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Efficacy and acceptability of psychosocial interventions in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence

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Abstract

Psychosocial interventions are recommended in schizophrenia and first-episode psychosis/early psychosis (EP). Nevertheless, literature is heterogeneous and often contradictory. We conducted an umbrella review of (network) meta-analyses of randomized controlled trials (RCTs) comparing psychosocial interventions vs treatment as usual (TAU)/active interventions(ACTIVE)/MIXED controls. Primary outcome was total symptoms (TS); secondary outcomes were positive/negative/depressive symptoms (PS/NS/DS), cognition, functioning, relapse, hospitalization, quality of life (QoL), treatment discontinuation. Standardized mean difference (SMD)/odds ratio (OR)/risk ratio (RR) vs TAU/ACTIVE/MIXED were summarized at end-of-treatment (EoT)/follow-up (FU). Quality was rated as high/medium/low (AMSTAR-PLUS).

Eighty-three meta-analyses were included (RCTs=1 246; n=84 925). Against TAU, regarding TS, Early Intervention Services (EIS) were superior EoT/FU in EP (SMD=-0.32/-0.21), cognitive behavioral therapy (CBT) in schizophrenia EoT/FU (SMD=-0.38/-0.19). Regarding secondary outcomes, in EP, EIS were superior for all outcomes EoT except cognition, and at FU for PS/NS/QoL, specific family interventions (FI-s) prevented relapse EoT; in schizophrenia, superiority emerged EoT for CBT for PS/NS/relapse/functioning/QoL; psychoeducation (EDU)/any FI for relapse; cognitive remediation therapy (CRT) for cognition/functioning; and hallucination-focused integrative treatment for PS.

Against ACTIVE, in EP, mixed family interventions (FI-m) were superior at FU regarding TS (SMD=-0.61) and for functioning/relapse among secondary outcomes. In schizophrenia, regarding TS, mindfulness and social skills training (SST) were superior EoT, CBT at FU; regarding secondary outcomes superiority emerged at EoT for computerized cognitive drill-and-practice training for PS/DS, CRT for cognition/functioning, EDU for relapse, individual placement and support for employment; and at FU CBT for PS/NS.

Against MIXED, in schizophrenia, CRT/EDU were superior for TS EoT (d=-0.14/SMD=-0.33), CRT regarding secondary outcomes EoT for DS/social functioning, both EoT/FU for NS/cognition/global functioning; compensatory cognitive interventions for PS/functioning EoT/FU and NS EoT; CBT for PS at FU, and EDU/SST for relapse EoT.

In conclusion, mental health services should consider prioritizing EIS/any FI in EP and CBT/CRT/any FI/IPS for schizophrenia, but other interventions may be helpful for specific outcomes.

Introduction

Schizophrenia is a chronic and debilitating disorder, with on average 14.5 years of potential life lost.[1] The efficacy of antipsychotic treatment for positive symptoms, preventing relapses, and extending life expectancy is supported by a large body of evidence.[2–4] However, despite pharmacological treatment, most subjects with schizophrenia do not achieve full recovery, defined as both clinical and functional improvement (i.e., being able to work, having meaningful relationships, coping with symptoms, reaching some degree of quality of life).[5] Moreover, considering only remission of symptoms, approximately 40%, 30%, and 30% achieve a "good", "intermediate", and "poor" outcome respectively.

With the long-term aim of helping people with schizophrenia improve the quality of their lives by managing their illness more effectively, living and participating in their communities, and achieve personally meaningful roles in their lives (i.e., recovery), numerous guidelines for the treatment of schizophrenia[6–10] recommend supplementing pharmacological treatments with psychosocial interventions. However, recommendations vary widely across different guidelines. For example, while the NICE[6], CANPSY-CANCOM[8] and RANZCP[10] guidelines recommend individual cognitive behavioural therapy (CBT) as first-line for schizophrenia, PORT guidelines[7] state that CBT should be reserved for people who "have persistent psychotic symptoms while receiving adequate pharmacotherapy". NICE guidelines recommend against social skills training (SST), while it is recommended, albeit under specific circumstances, by CANPSY-CANCOM and RANZCP. Finally, cognitive remediation therapy (CRT) is recommended by RANZCP, only under specific circumstances by CANPSY-CANCOM, but is not mentioned by NICE guidelines.

Notwithstanding the promising evidence for a wide range of therapeutic options for people with schizophrenia, in clinical practice, mental health professionals often have to select and allocate resources wisely. Moreover, recommendations are often based on criteria that solely consider the design of the source of evidence (i.e., systematic review/meta-analysis, randomized controlled trial (RCT)), rather than also its quality (methodological quality of systematic reviews/meta-analyses, sample size and quality of meta-analyzed RCTs, heterogeneity of findings). Finally, guidelines often suggest what should be used for a given condition, but lack a finer-grained approach providing guidance on which symptomatic and functional domains are expected to improve significantly, and which are not, which would enhance their clinical utility.

Umbrella reviews are systematic reviews of meta-analyses that are useful in filtering high to moderate quality evidence from a *mare magnum* of often biased published meta-analyses, providing a clinically relevant synopsis, and potentially impacting everyday clinical practice. To date, no umbrella review has pooled all available meta-analyses

on psychosocial interventions for early psychosis (EP) and/or schizophrenia, reported their effect sizes regarding symptomatic and functional domains, measured the quality of the evidence, and included both comparisons with treatment as usual (TAU) and with other active control interventions (ACTIVE), both at end-of-treatment (EoT) and at follow-up (FU). The present umbrella review aimed to fill this gap and inform clinicians and guidelines with more differentiated results.

Methods

Search Strategy

Systematic search of Scopus/PsychInfo/PubMed, last search 11/15/2021 using the following search key: *"(schizophrenia OR schizoaffective OR schizo-affective OR psychosis OR psychotic) AND (therapy OR therapies OR treatment OR treatments OR remediation OR intervention OR care OR education OR training) AND (meta-analy* OR metaanaly* OR "systematic review")"*. A manual search was also conducted for supported employment interventions. Title/abstract, full text screening, data extraction and quality assessment were performed by ≥2 independent authors (JR, MS, GC, GP), resolving any discrepancy via consensus with a third author (CUC).

Inclusion and exclusion criteria

Included were network meta-analyses/meta-analyses [(N)MAs] of RCTs that reported on the efficacy of any psychosocial intervention vs. TAU or any other ACTIVE, in patients with a mean sample age ≥18 years, diagnosed with schizophrenia or related disorders (EP defined as a clinical diagnosis of psychosis within 5 years of the first psychotic episode or presentation to mental health services-first episode psychosis/schizoaffective disorder/schizophreniform disorder/psychotic disorder not otherwise specified, based on DSM/ICD diagnosis). Control conditions were merged into three groups: TAU (TAU/Inactive control), ACTIVE, MIXED (some RCTs ACTIVE, others TAU). (N)MAs with ≥1 direct comparison (which were prioritized over meta-analyses), and meta-analyses with the largest number of studies for the same combination of intervention, control, outcome, and time point of assessment were included.

Data Extraction, Outcomes, and Data Synthesis

We extracted the following descriptive information for each (N)MA: median RCT duration, number of studies, number of participants, mean patient age, mean percentage of males, and mean percentage of inpatients. Heterogeneity and standardized effect sizes with 95% confidence intervals (CIs) were extracted: for continuous outcomes,

standardized mean difference (SMD), Hedges' g, or Cohen's d; for dichotomous outcomes as odds ratios (ORs) or risk ratios (RRs). Based on time-point of assessment, every outcome was categorized into end-of-treatment or follow-up (≥12 months/longest follow-up of ≥2 time points after end-of-treatment).

Meta-analyses with any one of the following three conditions were re-calculated with Comprehensive Meta-Analysis v 2.0.[11]: non-standardized effect size measure (e.g., mean difference), included other-than RCTs, applied fixed-effects model with heterogeneity (I^2) >50%. For (N)MAs reporting on ≥1 effect size per combination of interventions, control (TAU/ACTIVE/Mixed), and outcome, the estimate with the largest number of studies was included.

The primary outcome was total symptoms reduction, as measured by validated scales (e.g., Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale). Secondary outcomes included positive, negative and depressive symptoms, cognition, global/social/employment functioning, hospitalization, relapse, quality of life (QoL), and all-cause discontinuation as a measure of acceptability. We also extracted any other outcome provided by the included NMAs/meta-analyses. Finally, as meta-analyses of RCTs are currently deemed among the highest levels of evidence, and thus provide a basis for recommendations guiding clinical practice, we also extracted the recommendation made by the authors for or against the intervention(s) they studied. As previously described in another systematic review[12], we coded this information as "no recommendation" (i.e., no conclusion made about a possible efficacy), "partial recommendation" (i.e., described as at least somewhat beneficial or promising), "complete recommendation" (i.e., explicit recommendation or statement regarding an advantage over the control condition), or "recommendation against".

Quality assessment of the Meta-Analyses.

Quality of included meta-analyses was assessed using the A Measurement Tool to Assess Systematic Reviews (AMSTAR)-PLUS tool (AMSTAR-PLUS range 0-11, AMSTAR-Content range 0-8),[12] to supplement AMSTAR-PLUS[13] with an assessment of the quality of meta-analyzed trials. For NMAs we modified items 9 ("Were the methods used to combine the findings of studies appropriate?") of AMSTAR-PLUS into "Did authors mention transitivity assumption, and inconsistency?", and AMSTAR-Content's item 5 ("Were the methods used to combine the findings of studies appropriate?") into "Did the NMA neglect/violate transitivity assumption, and were results affected by inconsistency?", maintaining the same scoring.[14] We categorized quality into three levels: low/medium/high (L/M/H). AMSTAR-PLUS score was considered low when <4, medium when 4-7, and high when >7. AMSTAR-Content score was classified low if <4, medium when 4-6, and high when >6. Overall quality of included studies was rated choosing the lower of the AMSTAR-PLUS and AMSTAR-Content scores.[14]

We also reported on the number of high-quality studies based on the Cochrane Collaboration Risk of Bias Tool[15] whenever the included MA had performed a quality assessment of included RCTs, or when it displayed necessary data for re-evaluation with the Cochrane Risk of Bias Tool (if another method had been used). If this wasn't possible, we included scores based on JADAD[16] and CTAM[17] scales, with respective high quality thresholds (>4 and >65). Finally, due to concerns that RCTs originating from the Republic of China are often strongly biased (i.e., inadequate protocol, randomization, data reporting)[18, 19], we included in the main analysis only NMAs and MAs with <50% of Chinese RCTs.

Statistical Analysis

We planned to assess whether the quality of the reported evidence moderated effect sizes and authors' recommendations via meta-regression when ≥10 effect sizes/interventions were available for a given outcome.[20]

Results

Systematic search results.

Out of the initial 8 971 hits, we screened 8 077 (title/abstract) after duplicate removal, with full-text review of 493 articles. We finally included 78 meta-analyses and five NMAs in our systematic review (Supplementary Figure 1), of which 73 were considered in the main manuscript (10 included ≥50% Chinese RCTs). Findings from (N)MAs including ≥50% Chinese RCTs are reported in Supplementary Results. Descriptive characteristics of included studies are displayed in Supplementary Table 1, and a list of excluded articles with reasons for exclusion is shown in Supplementary Table 2. Altogether, included studies described 34 different specific interventions, and 19 combinations of different interventions in 1 246 RCTs and 84 925 subjects (duplicates removed). Overall, 15 interventions or combinations of interventions were compared with TAU, two with ACTIVE, and the remaining 36 with both TAU and ACTIVE and/or vs Mixed control conditions. Seven meta-analyses and one NMA focused on EP (53 RCTs, 7 010 subjects), examining seven interventions and one combination of interventions compared with TAU in six meta-analyses, and compared with ACTIVE and Mixed in one each. Descriptions of included interventions and categorization of control interventions are available in Supplementary Tables 3-4. Results including (N)MAs with ≥50% Chinese RCTs are available in Supplementary Results and Supplementary Tables 5-7.

Due to the heterogeneous definition of family interventions adopted in different (N)MAs (i.e. skills and/or behavioural-based interventions, with or without patient involvement), we called mixed family interventions (FI-m)

results from MAs which pooled different interventions involving family, and called specific family interventions (FI-s) those following clearly defined manual-based family interventions. For FI-s, pooled median ES across specific FI interventions were calculated across interventions to simplify results reporting since those were consistently significant or not significant across individual specific interventions. Information about specific family interventions were found in two (N)MAs.[21, 22]

Here we will present results for primary and secondary outcomes, with ES magnitude, number of studies, and quality as stated in methods. All extracted outcomes are available in Supplementary Table 8. All the abbreviations used throughout the manuscript are reported in Table 1.

Primary outcome (total symptoms) – Early psychosis

For total symptoms, Early Intervention Services (EIS) outperformed TAU EoT (ES=small, k=8, H)[23] and FU (ES=small, k=4, H)[23], while no data were found regarding CBT or any FI.

Versus ACTIVE control, only FI-m was superior to ACTIVE FU (ES=medium, k=6, M).[24] (Table 2; Figure 1)

Secondary outcomes – Early psychosis

EIS outperformed TAU on many outcomes, including positive symptoms EoT (ES=small, k=10, H)[23], and FU (ES=small, k=5, H)[23], negative symptoms EoT (ES=small, k=10, H)[23] and FU (ES=small, k=5, H)[23], depressive symptoms EoT (ES=small, k=5, H)[23], relapse EoT (ES=small, k=3, H)[23], hospitalization EoT (ES=small, k=10, H)[23], quality of life EoT (ES=small, k=4, H)[23] and FU (ES=small, k=3, H)[23], global functioning EoT (ES=small, k=7, H)[23], employment EoT (ES=large, k=6, H)[23] and all-cause discontinuation EoT (ES=small, k=10, H)[23]. CBT was effective at FU regarding positive symptoms (ES=medium, k=3, L)[25] and negative symptoms (ES=small, k=3, L)[25]. FI-s were advantageous regarding relapse EoT (ES=medium, k=8, M)[22].

Compared to ACTIVE, FI-m was superior on FU for relapse (ES=small, k=6, M)[17], and global functioning (ES=large, k=6, M)[17], whereas CBT was only superior for global functioning EoT (ES=small, k=3, L)[26] (Table 2; Figure 2).

Primary outcome (total symptoms) – Schizophrenia

CBT outperformed TAU in symptom reduction both EoT (ES=small, k=72, M)[27] and FU (ES=small, k=4, M),[28] while other interventions were significant only at EoT: assertive community treatment (ACT) (ES=medium, k=72, M)[27], adherence therapy (AT) (ES=medium, k=6, L)[29], psychoeducation (EDU) (ES=small, k=72, M)[27], FI-m

(ES=small, k=72, M)[27] also multi-family group-delivered (ES=small, k=5, M)[30], FI-s (ES=large, k=37, M)[22], Mindfulness (MIN) (ES=large, k=72, M)[27], and SST (ES=small, k=90, M)[31] also group-delivered (ES=medium, k=11, M)[30].

Nine different interventions were not significantly different from TAU in symptom reduction, for eight of which data were available only EoT (Acceptance Commitment Therapy (ACTher), Cognitive Behavioral Family Therapy (CBFT), intensive Case Management (CM), CRT, Experience Focused Counselling (EFC), Hallucination Focused Integrative Treatment (HFIT), MetaCognitive Training (MCT), Social Cognitive Training (SCT), and one both EoT and FU (Supportive Therapy (SUP)). (Table 3; Figure 1).

Versus Mixed, efficacy emerged EoT for individual CRT (ES=small, k=76, M)[32] and group-delivered CRT (ES=small, k=17, M)[30], individual EDU (ES=small, k=4, M)[33] and group-delivered EDU (ES=small, k=8, M)[30], for social skills training (SST) at FU (ES=small, k=11, L)[34], and both EoT/FU for CBT (ES=small/small, k=34/12, L)[35, 36] and MIN (ES=medium/large, k=5/5, L)[37]. ACTher, group CBT, Facial Affect Recognition Training (FRT), group interpersonal therapy, group MCT, and SST were not superior EoT. CRT was no longer efficacious at FU. (eTable 6).

Versus ACTIVE, significantly better results emerged EoT for MIN (ES=medium, k=72, M)[27], mindfulness-based psychoeducation (ES=large, k=90, M)[31], SST (ES=small, k=90, M)[31], and FU for CBT (ES=small, k=9, M)[38]. Computerized Cognitive Drill and Practice Training (CCDPT), CRT, EDU, Eye Movement Desensitization and Reprocessing, FI-m, HFIT, MCT, Supportive counselling (SC) were not superior to any ACTIVE EoT, ACTher and SUP were not at FU. (eTable 7, Figure 1).

Secondary outcomes – Schizophrenia

CBT was superior to TAU for the highest number of outcomes at EoT, including: positive symptoms (ES=small, k=72)[27], negative symptoms (ES=small, k=72)[27], relapse (ES=small, k=72)[27], global functioning (ES=medium, k=72)[27], social functioning (ES=medium, k=3)[33], and quality of life (ES=small, k=7).[39] However, results were not confirmed at FU (or unavailable: social functioning, quality of life). FI-s improved positive symptoms EoT (ES=medium, k=24)[22] and relapse EoT/FU (ES=small/small, k=82/42)[22], FI-m global functioning EoT

(ES=large, k=7)[27] and relapse EoT/FU (ES=medium/medium, k=72/72)[27], EDU prevented relapse (ES=small, k=72)[27] and hospitalization (ES=medium, k=5)[40] only EoT, as CRT did on global cognition (ES=small, k=46)[32] and global functioning (ES=small, k=30)[32]. Relapse prevention programme reduced relapse EoT/FU (ES=medium/large, k=72/72)[27]; finally, ACT and HFIT improved positive symptoms (ES=large, k=72[27]; ES=medium, k=46[39]), CBFT negative symptoms (ES=large, k=2)[21], ACTher depressive symptoms (ES=medium, k=2)[37], MIN global functioning (ES=large, k=72)[27], broad-Social Cognitive Training (SCT) social functioning (ES=large, k=31)[41], only EoT. No differences emerged or were available regarding acceptability. AVATAR therapy, intensive Case Management, EFC, Individual Placement and Support (IPS), MCT, targeted SCT, SST, anti-stigma interventions and SUP did not significantly differ from TAU, and the vast majority of data pertained to EoT efficacy. (Table 3).

Against Mixed control, CRT demonstrated the widest effects, proving superior both EoT and FU for negative symptoms (ES=small, k=82[32]; ES=medium, k=15[42]), global cognition (ES=small, k=135[32]; ES=small, k=11[43]) and global functioning (ES=small, k=95[32]; ES=small, k=12[44]); EoT for positive symptoms (ES=small, k=79)[32], depressive symptoms (ES=small, k=14)[44] and social functioning (ES=small, k=21)[44]. SST proved efficacious for negative symptoms EoT/FU (ES=small/small, k=17/10)[34], and EoT regarding relapse (ES=small, k=9)[45] and social functioning (ES=small, k=17)[34]. Compensatory cognitive interventions (CCI) were beneficial EoT/FU for positive symptoms (ES=small/small, k=18/8)[46] and global functioning (ES=small/small, k=26/11)[46], and EoT for negative symptoms (ES=small, k=16)[46]. CBT was superior for positive symptoms EoT (ES=small, k=33)[35] and FU (ES=small, k=11)[47], and EoT for negative symptoms (ES=small, k=34)[35] and global functioning (ES=small, k=26)[48]. ACTher improved relapse (ES=medium, k=3)[33] and hospitalization (ES=medium, k=3)[37], EDU relapse (ES=small, k=7)[33] and social functioning (ES=small, k=4)[33], all only EoT. Finally, FI-m was efficacious only for relapse (ES=small, k=11)[49] and IPS for employment (ES=large, k=4)[50], all EoT (eTable 6)**.**

Versus ACTIVE, CBT was superior only FU for positive (ES=small, k=9)[51] and negative symptoms (ES=small, k=8)[51]. At EoT, CCDPT was superior to ACTIVE regarding positive symptoms (ES=small, k=10)[52] and depressive symptoms (ES=small, k=5)[52], and CRT regarding global cognition and global functioning (ES=small/small, k=26/21)[32]. MIN was superior only for negative symptoms EoT (ES=small, k=3)[37], and IPS for employment EoT (ES=medium, k=13)[53]. SUP was less effective than ACTIVE regarding positive symptoms EoT (ES=small, k=46)[39] and hospitalization FU (ES=small, k=4)[54], as EDU was for relapse EoT (ES=small,

k=72)[27]. Finally, ACTher, befriending, FI-m, FI-s, MCT, and SST did not significantly differ from ACTIVE for any outcome. (Supplementary Table 7).

Quality appraisal of included studies

Overall, the quality of the NMAs and meta-analyses was high regarding methodology (median AMSTAR-Plus score=8, IQR=2), but low when considering the quality of included RCTs (median AMSTAR-Content score=3, IQR=2). Out of 73 meta-analyses, only one[23] (1.3%) was rated high quality, 31[22, 24, 41–47, 51–53, 27, 54–63, 28, 64, 30–33, 38, 39] (42.5%) were rated medium quality, and the remaining 41[21, 25, 49, 50, 65–72, 26, 73–82, 29, 83–92, 34, 93, 35–37, 40, 48] (56.2%) had low quality. Overall, the median percentage of high-quality studies was 25.0% (mean=27%). The median percentage of high-quality RCTs was 40% (mean=40%) in high-quality meta-analyses, 23.0% (mean=27.0%) in medium-quality meta-analyses, and 25% (mean=26.0%) in low quality meta-analyses (Table 4).

Meta-regression

In the main analyses, for comparisons against TAU, quality was not a significant moderator of the effect size for total symptom change, even when including studies with ≥50% Chinese RCTs. For comparisons against Mixed, in main analyses, AMSTAR-Content lower quality significantly moderated larger effect sizes (beta=0.06 [0.03; 0.10], p<0.0001). Against ACTIVE, higher recommendations were associated with significantly lower effect sizes (beta=0.26 [0.01; 0.52], p=0.04) in the main analyses, which was maintained including studies with ≥50% Chinese RCTs (beta=0.30 [0.007; 0.60], p=0.04).

Discussion

To the best of our knowledge, this is the first umbrella review systematically and quantitatively assessing efficacy, acceptability, and quality from (N)MAs regarding psychosocial interventions in EP/schizophrenia. When pooling data from 73 meta-analyses (with <50% Chinese trials) in subjects diagnosed with EP/schizophrenia, with at least medium quality according to a-priori established criteria, the most solid evidence supported EIS/any FI for EP both EoT and FU, and supported CBT, CRT and, to a lesser extent, any FI, for schizophrenia regarding primary and secondary outcomes, either versus TAU or ACTIVE, both EoT and FU, and IPS for employment. Against Mixed control, CRT confirmed its beneficial profile, where efficacy of CBT and SST was supported by mostly low-quality evidence**;** also

CCI emerged as a possible resource. Across meta-analyses with <50% Chinese studies, the quality of the included studies was associated with the magnitude of the reported effect size only regarding Mixed control condition, mitigating potential concerns regarding the conclusions for TAU/ACTIVE comparisons derived from NMAs/meta-analyses including <50% of Chinese RCTs.

This systematic overview advances the field by filtering the enormous body of evidence on psychosocial interventions in EP/schizophrenia, keeping only top-tier evidence (i.e., (N)MAs of RCTs), rating its quality, and providing clinicians with an informative synopsis on what works better than TAU and/or ACTIVE, on which symptoms, at what time-points, and based on what quality of evidence. These findings provide more differentiated and fine-grained support for most of the main treatments suggested by NICE[6], RANZCP,[10] and CANPSY[8] plus CANCOM,[9] namely EIS, any FI in EP both EoT and FU on a wide range of outcomes, CBT and CRT in schizophrenia, at least EoT and on a narrower set of outcomes. Our results also do not support unrecommended art therapies or adherence treatment.

However, results are partially in contrast with PORT[7] guideline recommendations, again, at least in the EoT. First, CBT should not be reserved to non-responders to pharmacological treatment. Second, skills training and token economy interventions are not, according to the present results, supported by at least medium quality studies, nor are they superior to TAU. This discordance between our results and PORT might possibly be due to the fact that PORT recommendations were published >10 years ago.

Importantly, in EP, EIS are effective on a large set of outcomes, including both symptoms and functioning. In schizophrenia, CBT was the intervention whose efficacy persisted FU for the larger number of outcomes, with CRT following regarding specific domains. However, meta-analyzed data for the FU efficacy of other psychosocial interventions was almost absent; only family involvement looks beneficial for relapse prevention. Given that schizophrenia is a chronic disorder, the persistence of beneficial effects of psychosocial interventions in the medium/long-term is essential. Moreover, since depressive symptoms are frequent and associated with suicide risk in schizophrenia, CRT should also be considered for people with schizophrenia with depression. Finally, IPS was the only intervention efficacious for employment.

Overall, there seems to be a gap between the large set of outcomes that can be improved in EP as opposed to schizophrenia, and the maintenance of beneficial effects across the large number of outcomes during FU. It is unclear, however, whether a temporal “window of opportunity” exists during which there is a greater opportunity to modify

the schizophrenia course, and that missing to intervene with EP during this time frame negatively impacts the long-term outcome.[94, 95] Alternatively, it is also possible that the improved outcomes in EP compared to more chronically ill patients is due to the use of more comprehensive and integrated care models and programs for EP, and that similar programs could produce comparable benefits in more chronically ill patients, as has been shown before[96, 97].

This said, some important considerations should be made. Several other interventions have been explored by our review, not used in routine practice and regarding which knowledge is limited. For example, CCDPT emerged as an effective treatment versus other ACTIVE interventions for depressive symptoms (which are poorly targeted by the psychosocial interventions covered in our umbrella review), supported by medium quality evidence.[52] However, the RCTs included by this meta-analysis are highly heterogeneous and puzzling regarding randomization,[98] intervention,[99] control condition,[100] outcome measurement, raising questions about the quality of the actual meta-analysis in question.[101] Another example is CCI: the meta-analysis which studied this approach[46] included RCTs with such a broad range of different strategies that they lack cohesion as a type of intervention. Also, especially data from NMAs led to the inclusion of interventions not well established and with unclear differentiation from other already existing treatments (i.e., EFC, HFIT).

Also, even in better known interventions, issues of complexities and blending of different interventions and components emerged. For instance, FI-m appeared to include a wide range of related interventions that, even if similar for some aspects, may nevertheless have several differences; in this already difficult context, it appears even harder to understand a possible unique contribution of interventions such as family psychoeducation or cognitive behavioral family intervention. Only one recent NMA[22] specifically selected different family intervention approaches and provided individual data, where previous works pooled together interventions characterized by different components (e.g. psychoeducation only, addition of skills based/behavioural techniques, with/without patient involvement). A higher attention in reducing heterogeneity in interventions' design when analyzing efficacy and tolerability data would be desirable in order to increase the reliability and replicability of results.

More broadly speaking, some of the meta-analytic literature on psychosocial interventions in schizophrenia appears to be problematic in non-specific or incorrect methodology and terminology used, including that the terminology adopted by some authors of meta-analyses appeared idiosyncratic, not standard, or not consistent with previous research on similar interventions. Despite our effort to grade the quality of the evidence with an accurate tool, we believe that a

proper instrument to better evaluate quality of psychosocial interventions (N)MAs and RCTs is currently lacking and needs to be developed.

Surprisingly, very little evidence emerged for IPS effectiveness for employment, and from a meta-analysis[53] which again, more deeply investigated, appears inconsistent in terms of categorization of interventions and outcome assessment, likely because it investigated any treatments that aimed to increase employment. There are several other meta-analyses[102–104] supporting the efficacy of IPS, but which have been conducted in people with severe mental illness, without conducting specific analyses for schizophrenia. This fact could explain the apparent contradiction between little evidence in support of IPS in schizophrenia and positive results in other meta-analyses.

Furthermore, it is often unclear whether meta-analyzed outcomes match the purpose for which the intervention was delivered in the included RCTs. For example, an intervention delivered specifically for psychotic symptoms could have a little or non-significant effect on functioning, which might otherwise become larger if that symptomatic domain was included among the specific treatment goals. Additionally, differences in inclusion criteria across studies could influence results of studies targeting different outcomes. For example, some studies of CBTp target psychotic symptoms, and have inclusion criteria such as a certain level of severity, or persistence in psychotic symptoms. Another study of CBTp might target psychosocial functioning, and not have the same inclusion criterion regarding psychotic symptoms. The severity of psychotic symptoms might be much lower in the second group, reducing the potential for CBTp to further reduce psychotic symptoms in that sample. If CBTp had the same effect on people with prominent psychotic symptoms in both studies, the lower observed effect size for the second study would reduce the effect size of the first study when the data were combined, resulting in an under-estimate of the effects of CBTp on psychotic symptoms when they are present. Similarly, regarding family interventions, studies conducted with clients recently discharged from the hospital tend to find stronger effects for family intervention than studies conducted with stable outpatients, because the former group is at greater risk for relapse/rehospitalization, increasing the sensitivity of this outcome to change[105].

Limitations

Several limitations should be considered. First, we selected the largest meta-analyses, possibly excluding relevant individual RCTs or earlier meta-analyses of higher quality. Second, we pooled together the control conditions, leading to a loss of granularity regarding potential differences in the efficacy between different active treatment conditions. Third, the most common comparator, TAU, which is also not a homogeneous condition, is not equivalent to placebo.

Therefore, the effect sizes reported for psychosocial interventions may be underestimated. Fourth, psychosocial interventions can hardly be blinded for the patient, and rarely masked raters are used, possibly overestimating effect sizes, especially when compared to those reported for pharmacological interventions.[106] Fifth, the number of studies and participants varied across interventions, comparisons and outcomes. Sixth, far less data were available for FU outcomes. However, since schizophrenia is a chronic condition, such RCTs and their meta-analyses are much needed, despite difficulties of conducting them. Finally, included studies focused on adults.

Conclusions

With the previous said caveats and limitations, this umbrella review supports the advantages of EIS in EP, also involving family members as early as possible, in order to minimize relapse and maximize total, positive, negative symptoms, quality of life and functioning outcomes in the EoT and FU. In individuals with schizophrenia, CBT or CRT in conjunction with pharmacotherapy and family involvement should be first-line treatments, but more limited FU results should be expected. IPS is the only intervention that improves employment-related outcomes. Future studies should test CRT in EP, to assess whether its efficacy is confirmed. Furthermore, more FU RCTs of psychosocial interventions and large effectiveness studies in real-world samples are needed, as well as better designed (N)MAs.

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Authors' contribution statement

CUC, GC, JR, MS conceived the study. EE, GC, GP, MS, NDT, SR, conducted literature screening and data extraction including quality assessment. CUC, GC, KTM, MS, drafted the first version of the manuscript. All authors critically revised and finally approved the submitted version of the present work.

Supplementary information is available at MP's website.

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Figures and tables legends

Figure 1. Legend. EIS, early intervention services; ACT, acceptance-commitment therapy; AT, adherence therapy; BF, befriending; CBFT, cognitive-behavioral family therapy; CBT, cognitive-behavioral therapy; CCDPT, Computerize cognitive drill and practice training; EDU, psychoeducation, EFC, experience focused counselling; FI-m, mixed family intervention; FI-s, specific family interventions; FRT, facial affect recognition training; HFIT, hallucination focused integrative treatment; MCT, meta-cognitive training; SST, social skills training, SUP, supportive therapy. Dotted lines indicate low quality; continuous lines indicate medium/high quality. For FI-s, median ES is reported.

Figure 2. Legend. EP, early psychosis; ACT, assertive community treatment; ACTHer, acceptance commitment therapy AT, adherence therapy; AVATAR, AVATAR therapy; BF, befriending; CBFT, cognitive-behavioral family therapy; CBT, cognitive-behavioral therapy; CCDPT, Computerize cognitive drill and practice training; CCI, compensatory cognitive interventions; CM, intensive case management; CRT, cognitive remediation therapy; DT, distraction techniques; EDU, psychoeducation, EFC, experience focused counselling; EIS, early intervention services; EoT, end of treatment; FI-m, mixed family intervention; FI-s, specific family interventions; FRT, facial affect recognition training; FU, follow up; G, group intervention; HFIT, hallucination focused integrative treatment; IPS; individual placement and support; MCT, meta-cognitive training; MIN, mindfulness; RPP ,relapse prevention programme; b-SCT, broad social cognition training; t-SCT, targeted social cognition training; SCZ, schizophrenia; SST, social skills training; STI, anti-stigma intervention; SUP, supportive therapy; sympt, symptoms. Quality indicated as high (H), medium (M), low (L). Black cells indicate intervention worse than control for that outcome. No evidence was available vs MIXED for early psychosis. For FI-s, pooled median ES across specific FI interventions is reported.

Table 2. Legend. CBT, cognitive behavioral therapy; EDU, psychoeducation; EIS, early intervention services; FI-m, mixed family interventions; FI-s, specific family interventions; ns, not significant. Results are presented within each cell as effect size (ES), k (studies in MA), and quality (L for low, M for medium, H for high quality) according to AMSTAR-PLUS (AMSTAR: 0-3 = low, 4-7 = medium, 8-11 = high; AMSTAR-Content: 0-3 = low, 4-6 = medium; 7-9 = high, with final quality assigned as the lowest of the two scores). For FI-s, pooled median ES across specific FI interventions is reported.

Table 3. Legend. ACT, assertive community treatment; ACTher, acceptance commitment therapy; AT, adherence therapy; AVATAR, AVATAR therapy; CBFT, cognitive behavioral family therapy; CBT, cognitive behavioral therapy; CM, intensive case management; CRT, cognitive remediation therapy; EDU, psychoeducation; EFC, experience focused counselling; EIS, early intervention services; FI-m, mixed family interventions; FI-s, specific family interventions; G, group intervention; HFIT, hallucination focused integrative treatment; IPS, individual placement and support; MCT, metacognitive training; MIN, mindfulness; ns, not significant; RPP, relapse prevention programme; RR, risk ratio; b-SCT, broad social cognition training; t-SCT, targeted social cognition training; SMD, standardized mean difference; SST, social skills training; STI, anti-stigma interventions; SUP, supportive therapy. No data was available for primary and secondary outcomes vs TAU at the defined time points for the following interventions: befriending; cognitive remediation therapy; computerized cognitive drill and practice training; distraction techniques; E-health interventions; facial affect recognition

training; observation and imitation; supportive counselling, virtual reality. Results are presented within each cell as effect size (ES), k (studies in MA), and quality (L for low, M for medium, H for high quality) according to AMSTAR-PLUS (AMSTAR: 0-3 = low, 4-7 = medium, 8-11 = high; AMSTAR-Content: 0-3 = low, 4-6 = medium; 7-9 = high, with final quality assigned as the lowest of the two scores). For FI-s, pooled median ES across specific FI interventions is reported.

Table 4. Legend. AT, adherence therapy; CBFI, cognitive behavioral family therapy; CBT, cognitive behavioral therapy; CRT, cognitive remediation therapy; CCDPT, Computerize cognitive drill and practice training; EI, early intervention; FI-m, mixed family interventions; FI-s, specific family interventions; FRT, facial affect recognition training; IPS, individual placement and support; MCT, meta-cognitive training; NA, not ascertainable; O&I, observation and imitation; PE, psychoeducation; SE, supported employment; SST, social skills training; SYS, systemic therapy; 3WP, third wave psychotherapies.

Table 1. List of abbreviations used throughout the text.

Abbreviation	Meaning
ACT	Assertive Community Treatment
ACTher	Acceptance Commitment Therapy
AT	Adherence Therapy
CBFT	Cognitive Behavioral Family Therapy
CBT	Cognitive Behavioral Therapy
CCDPT	Computerised Cognitive Drill-and-Practice Training
CCI	Compensatory Cognitive Interventions
CI	Confidence Interval
CM	intensive Case Management
CRT	Cognitive Remediation Therapy
EDU	Psychoeducation
EFC	Experience Focused Counselling
EIS	Early Intervention Services
EoT	End of Treatment
EP	Early Psychosis
ES	Effect Size
FI	Family Interventions
FI-m	mixed Family Interventions
FI-s	specific Family Interventions
FRT	Facial affect Recognition Training
FU	Follow Up
H	High quality
HFIT	Hallucinations Focused Integrative Treatment
IPS	Individual Placement and Support
IQR	InterQuartile Range
L	Low quality
M	Medium quality
MCT	MetaCognitive Training
MIN	Mindfulness
(N)MA	(Network) Meta-Analyses
OR	Odds Ratio
QoL	Quality of Life
RCT	Randomized Controlled Trial

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RR	Risk Ratio
SC	Supportive Counselling
SCT	Social Cognitive Training
SMD	Standardized Mean Difference
SST	Social Skills Training
SUP	Supportive Therapy
TAU	Treatment As Usual

Table 2. Meta-analytic estimates of efficacy and acceptability of psychosocial interventions in subjects with early psychosis

Outcome	Total symptoms		Positive symptoms		Negative symptoms		Depressive symptoms		Cognition		Relapse		Hospitalization		Quality of Life		Global functioning		Social functioning		Employment		All-cause discontinuation	
Time-point	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**	**EoT**	**FU**
CBT vs TAU			ns, L[25]	SMD -0.6, L[25]	ns, L[25]	SMD -0.45, L[25]					ns, M[27]	ns, L[25]		ns, L[25]										
EDU vs TAU											ns, M[27]													
EIS vs TAU	SMD -0.32, H[23]	SMD -0.21, H[23]	SMD -0.22, H[23]	SMD -0.15, H[23]	SMD -0.28, H[23]	SMD -0.25, H[23]	SMD -0.19, H[23]	ns, H[23]			RR 0.71, H[23]		RR 0.74, H[23]		SMD -0.23, H[23]	SMD -0.27, H[23]	SMD -0.21, H[23]				SMD -0.89, H[23]		RR 0.70, H[23]	
FI-s vs TAU											OR 0.27, M[22]													
CBT vs Active																	Hedges' g -0.34, L[26]							
EDU vs Active											ns, M[27]													
FI-m vs Active		SMD -0.61, M[24]									ns, M[27]	RR 0.42, M[24]						SMD -1.36, M[24]						

Table 3. Meta-analytic estimates of efficacy and acceptability of psychosocial interventions compared with treatment as usual in subjects with schizophrenia

Outcome	Total symptoms		Positive symptoms		Negative symptoms		Depressive symptoms		Cognition		Relapse		Rehospitalization		Quality of Life		Global functioning		Social functioning		Employment		All-cause discontinuation	
Time-point	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU	EoT	FU
ACT	SMD -0.56, 72, M[27]		SMD -0.93, 72, M[27]		ns, 72, M[27]		ns, 72, M				ns, 72, M[27]	ns, 72, M			ns, 72, M[27]		ns, 72, M[27]						ns, 72 M[27]	
ACTher	ns, 37, M[39]				ns, 32, M[39]		SMD -0.63, 2, L[37]				ns, 72, M[27]						ns, 20, M[39]						ns, 72, M[27]	
AT	SMD -0.56, 6, L[29]																							
AVATAR					ns, 32, M[39]		ns, 22, M[39]																	
CBFT	ns, 2, L[21]		ns, 2, L[21]		SMD -1.17, 2, L[21]																			
CBT	SMD -0.38, 72, M[27]	SMD -0.19, 4, M[28]	SMD -0.29, 72, M[27]	ns, 3, M[28]	SMD -0.31, 72, M[27]	ns, 3, M[28]	ns, 72, M[27]	ns, 2, M[28]			OR 0.45, 72, M[27]	ns, 72, M[27]		ns, 4, L[38]	SMD -0.42, 7, M[39]		SMD -0.63, 72, M[27]	ns, 2, L[38]	SMD -0.68, 3, M[33]				ns, 72, M[27]	ns, 7, L[38]
CM	ns, 72, M[27]		ns, 72, M[27]		ns, 72, M[27]		ns, 72, M[27]				ns, 72, M[27]	ns, 72, M[27]			ns, 72, M[27]		ns, 72, M[27]						ns, 72, M[27]	
CRT	ns, 72, M[27]		ns, 2, M[33]						Cohen's d -0.28, 46, M[32]		ns, 72, M[27]	ns, 72, M[27]					Cohen's d -0.23, 30, M[32]						ns, 72, M[27]	
EDU	SMD -0.46, 72, M[27]						ns, 72, M[27]				OR 0.63, 72, M[27]	ns, 72, M[27]	Cohen's d -0.53, 5, L[40]	ns, 3, L[40]			ns, 72, M[27]						ns, 72, M[27]	
EFC	ns, 37, M[39]						ns, 22, M[39]																ns, 47, M[39]	
FI-m	SMD -0.31, 72, M[27]		ns, 72, M[27]		ns, 72, M[27]		ns, 72, M[27]				OR 0.35, 72, M[27]	OR 0.39, 72, M[27]		ns, 4, L[77]			SMD -1.43, 72, M[27]						ns, 72, M[27]	
FI-s	SMD -0.84, M[22]		SMD -0.60, M[22]		ns, M[22]		ns, M[22]				OR 0.49, M[22]	OR 0.38, M[22]			ns, M[22]		ns, M[22]						ns, M[22]	
G-FI	Hedges' g -0.39, 5, M[30]																							
HFIT	ns, 37, M[39]		SMD -0.69, 46, M[39]		ns, 32, M[39]		ns, 22, M[39]								ns, 7, M[39]		ns, 20, M[39]						ns, 47, M[39]	
IPS							ns, 3, M[64]								ns, 5, M[64]		ns, 3, M[64]							
MCT	ns, 37, M[39]		ns, 46, M[39]		ns, 32, M[39]																		ns, 47, M[39]	

MIN	SMD -1.07, 72, M[27]		ns, 46, M[39]				ns, 22, M[39]										SMD -1.26, 72, M[27]					ns, 72, M[27]	
RPP											OR 0.33, 72, M[27]	OR 0.22, 72, M[27]										ns, 72, M[27]	
b-SCT	ns, 31, M[41]																		Cohen's d -0.82, 31, M[41]					
t-SCT	ns, 31, M[41]																		ns, 31, M[41]					
SST	SMD -0.46, 90, M[31]		ns, 46, M[39]		ns, 32, M[39]						ns, 72, M[27]								ns, 5, L[34]				ns, 72, M[27]	
G-SST	Hedges' g -0.53, 11, M[30]																							
STI							ns, 2, L[83]	ns, 2, L[83]																
SUP	ns, 37, M[39]	ns, 2, L[54]	ns, 46, M[39]														ns, 20, M[39]					ns, 47, M[39]	

Table 4. Quality of included meta-analyses

Study (MA)	Intervention	Control	1.Double blinded studies	2.Sample size	3.Largest study	4. Observed cases data	5.Heterogeneity	6.Publication bias	Content Score	AMSTAR score	AMSTAR-Plus Total Score	Overall quality	High quality studies / k	% high quality studies
Allott 2020[46]	Compensatory cognitive interventions	Mixed	0	2	0	0	1	1	4	9	13	M	NA	60 %
Barnicot 2020[33]	Mixed	Mixed	0	2	1	0	0	1	4	8	12	M	2 / 34	5.9 %
Bighelli 2018[39]	Mixed	Mixed	0	2	1	1	1	1	6	10	16	M	5 / 53	9.4 %
Bighelli 2021[27]	Mixed	Mixed	0	2	1	1	0	1	5	10	15	M	1 / 72	1.4 %
Bird 2010[25]	CBT	TAU	0	1	0	1	0	0	2	8	10	L	NA	NA
Bond 2014[65]	EI + SE	TAU	0	2	0	0	1	0	3	4	7	L	NA	NA
Bordon 2017[66]	FRT	Mixed	0	0	0	0	0	0	0	7	7	L	0 / 8	0.0 %
Buckley 2015[54]	Supportive	Mixed	0	2	0	1	1	0	4	6	10	M	2 / 24	8.3 %
Burlingame 2020[30]	Group treatments	Mixed	0	2	0	1	0	1	4	8	12	M	12 / 52	23.1 %
Burns 2014[36]	CBT	Mixed	0	1	0	0	0	1	2	7	9	L	NA	NA
Camacho-Gomez 2019[24]	FI-m	Active	0	2	0	0	1	1	4	10	14	M	1 / 11	9.1 %
Campbell 2011[50]	IPS	Mixed	0	0	0	0	0	0	0	1	1	L	NA	NA
Carmona 2017[53]	Mixed	Mixed	0	2	1	0	1	1	5	9	14	M	NA	NA
Cella 2017[42]	CRT	Mixed	0	2	0	0	1	1	4	8	12	M	24 / 45	53.3 %
Cella 2020[85]	CRT	Mixed	0	2	0	1	0	0	3	10	13	L	0 / 20	0.0 %
Chan 2015[67]	CRT + SE	Active	0	1	0	0	0	1	2	9	11	L	2 / 8	25.0 %
Correll 2018[23]	EI	TAU	1	2	2	1	1	1	8	10	18	H	4 / 10	40.0 %
Crawford-Walker 2010[68]	Distraction	Mixed	0	0	0	1	0	0	1	10	11	L	0 / 5	0.0 %
d'Arma 2020[86]	Mixed	Mixed	0	2	0	0	1	0	3	7	10	L	1 / 20	5.0 %
Degnan 2018[69]	Mixed	Mixed	0	2	1	0	0	0	3	6	9	L	0 / 46	0.0 %
Eichner 2016[55]	MCT	Mixed	0	1	0	1	1	1	4	8	12	M	7 / 15	46.7 %
Frawley 2021[26]	IPS	Mixed	0	0	0	0	0	0	0	5	5	L	NA	NA
Fusar-Poli 2014[56]	Mixed	TAU	0	2	0	1	0	1	4	11	15	M	NA	NA
Gray 2016[29]	AT	TAU	0	1	0	0	0	0	1	8	9	L	3 / 6	50.0 %
Hazell 2016[70]	CBT- low intensity	Mixed	0	1	0	0	0	0	1	6	7	L	NA	NA
Heavens 2019[71]	CBT-anxiety	TAU	0	1	0	0	1	0	2	9	11	L	3 / 9	33.3 %
Jansen 2020[37]	Mixed	Mixed	0	2	1	0	0	0	3	10	13	L	2 / 16	12.5 %
Jauhar 2014[35]	CBT	Mixed	0	2	0	0	0	0	2	9	11	L	16 / 52	30.8 %
Jones 2004[38]	CBT	TAU	0	2	0	1	1	0	4	9	13	M	0 / 19	0.0 %
Jones 2018b[51]	CBT	Active	0	2	1	1	1	1	6	11	17	M	16 / 36	44.4 %
Kambeitz-Ilankovic 2019[44]	CRT	Mixed	0	2	0	0	1	1	4	8	12	M	NA	NA
Kurtz 2008[45]	SST	Mixed	0	2	1	0	1	1	5	6	11	M	NA	NA
Laws 2018[48]	CBT	Mixed	0	2	0	0	0	1	3	6	9	L	NA	NA
Lejeune 2021[87]	CRT	Mixed	0	2	0	0	0	0	2	8	10	L	41 / 72	56.9 %
Lincoln 2007[40]	PE	TAU	0	2	0	0	0	0	2	4	6	L	NA	NA
Liu 2018[72]	MCT	TAU	0	1	0	0	0	1	2	6	8	L	10 / 11	90.9 %
Lopez-Morinigo 2020[88]	MCT	Mixed	0	1	0	0	0	0	1	6	7	L	NA	NA

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Study (MA)	Intervention	Control	1.Double blinded studies	2.Sample size	3.Largest study	4. Observed cases data	5.Heterogeneity	6.Publication bias	Content Score	AMSTAR score	AMSTAR-Plus Total Score	Overall quality	High quality studies / k	% high quality studies
Louise 2018[73]	3WP	Mixed	0	1	0	0	1	1	3	10	13	L	6 / 10	60.0 %
Lutgens 2017[59]	Mixed	Mixed	0	2	2	1	0	0	5	9	14	M	NA	NA
Ma 2019[21]	CBFI	TAU	0	0	0	0	0	0	0	8	8	L	0 / 2	0 %
Mari 1994[74]	FI-m	TAU	0	0	0	1	0	0	1	3	4	L	NA	NA
McGlanaghy 2021[31]	Mixed	Mixed	0	2	1	1	1	0	5	7	12	M	14 / 90	15.0 %
Mehl 2015[57]	CBT	TAU	0	2	2	0	0	0	4	9	13	M	NA	NA
Nijman 2020[41]	Mixed	TAU	0	2	0	1	0	1	4	9	13	M	6 / 44	13.0 %
Orfanos 2015[75]	Group psychotherapy	Mixed	0	2	1	0	0	0	3	7	10	L	6 / 32	18.8 %
Paterson 2018[76]	Mixed	Mixed	0	2	0	0	0	0	2	10	12	L	1 / 6	16.7 %
Pilling 2002a[49]	FI-m	Mixed	0	2	0	1	0	0	3	5	8	L	NA	NA
Pilling 2002b[77]	SST, CRT	Mixed	0	0	0	1	0	0	1	3	4	L	NA	NA
Pina 2020[89]	Positive psychology interventions	TAU	0	0	0	0	0	0	0	7	7	L	NA	NA
Polese 2019[78]	CBT	TAU	0	1	0	0	1	1	3	10	13	L	NA	NA
Prikken 2018[52]	CCDPT	Active	0	2	0	0	1	1	4	10	14	M	6 / 24	25.0 %
Puntis 2020a[60]	EIS	TAU	0	2	1	1	1	0	5	11	16	M	1 / 4	25.0 %
Puntis 2020b[61]	EIS	TAU	0	1	1	1	1	0	4	11	15	M	1 / 3	33.3 %
Riehle 2020[62]	CBT	Mixed	0	1	1	1	1	1	5	6	11	M	NA	NA
Rodolico 2022[22]	FI-s	Mixed	0	2	1	1	1	1	6	9	15	M	0 / 82	0.0 %
Sarin 2011[28]	CBT	Mixed	0	2	2	1	0	0	5	8	13	M	22 / 22	100 %
Todorovic 2020[90]	CBT	TAU	0	1	0	0	1	0	2	10	12	L	2 / 4	50.0 %
Turner 2014[79]	Mixed	Active	0	2	1	0	0	0	3	9	12	L	14 / 48	29.2 %
Turner 2017[34]	SST	Mixed	0	2	0	0	0	0	2	7	9	L	0 / 27	0.0 %
Turner 2020a[63]	CBT	Active	0	2	1	0	0	1	4	6	10	M	0 / 23	0.0 %
Turner 2020b[91]	CBT	Mixed	0	2	1	0	0	0	3	8	11	L	24 / 35	68.6 %
Valiente 2019[58]	Mixed	Mixed	0	2	1	1	0	0	4	10	14	M	NA	NA
Valimaki 2012[80]	Virtual reality	TAU	0	0	0	0	1	0	1	7	8	L	0 / 3	0 %
Van der Krieke 2014[81]	E-health	TAU	0	2	0	0	0	0	2	8	10	L	NA	NA
Velthorst 2014[82]	CBT	Mixed	0	2	0	0	0	0	2	9	11	L	16 / 30	53.3 %
Vita 2021[32]	CRT	Mixed	0	2	1	1	1	1	6	10	16	M	73 / 135	54.1 %
Wallstroem 2021[64]	IPS	TAU	0	2	1	0	1	0	4	6	10	M	NA	NA
Wood 2016[83]	Anti-Stigma	TAU	0	1	0	0	1	0	2	9	11	L	NA	NA
Wood 2020[92]	Mixed	Mixed	0	2	1	0	0	0	3	9	12	L	0 / 18	0.0 %
Wykes 2011[43]	CRT	Mixed	0	2	0	1	0	1	4	9	13	M	13 / 39	33.3 %
Yeh 2019[84]	O&I	Mixed	0	0	0	0	1	1	2	8	10	L	4 / 14	28.6 %
Yeo 2021[93]	Social cognitive training	Mixed	0	2	0	0	0	0	2	8	10	L	12 / 42	28.6 %
Zimmermann 2005[47]	CBT	Mixed	0	2	2	0	0	0	4	3	7	M	NA	NA
			AMSTAR Content			AMSTAR-11			AMSTAR-PLUS Total			% high quality RCTs		
Median score (interquartile range)			3 (2)			8 (2)			11 (4)			25.0 %		