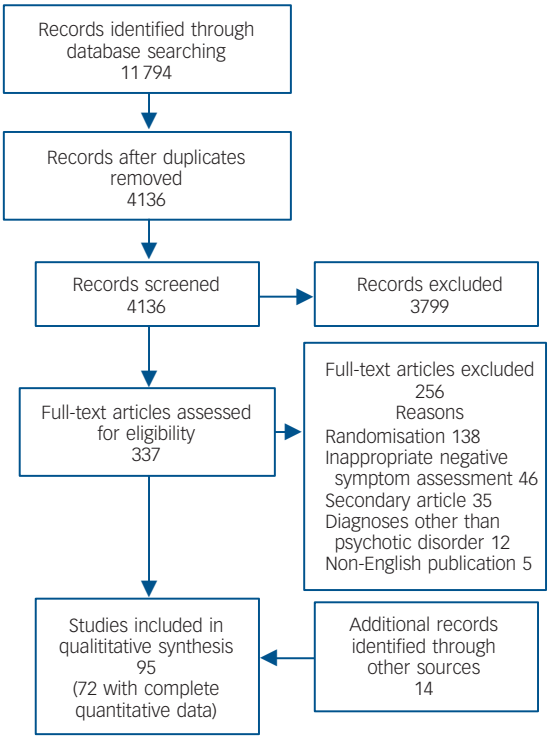

Fig. 1 PRISMA flow diagram.

Inclusion/exclusion criteria

Studies were included if they met the following criteria: RCT design; investigation of a psychological or psychosocial intervention; report of negative symptom outcomes using a valid and reliable negative symptom measurement (such as the Scale for Assessment of Negative Symptoms (SANS), the Negative Symptom subscale of the Positive and Negative Symptom Scale (PANSS)); a majority sample with a diagnosis of a schizophrenia spectrum or other non-organic psychotic disorder. Random crossover trials were included, although only between-group comparisons data, prior to the crossover, were extracted. We excluded the following types of studies: those published in a language other than English; quasi-experimental study designs; theoretical papers; case studies; meta-analyses; other reviews; qualitative reports and designs utilising cluster random trials as well as medication efficacy trials even if the latter used a psychological or psychosocial intervention as a supplementary treatment.

Screening

The first author (D.L.) and a research assistant independently screened all citation titles for their broad applicability using computer-based software (Distiller SR[17]). Titles that clearly did not meet inclusion criteria were removed from citation listings. At the second stage a more detailed independent screening by both raters was conducted on all abstracts. Disagreements at both the first and second screening were resolved between the first author (D.L.) and research assistant through discussion with the senior author (A.M.). The first author (D.L.) extracted the full texts of selected articles for the final screening (Fig. 1).

Data extraction and quality assessment

Information on the nature of the experimental intervention and control, characteristics of the study sample, outcome measures and effect sizes were extracted. Study quality was assessed from a critical appraisal checklist.[18–21] on standardisation of treatment, recruitment, sequence generation, allocation concealment, comparability of groups, equality of care between groups, masked assessment, inclusion/exclusion criteria, attrition, adherence and intention-to-treat analysis. Studies were considered to be of poor quality if they presented high or unclear risk of bias for either the sequence generation or allocation concealment, or presented two or more risks of bias. Sample size was not included within the measure of quality. Disagreements on quality were resolved by discussion among authors (D.L., G.G. and A.M.).

Quantitative analysis

A quantitative summary of the literature was obtained through meta-analytic methods. Measures of effect were calculated from data available or from standard errors reported ($n = 72$ studies). Standard mean difference (SMD) reported, or Cohen's d can be interpreted such that 0.2, 0.5, and 0.8 are equated with effect sizes of small, medium, and large.[22] Studies for which such data were not available were included in the qualitative analysis only. We pooled estimates using the DerSimonian & Laird random-effects model. High heterogeneity between studies was expected and evaluated through I^2 tests as well as through stratified analysis by type of intervention, control and study quality. Publication bias was determined with a funnel plot that provides a visual representation of how the odds ratio for each individual study varied from the pooled odds ratio. Analyses were conducted in Stata 12.1. No data of negative symptom outcomes for controls within treatment as usual (TAU) and waitlist conditions post treatment end are included in this review. Several RCTs included either two active controls or an active control alongside a TAU group. In such cases, for the overall pooled effect size, we included only the TAU group as this was the comparison control used most often across studies. Post-treatment follow-up data are described qualitatively. The PRISMA checklist was followed for the reporting of all outcomes.[23] The protocol for this review is available on PROSPERO (CRD42014015244).

Results

Study selection

A total of 11 794 publications were initially retrieved and, after removing duplicates and adding studies from hand searches, 4150 publication citations remained for broad screening. A further 3799 studies were excluded. Pharmacological trials and studies without a randomisation design were the main reasons for exclusion. A total of 95 studies that met the inclusion criteria were thus identified (Fig. 1).[23] Of these, 72 studies provided data on negative symptom outcome and were included in the meta-analysis.

Cognitive–behavioural therapies (CBT)

A total of 26 studies investigated the effectiveness of CBT in psychosis.[24–53] Of these, two were CBT interventions adapted specifically for treating negative symptoms.[28,29,39] Highly significant heterogeneity between CBT studies was found, $I^2 = 73.6\%$, $P < 0.001$ (online Table DS1). Details of study characteristics are presented in Table DS2. Treatment was offered over a mean of 6 months (range 1.25–18) for a mean of 28 sessions, each session lasting a mean of 66 min (range 45–90).

Overall, evidence indicated CBT to be an effective intervention for negative symptoms (pooled SMD −0.34, 95% CI −0.55 to −0.12, Fig. 2(a)). Compared with TAU, 59% (10/17) of studies reported CBT to be more effective at the end of treatment (pooled

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SMD −0.43, 95% CI −0.55 to −0.30). Compared with active control, none of 12 studies suggest a benefit of CBT (pooled SDM −0.11, 95% CI −0.26 to 0.04), although 7 reported substantial but equal improvements in both active conditions. For studies that reported long-term follow-up (mean 27 months), CBT was beneficial compared with TAU across 57% (8/14) of the comparisons. None of the studies with active controls reported such effect, except for one using befriending as the active control.[31,54] There were no differences in effects as a result of differences in study quality.

Skills training, occupational therapy and cognitive adaptation training

A total of 17 RCTs using skills training ($n=11$),[55–65] occupational therapy ($n=3$),[66–68] cognitive adaptation training ($n=2$)[69,70] or vocational training ($n=1$)[71] were included. Only one study was designed specifically to treat negative symptoms[65] and there was highly significant heterogeneity between studies, $I^2=85.8\%$, $P<0.001$ (online Table DS1). Study characteristics are available in Table DS3. Treatment was offered over a mean of 7 months (range 1.5–24) for a mean of 25.5 sessions (range 12–76) with a mean length of 86 min per session (range 45–180). One active control study compared two variations of skills training: social skills and relapse prevention skills.[58]

Overall 53% (9/17) of the studies favoured the experimental intervention at the end of treatment (pooled SMD −0.44, 95% CI −0.77 to −0.10, Fig. 2(a)). This effect was largely driven by studies using TAU as the control (pooled SMD −0.42, 95% CI −0.56 to −0.28) and was not present in studies using an active control (pooled SMD −0.05, 95% CI −0.30 to 0.19). Stratified analyses indicated a significant effect of skills training (pooled SMD −0.31, 95% CI −0.45 to −0.17) and of occupational therapy (pooled SMD −1.00, 95% CI −1.48 to −0.51) only. In the study that compared different skills-training programmes, no significant differences were reported.[58] High- and medium-quality studies reported more favourable outcomes (pooled SMD −0.42, 95% CI −0.56 to −0.28) than those of low quality (pooled SMD 0.00, 95% CI −0.26 to 0.26). Of five studies with follow-up negative symptom data,[57,61–63,69] three favoured the experimental intervention at 1 month,[63] 3 months[61] and 6 months.[62] The benefit of skills training over social milieu therapy that was reported at 3 months was not maintained at 6-month follow-up in one study.[61]

Neurocognitive therapies

A total of 16 studies used neurocognitive interventions including cognitive remediation ($n=11$);[72–82] cognitive training ($n=2$);[83,84] cognitive rehabilitation ($n=1$);[82] neurocognitive therapy ($n=1$);[85] and cognitive enhancement ($n=1$).[86] Another study focused on improving cognitive strategies related to attention, verbal memory and planning.[87] Three interventions studied were designed primarily to improve negative symptom outcomes[76,83,87] (see online Table DS4 for study characteristics). There was highly significant heterogeneity between studies, $I^2=74.2\%$, $P<0.001$ (online Table DS1). Across studies, treatment was offered over a mean of 3.75 months (range 2–24) with a mean of 42 sessions (range 16–120), delivered for a mean of 76 min (range 15–150). Seven studies utilised computer technology for treatment delivery[77,78,80–82,86,87] including two specifically designed for the amelioration of negative symptoms.[83,87] Active controls included computer games[81] and supportive therapy.[86]

Neurocognitive interventions were effective in only a minority of studies ($n=5$, 31%) and data show no overall effect (pooled SMD –0.15, 95% CI –0.41 to 0.11, Fig. 2(b)), regardless of control type and/or study quality. No significant differences were found between modes of neurocognitive treatment delivery.[78,87] Two of five studies with long-term follow-up data[72–74,77,87] reported a significant effect at 3 months[84] and 9 months,[85] and another study reported a significant benefit of cognitive remediation at 4- but not at 9-month follow-up, compared with group leisure activities.[72]

Exercise therapy

Ten RCTs of exercise therapy on negative symptoms[88–97] were reported (see online Table DS5 for study characteristics). Exercises investigated were yoga,[89,90,92,94] aerobic,[91,93] resistance training,[97] structured walking, tai chi[88] and traditional dance.[96] Of these only one study was designed to measure negative symptoms as a primary outcome.[88] Significant heterogeneity between studies was found, $I^2=54.8\%$, $P=0.039$ (online Table DS1). Exercises were offered over a mean of 3 months (range 2 weeks to 8 months) with an average of 26.7 sessions (range 8–48) and a mean of 53 min per session (range 40–60).

An effect of exercise on negative symptoms was found (pooled SMD −0.36, 95% CI −0.71 to −0.01, Fig. 2(b)) that was largely the result of four of seven (57%) comparisons with TAU (pooled SMD −0.42, 95% CI −0.76 to −0.09) whereas active control comparisons showed no effect (pooled SMD −0.07, 95% CI −0.37 to 0.23). Overall, lower-quality studies showed greater effects (pooled SMD −0.37, 95% CI −0.74 to −0.00) than higher-quality studies (pooled SMD 0.14, 95% CI −0.42 to 0.14). Resistance training and exercise as active control comparisons were equally effective in treating negative symptoms.[97] Too few studies were available to warrant a comparison of differences in exercise intervention types. None of the three studies with follow-up assessments found any treatment effect at 1 month,[92] 1.5 months[88] and 3 months.[94]

Art and music therapies

Seven RCTs were art- or music-based interventions: two fine arts[98,99] and five music based[100–104] (see online Table DS6 for study characteristics) with highly significant heterogeneity between studies, $I^2=94.9\%$, $P<0.001$ (online Table DS1). Treatment was offered over a mean of 4.25 months (range 1–12 months), for a mean of 22 sessions (range 10–52) with a mean of 62.5 min (range 45–90) per session.

Considered together, arts-based treatments were not effective at treating negative symptoms with 57% (4/7) demonstrating no effect (pooled SMD −0.14, 95% CI −0.78 to 0.50, Fig. 2(b)). However, whereas fine-arts-based therapies were not advantageous (pooled SMD 0.57, 95% CI 0.41–0.74), sensitivity analysis revealed a distinct benefit of music-based therapies compared with TAU (pooled SMD −0.58, 95% CI −0.82 to −0.33).[101,103,104] There were no differences in end-of-study outcomes as a result of differences in study quality. Three studies with follow-up data reported no significant lasting[99,104] or emerging[98,99] benefit.

Family-based interventions

Six RCTs investigating family-based interventions reported negative symptom outcomes[105–110] (see online Table DS7 for study characteristics) with marginally significant heterogeneity between studies, $I^2=65.4\%$, $P<0.056$ (online Table DS1). The mean duration of treatment was 10.9 months (range 2.5–18) with a mean of 23 sessions (range 10–45) and the mean session duration of 97.5 min (range 60–120).[105,106,108,110] One study did not provide standardised treatment[106] and two did not specify.[109,110] Family interventions were delivered within: multiple

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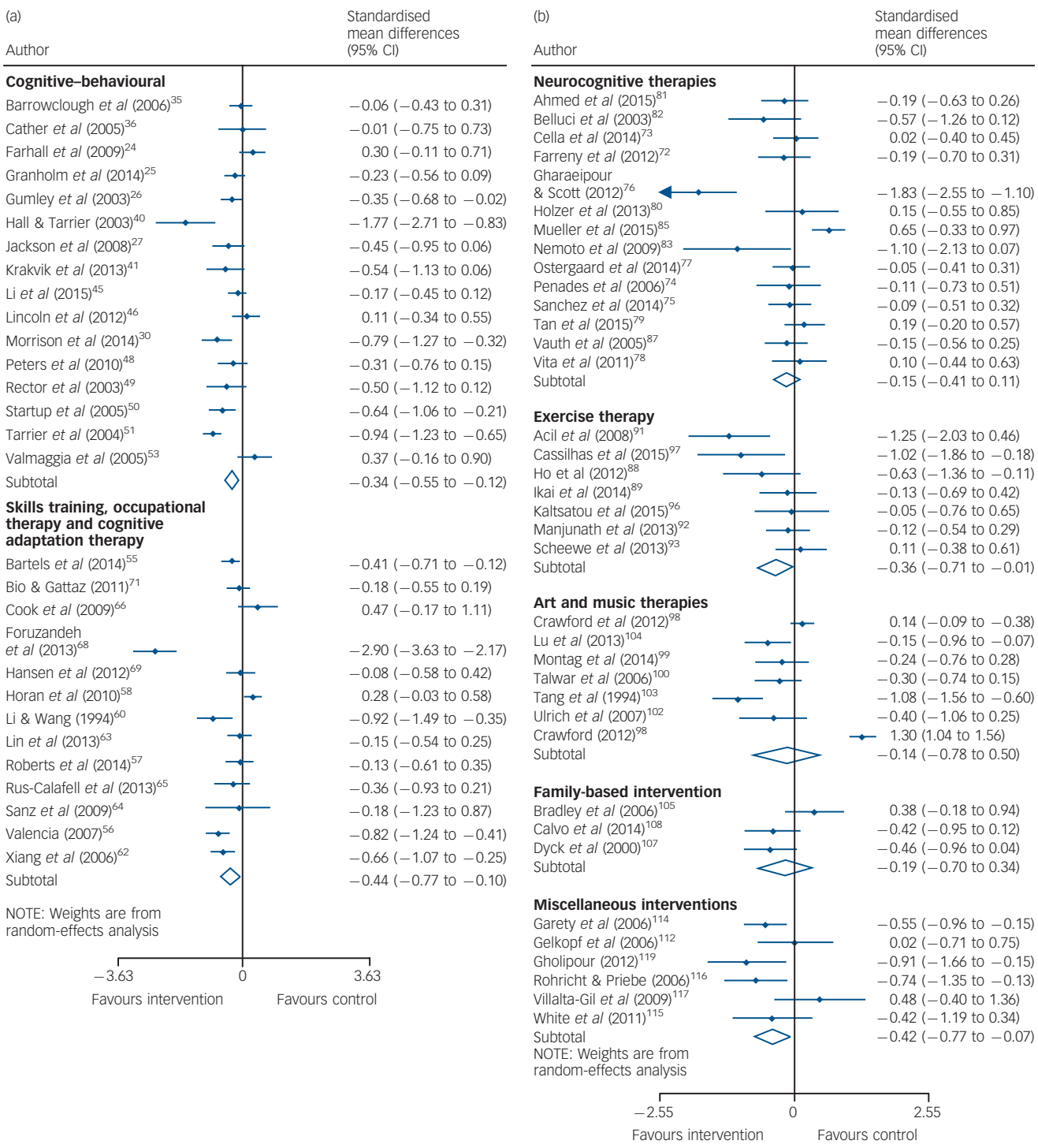

Fig. 2 Forest plots.

(a) Cognitive–behavioural therapy, skills training, occupational therapy and cognitive adaptation therapy; (b) neurocognitive therapies, exercise therapy, art and music therapies, family-based interventions and miscellaneous interventions.

family groups,[106,107,109] single family groups[110] or a combination of both.[105,108] One study also used individualised sessions of psychotherapy.[109] All studies focused primarily on providing psychoeducation;[105–109] two studies also included large components of social-skills training.[106,110] Only one study was designed to measure negative symptom outcomes.[107]

No effect of family intervention was detected either individually or overall (pooled SMD −0.19, 95% CI –0.70 to 0.34) regardless of control comparison. There were no differences in end-of-study outcomes as a result of differences in study quality. Neither of the two studies with follow-up reported a significant effect.[109,110]

Miscellaneous interventions

The following unclassified interventions ($n = 10$) were included: humour therapy ($n = 2$);[111,112] specialised early intervention for FEP (SEI: $n = 2$);[113,114] acceptance and commitment therapy ($n = 1$);[115] body psychotherapy ($n = 1$);[116] dog-assisted psychological

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treatment ($n = 1$);[117] adherence therapy ($n = 1$);[118] token therapy ($n = 1$);[119,120] and motivation approach to learning arithmetic ($n = 1$).[120] Body psychotherapy, motivational learning and humour therapy were designed specifically to treat negative symptoms (see online Table DS8 for study characteristics). Heterogeneity between studies was found to be non-significant, $I^2 = 33.3\%$, $P = 0.174$ (online Table DS1). The mean duration of treatment was 2.25 months (range 1–3), excluding both SEI studies that were conducted over a span of 1.5 years[114] and 2 years.[113] Whereas SEI interventions were intensive over the entire period of 1.5–2 years, for the other studies mean number of sessions offered was 24 (range 8–60) over an average session length of 66 min (range 30–120).

A significant effect of all miscellaneous studies was found (pooled SMD −0.42, 95% CI −0.77 to −0.07, Fig. 2(b)) driven largely by TAU as opposed to active control comparisons (pooled SMD −0.48, 95% CI −0.75 to −0.21; pooled SMD −0.33, 95% CI −0.67 to 0.02, respectively). Higher-quality studies reported greater overall effects (pooled SMD −0.61, 95% CI −0.87 to −0.36) compared with low-quality studies (pooled SMD 0.08, 95% CI –0.37 to 0.52). Compared with supportive counselling, body psychotherapy was found to be more effective and the effect was retained at 4-month follow-up (pooled SMD −0.74, 95% CI −1.35 to −0.13).[116] Token therapy was more effective than TAU (pooled SMD −0.91, 95% CI −1.66 to −0.15) but not active control (exercise). Treatment in an SEI service was more effective than TAU (regular care) (pooled SMD −0.38, 95% CI −0.53 to −0.22) but the effect was not retained after transfer to regular care.[121] Compared with TAU, adherence therapy[118] and acceptance and commitment therapy[115] were not effective. Token therapy was not more effective on negative symptoms than an exercise active control.[119] Overall, medium- and high-quality studies were more likely to report a significant effect at end of treatment (pooled SMD −0.61, 95% CI −0.87 to −0.36) than were low-quality studies (pooled SMD 0.08, 95% CI −0.37 to 0.52).

Additional analyses

The above results raise several other questions for which we conducted the following additional analyses.

Is the impact of interventions greater in the early *v.* later phases of illness?

Using study reports of mean patient age as a proxy measure of early *v.* later phase we used a cut-off of 35 years, as indicated by criteria for entrance into early-intervention programmes.[122] We found no difference in negative symptom outcomes across those studies with a mean patient age ⩽35 years (pooled SMD −0.342, 95% CI −0.528 to −0.156) compared with those with a mean patient age >35 years (pooled SMD −0.284, 95% CI −0.520 to −0.048). We also tested this by comparing outcomes for those receiving SEI (pooled SMD −0.340, 95% CI −0.474 to −0.206) as compared with those treated in other regular services (pooled SMD −0.304, 95% CI −0.467 to −0.141). This also did not reveal any differences in outcome on negative symptoms across the two types of services.

Are there differences in effectiveness of intervention provided in individual *v.* group format?

An investigation into intervention format revealed no differential effects of group (pooled SMD −0.31, 95% CI −0.601 to −0.019), individual (pooled SMD −0.313, 95% CI −0.505 to −0.120) and combined formats (pooled SMD −0.243, 95% CI −0.483 to −0.004).

Does intensity of interventions have an impact on effectiveness?

As psychotherapy is traditionally offered over 45 to 50 min per week,[123] we used a cut-off of 45 min per week as a measure of high *v.* low intensity of treatment. We found that interventions lasting over 45 min per week were more effective (pooled SMD −0.341, 95% CI −0.558 to −0.125) than those offered over less than 45 min per week (pooled SMD −0.024, 95% CI −0.373 to 0.324).

Why might differences in effect of interventions emerge only when TAU is used as the control condition and not when active controls are used?

The putative mechanisms that might be responsible for the effectiveness of experimental interventions, when compared with TAU as controls, might be similar to those incorporated in some of the active controls used. In order to explore this question, we assigned a putative mechanism of action to each intervention tested based on the content of the intervention: behaviour activation (for example CBT, activity groups, recreation, crafts[124,125]), social engagement (for example supportive therapy, befriending[126]), skill enhancement (for example skills training, occupational therapy, vocational rehabilitation[127]), neurocognitive (for example cognitive remediation, cognitive rehabilitation[128]) and non-specific (for example video games[91]). We found similar effects from experimental interventions and active controls when the latter utilised one of the following mechanisms of action: skill enhancement (pooled SMD 0.206, CI −0.039 to 0.451); behavioural activation (pooled SMD −0.066, 95% CI −0.257 to 0.124); non-specific mechanism of action (pooled SMD −0.068, 95% CI −0.402 to 0.226); social engagement (pooled SMD −0.276, 95% CI −0.608 to 0.056) and neurocognitive (pooled SMD −0.431, 95% CI −1.48 to 0.618).

Publication bias

Results of the funnel plot used to determine publication bias indicate a large grouping of studies left of the mean, suggesting that those studies reporting negative effects may have been less likely to have been published (online Fig. DS1).

Discussion

Main findings

Our meta-analysis and systematic review revealed evidence that negative symptoms can be improved at least modestly with psychosocial and psychological interventions. Although guidelines have traditionally supported the use of CBT, findings from skills-based interventions (SBIs) suggest that the latter are likely to have comparative, if not enhanced utility, as long as the treatment is continued. Although there is some suggestion for the effectiveness of physical activity and music, study quality for these interventions was generally not satisfactory and higher-quality studies are indicated. The largest number of studies was available in support of CBT and SBI. Overall the quality of most studies was medium.

Across study domains, effect sizes of decrease in negative symptoms over time tended to be small. Only SBIs, CBT, music therapy, exercise, body psychotherapy and SEI demonstrated overall moderate effect sizes, largely in comparison with TAU. Neurocognitive, family-based and humour therapies were not found to be an effective treatment for negative symptoms, even compared with TAU.

Across interventions, we found that skill enhancement and behavioural activation were more successful than TAU in targeting negative symptoms in psychosis. This finding has face validity in

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that improved skills, and particularly social skills, are likely to be associated with increases in prosocial behaviours (and *vice versa*), that are key indicators of negative symptom improvement. Sensitivity analyses of active control interventions suggest that certain active mechanisms of action are present in both experimental and active controls and, therefore, explain lack of differences in outcome when experimental interventions are compared with active controls. Further, we found that across all experimental interventions, treatment intensity of at least more than 45 min per week is associated with a better outcome. All things being equal, consistency and repetition may partially explain this effect, as may increased social contact. Indeed, we found that group format was as effective as individual format, suggesting some advantages in terms of cost-effectiveness.

Interpretation of our findings

Most studies available for review were not designed to treat negative symptoms and we used data reported on change in negative symptoms irrespective of the primary outcome for the study. As a result, patients were not selected for their negative symptom status. However, notwithstanding differences in rating scales used, our findings from a large number of CBT and SBI studies allowed adequate data comparisons. The results from these suggest that those with higher levels of negative symptoms on entry undergo the greatest negative symptom improvement. This suggests the utility of CBT and SBIs among populations with high levels of negative symptoms. However, few studies selected patients with high levels of negative symptoms.

The quality of evidence from the majority of studies in this review was at best moderate. Many studies used small samples and did not account for attrition, limiting the power of many studies to detect significant results. Larger CBT and SBI studies were somewhat more likely to report a significant effect of the experimental intervention, suggesting a need for studies of other psychosocial and psychological interventions to be designed with adequate power.

Consistency of findings was difficult to establish. We found much evidence of high heterogeneity across studies. Within intervention categories there was great variation with regard to treatment protocol, population, type of control and measurement used. Despite this, our conclusions of somewhat limited evidence for the effectiveness of psychological and psychosocial interventions are perhaps not surprising, given the nature of negative symptoms and the overall prolonged length of illness of study participants. Treatment success is often dependent upon participation, motivation and communication,[129] suggesting that greater levels of negative symptoms may preclude the very outcomes being targeted.[130] That patients were often older, from in-patient settings and chronically ill suggest that they may be struggling from unresolved side-effects from medications, symptoms, social decline and a gradual deterioration of hope that may further challenge treatment outcomes.[130] In contrast, very few studies included in this review were targeted towards those in the earliest phases of psychosis. Although sensitivity analyses did not indicate any marked difference in negative symptom outcomes according to age, some benefit of younger age, likely reflective of an earlier phase in the course of illness, and treatment in an early-intervention service, was suggested from the data. It is of note that we were limited to utilising study reports of mean patient age that most likely included wide variation with general inclusion criteria of patients aged 18–60/65. Indeed, the encouraging results of SEI with FEP populations[113,114] confirm the important role of high-quality interventions delivered early on in the course of illness and the role of combined treatments that individually have well-established evidence of efficacy. Further RCTs delivering treatment during this critical period in psychosis may show more promising results.

Limitations

This meta-analysis and review has several other limitations. Given that virtually all patients across studies continued to be prescribed antipsychotic medications, findings regarding the utility of interventions must be examined within this context of drug therapy. We also excluded non-English language studies, although some studies were conducted outside North America or Europe. We were not able to compare monetary as well as other cost benefits of treatment, including adverse effects, that might further indicate increased utility of any one treatment. The only study[29] that examined adverse effects, defined as 'suicides, suicide attempts, suicidal crises, and severe symptom exacerbations over a period of 12 months after inclusion in the study' compared CBT with cognitive remediation in a sample of 198 patients with schizophrenia. They found that although there were adverse events over the course of the trial, the difference between groups was not significant and did not suggest a subgroup of patients who might necessitate additional monitoring. Finally, we were also not able to differentiate between treatment effects on specific domains (expressive *v.* motivational) of negative symptoms as well as on primary *v.* secondary negative symptoms. The latter include depression, and the possible side-effects of continued antipsychotic medications that may mask as negative symptoms.[131] This disentanglement would allow us to determine to what extent interventions were targeting specific areas of negative symptoms as well as enduring primary *v.* secondary and transient negative symptoms. Future intervention studies designed to target and measure negative symptoms in psychosis as a primary outcome may provide greater clarity as to treatment mechanisms and related outcomes. This would eventually assist in designing more effective psychological and psychosocial interventions for treatment of negative symptoms in future.

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