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Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis

A Systematic Review, Meta-analysis, and Meta-regression

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Key Points

Question

Are early intervention services superior to treatment as usual regarding symptom-related and illness-related treatment outcomes in patients with early-phase psychosis?

Findings

In this meta-analysis of 10 randomized clinical trials (n = 2176 patients), early intervention services were associated with better outcomes than treatment as usual at the end of treatment regarding all meta-analyzable outcomes. These outcomes included all-cause treatment discontinuation from early intervention services or treatment as usual and at least 1 psychiatric hospitalization.

Meaning

In early-phase psychosis, early intervention services were associated with superior outcomes compared with treatment as usual, which supports the need for funding and use of early intervention services in patients with early-phase psychosis.

Abstract

Importance

The value of early intervention in psychosis and allocation of public resources has long been debated because outcomes in people with schizophrenia spectrum disorders have remained suboptimal.

Objective

To compare early intervention services (EIS) with treatment as usual (TAU) for early-phase psychosis.

Data Sources

Systematic literature search of PubMed, PsycINFO, EMBASE, and ClinicalTrials.gov without language restrictions through June 6, 2017.

Study Selection

Randomized trials comparing EIS vs TAU in first-episode psychosis or early-phase schizophrenia spectrum disorders.

Data Extraction and Synthesis

This systematic review was conducted according to PRISMA guidelines. Three independent investigators extracted data for a random-effects meta-analysis and prespecified subgroup and meta-regression analyses.

Main Outcomes and Measures

The coprimary outcomes were all-cause treatment discontinuation and at least 1 psychiatric hospitalization during the treatment period.

Results

Across 10 randomized clinical trials (mean [SD] trial duration, 16.2 [7.4] months; range, 9-24 months) among 2176 patients (mean [SD] age, 27.5 [4.6] years; 1355 [62.3%] male), EIS was associated with better outcomes than TAU at the end of treatment for all 13 meta-analyzable outcomes. These outcomes included the following: all-cause treatment discontinuation (risk ratio [RR], 0.70; 95% CI, 0.61-0.80; $P < .001$), at least 1 psychiatric hospitalization (RR, 0.74; 95% CI, 0.61-0.90; $P = .003$), involvement in school or work (RR, 1.13; 95% CI, 1.03-1.24; $P = .01$), total symptom severity (standardized mean difference [SMD], −0.32; 95% CI, −0.47 to −0.17; $P < .001$), positive symptom severity (SMD, −0.22; 95% CI, −0.32 to −0.11; $P < .001$), and negative symptom severity (SMD, −0.28; 95% CI, −0.42 to −0.14; $P < .001$). Superiority of EIS regarding all outcomes was evident at 6, 9 to 12, and 18 to 24 months of treatment (except for general symptom severity and depressive symptom severity at 18-24 months).

Conclusions and Relevance

In early-phase psychosis, EIS are superior to TAU across all meta-analyzable outcomes. These results support the need for funding and use of EIS in patients with early-phase psychosis.

Introduction

Outcomes in people with schizophrenia spectrum disorders have remained suboptimal.[1] Schizophrenia is among the 10 most debilitating disorders in the United States,[2] being associated with high disability[3] and enormous personal and societal cost.[1]

The results of a 2013 meta-analysis[4] suggested that, during the last 5 decades, recovery from schizophrenia remained low (median, 13.5%), without significantly improving. Furthermore, individuals with schizophrenia die on average 15 to 20 years prematurely,[5,6,7] with an increasing mortality gap.[8] Because people with early-phase schizophrenia spectrum disorders have not endured many years of illness and functional decline and generally respond better to treatment, there has been an increasing focus on early identification and optimized treatment.[1,9] Several research programs for patients with early-phase schizophrenia spectrum disorders yielded promising results for early intervention services (EIS) that are specifically designed to meet the needs of patients with early-phase psychosis.[10] Early intervention services require a multidisciplinary team of mental health professionals who provide multimodal treatment, including different psychosocial and psychopharmacological interventions that are tailored to the needs of each patient. In EIS programs, these services are provided from one team in a coordinated, integrated fashion instead of referring patients to different health care providers for each service.[11,12,13,14,15] These programs aim at decreasing psychosis symptoms, improving functional outcomes, and reducing long-term disability during what has been called a critical illness period.[16]

In this context, the level of efficacy and effectiveness of EIS for patients with first-episode and early-phase schizophrenia spectrum disorders has been debated. This debate is especially true given necessary societal decisions about resource allocation and funding in times of health care cost cuts and frugality across the world.

To date, only 1 meta-analysis,[17] which included 4 randomized clinical trials (RCTs), has compared the effectiveness of EIS vs treatment as usual (TAU) for early-phase psychosis, indicating superiority of EIS approaches. Aside from the limited number of studies included, only published data were used, no subgroup or meta-regression analyses were conducted, and the time course of the treatment effect was not examined.

Because additional RCTs[9,18,19,20,21,22,23] of EIS vs TAU have been published, we conducted a comprehensive meta-analysis of all available studies, including additional unpublished data that we received from the authors of all meta-analyzed studies. We hypothesized that EIS would be superior to TAU and expected that a more comprehensive assessment of the treatment effects could inform our understanding of the influence of EIS programs and result in their refinement and implementation across the world.

Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A predetermined but unpublished protocol was followed (eMethods 1 in the Supplement).[24,25]

Literature Search

Three of us (B.G., A.P., and A.K.) independently conducted a systematic literature search in PubMed, PsycINFO, EMBASE, and ClinicalTrials.gov through June 6, 2017, without language restrictions. This search was supplemented by a manual review of reference lists from eligible publications and relevant review articles (eMethods 2 in the Supplement).

Inclusion Criteria

Inclusion criteria were 4-fold. First, a study had to be an RCT to be included. Second, participants had to have a study-defined diagnosis of first-episode psychosis or a study-defined diagnosis of early-phase schizophrenia spectrum disorders (schizophrenia, psychotic disorder not otherwise specified, schizoaffective disorder, schizophreniform disorder, or delusional disorder). Third, the study had to have EIS specifically designed for the needs of people with early-phase psychosis and consisting of a multimodal treatment program, including several psychosocial and psychopharmacological interventions (eg, case management, psychotherapy, supported employment and education, and family support) that are provided from one team in a coordinated, integrated fashion. Fourth, the study had to have a control group consisting of a nonspecialized TAU protocol. Excluded were RCTs randomizing patients to maintenance of EIS vs a step-down or less intense maintenance treatment.

Data Abstraction

Three of us (B.G., A.P., and A.K.) independently identified, checked, and extracted data from eligible trials for all follow-up time points of the treatment phase. Inconsistencies were resolved by involvement of a fourth reviewer (one of us, C.U.C.). Authors were contacted for missing information or unpublished original data.

Outcome and Data Synthesis

The coprimary outcomes were all-cause treatment discontinuation and at least 1 psychiatric hospitalization during the treatment period (excluding a potential initial hospitalization before the initiation of the EIS intervention). Treatment discontinuation is a commonly used outcome in psychiatric research because it is a good indicator of treatment failure for lack of efficacy or tolerability, safety, or acceptability (with nonadherence being a major problem with psychiatric interventions), while hospitalizations are an

indicator of marked symptom exacerbation or relapse, as well as of increased health care costs. Therefore, these coprimary outcomes are good indicators of real-life feasibility, acceptability, and effectiveness of an intervention.

Key secondary outcomes were involvement in school or work, total symptom severity improvement, and global functioning (including social and role functioning). These areas represent the illness itself, as well as additional burden of the disease that leads to a poor long-term prognosis.

Additional outcomes included the following: the mean number of psychiatric hospitalizations and bed-days during treatment, study-defined relapse, remission (symptom stability or minimum symptom severity) and recovery (symptom stability or minimum severity plus improved social, educational, and vocational attainment), symptom severity (positive, negative, general, and depressive symptoms[26]), and subjective quality of life. Details on outcome definitions and scales are provided in eMethods 3 in the Supplement.

All eligible trials were assessed for methodological quality using the Cochrane Collaboration's tool for assessing risk of bias.[27] We extracted data on study design and patient, illness, and treatment components.

Statistical Analysis

We conducted a random-effects meta-analysis[28] of outcomes for which at least 2 studies contributed data using Comprehensive Meta-Analysis, version 3 (http://www.meta-analysis.com) (performed by B.G.). Intent-to-treat data were used whenever possible. Continuous outcomes were expressed as the standardized mean difference (SMD), which equals Cohen *d*, preferring change scores (unless skewed, with the SD exceeding twice the mean) over time point and end point scores, while categorical data were expressed as the pooled risk ratio (RR) using the inverse variance method, each with their 95% CIs. Negative SMD favored EIS when smaller values are better (psychopathology), and positive SMD favored EIS when larger values are better (global functioning and quality of life). Effect sizes of 0.2 were considered small, effect sizes of 0.5 were considered medium, and effect sizes of 0.8 were considered large.[29] Risk ratios less than 1 indicate that a specific adverse categorical outcome (all-cause discontinuation, hospitalization, and relapse) occurred less frequently in EIS, and RRs greater than 1 indicate that a desired categorical outcome (remission, recovery, and involvement in school or work) occurred more frequently in EIS. For categorical outcomes, numbers needed to treat (NNTs) were calculated by dividing 1 by the absolute risk difference. Numbers needed to treat of 10 or less were considered clinically relevant.[30] We explored study heterogeneity using the χ^2 test of homogeneity and I^2 statistics, with $P < .05$ and $I^2 > 50\%$, respectively, indicating significant heterogeneity. All analyses were 2-tailed with an α of .05.

In the primary analyses, EIS and TAU were compared at study end point. We conducted subgroup and exploratory maximum likelihood random-effects meta-regression analyses of the coprimary outcomes and the 3 key secondary outcomes to identify potential moderators or mediators (eMethods 4 in the Supplement). To allow comparability of studies using the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) in the meta-regression, we converted the baseline BPRS scores to PANSS scores using an established method.[31] Treatment intensity was defined as the number of therapeutic interventions per month.

The following post hoc sensitivity analyses were added. First, meta-regression analyses were performed to investigate the potential influence of the overall attrition rate and between-group attrition difference on the coprimary outcomes and the 3 key secondary outcomes (eMethods 5 in the Supplement). Second, a subgroup analysis was performed that excluded 2 studies[20,22] from Mexico because their effect sizes were particularly large.

Finally, we inspected funnel plots. The regression test by Egger et al[32] and the trim-and-fill method by Duval and Tweedie[33] were used to examine the presence of publication bias.

Results

Search

The initial search identified 8935 records, and study selection procedures yielded 41 articles and 1 book chapter reporting on 10 meta-analyzable EIS trials (Figure 1 and eTable 1 in the Supplement). All studies were published, but unpublished data were obtained from all 10 studies to be included in the meta-analysis. Study authors either shared their original data set or reanalyzed the data as needed. Across the 10 RCTs, the mean (SD) trial duration was 16.2 (7.4) months (range, 9-24 months). Among 2176 total patients, the mean (SD) age was 27.5 (4.6) years, and 1355 (62.3%) were male.

Study, Patient, and Treatment Characteristics

Altogether, 10 studies[9,18,19,20,21,22,34,35,36,37] (n = 2176 patients) were included. Patients had a mean (SD) baseline PANSS-converted BPRS score of 72.8 (11.7) (9 studies), a mean (SD) total illness duration (defined as the interval between the onset of positive psychotic symptoms and the study entry) of 159.8 (125.4) weeks (6 studies), and a mean (SD) duration of untreated psychosis (DUP) (defined as the interval between the onset of positive psychotic symptoms and the first antipsychotic treatment) of 79.9 (71.1) weeks (5 studies). All EIS programs were team-based, multicomponent interventions, which included a mean (SD) of 4.8 (0.9) components (range, 4-6 components). All EIS interventions included psychopharmacological treatment by a licensed and qualified prescriber (with steady medication review and monitoring) and family psychoeducation and counseling. Other common components were cognitive behavior therapy (7 studies), family therapy (7 studies), vocational and educational counseling (5 studies), social skills training (5 studies), and crisis response team and crisis management (4 studies). Fidelity of EIS intervention was assessed in all studies via treatment and team supervision. Rating scales to measure fidelity were used in 6 studies, confirming medium to high fidelity in the 3 studies that reported measurement-based outcomes on the fidelity testing (more details are listed in Table 1, eTable 2, and eTable 3 and in the Supplement).

There was a 2-fold higher treatment intensity in EIS vs TAU (4 studies; ratio of EIS to TAU, 2.14; range, 1.36-3.00). The mean (SD) number of low-risk ratings across the 7 domains of the Cochrane Collaboration's tool for assessing risk of bias (higher numbers are better) was 5.2 (0.9) (range, 4-7), indicating an overall low risk of bias. Masking of participants and personnel was rated as high risk in all but 3 studies because knowledge of the treatment received is almost inevitable with these types of setting- and service-based interventions (eTable 4 and eTable 5 in the Supplement).

All-Cause Treatment Discontinuation

All-cause treatment discontinuation was significantly lower with EIS than with TAU (21.3% vs 31.3%) in 10 studies among 2173 patients (RR, 0.70; 95% CI, 0.61-0.80; $P < .001$; NNT, 12.4; 95% CI, 7.3-40.5; $P = .005$). The regression test by Egger et al[32] did not indicate publication bias (Figure 2 and eFigure 1 and eFigure 2 in the Supplement).

Effect sizes did not differ statistically between any analyzed subgroups (eTable 6 in the Supplement). Higher baseline PANSS negative scores were associated with even less treatment discontinuation in EIS (coefficient, −0.08; 95% CI, −0.15 to −0.01; $P = .03$).

At Least 1 Psychiatric Hospitalization

Risk of at least 1 psychiatric hospitalization in 10 studies among 2105 patients was significantly lower with EIS than TAU (32.3% vs 42.4%) (RR, 0.74; 95% CI, 0.61-0.90; $P = .003$; NNT, 10.1; 95% CI, 6.4-23.9; $P = .001$). The regression test by Egger et al[32] indicated potential publication bias. After statistical

adjustment for 5 potentially missing studies using the trim-and-fill method by Duval and Tweedie,[33] the RR increased to 0.87 (95% CI, 0.71-1.07) (Figure 2 and eFigure 3 and eFigure 4 in the Supplement).

In subgroup analyses, a significant between-subgroup difference was only found regarding presence or absence of fidelity monitoring. Studies that included fidelity monitoring had comparatively fewer hospitalizations with EIS than with TAU (RR, 0.88 vs 0.50; $P = .001$). In meta-regression analyses, larger study sample size was associated with lower hospitalization risk (coefficient, 0.001; 95% CI, 0.000-0.002; $P = .002$) (eTable 6 in the Supplement).

The number of psychiatric hospitalizations (mean [SD], 0.41 [0.30] for EIS and 0.59 [1.11] for TAU) and the number of bed-days during treatment (mean [SD], 21.20 [48.94] for EIS and 30.41 [61.05] for TAU) were significantly lower in EIS than in TAU. The SMD for hospitalizations was −0.17 (95% CI, −0.31 to −0.03; $P = .02$), and the SMD for bed-days was −0.17 (95% CI, −0.29 to −0.05; $P = .006$). These results are shown in eFigure 5 and eFigure 6 in the Supplement.

Total and Specific Symptom Severity

Total symptom severity improvement in 8 studies among 1179 patients was significantly greater in EIS than in TAU (SMD, −0.32; 95% CI, −0.47 to −0.17; $P < .001$). Effect sizes did not differ statistically between any analyzed subgroups. However, in meta-regression analyses of continuous variables, younger age, male sex, higher baseline symptom severity (PANSS total, PANSS negative, and PANSS positive), and percentage of patients with schizophrenia were each associated with larger advantages for EIS (Figure 2 and eTable 7 and eFigure 7 in the Supplement).

Superiority of EIS was supported by analysis of positive symptom severity (SMD, −0.22; 95% CI, −0.32 to −0.11; $P < .001$), negative symptom severity (SMD, −0.28; 95% CI, −0.42 to −0.14; $P < .001$), general symptom severity (SMD, −0.30; 95% CI, −0.47 to −0.13; $P = .001$), and depressive symptom severity (SMD, −0.19; 95% CI, −0.35 to −0.03; $P = .02$). These results are shown in Figure 2 and eFigures 8, 9, 10, and 11 in the Supplement.

Relapse, Remission, and Recovery

Relapse rates in 7 studies among 1275 patients were significantly lower in EIS than in TAU (19.6% [141 of 719] vs 29.1% [162 of 556]) (RR, 0.71; 95% CI, 0.53-0.93; $P = .01$; NNT, 10.0; 95% CI, 5.5-54.0; $P = .02$). Patients in EIS more often achieved study-defined remission in 7 studies among 1229 patients (57.3% vs 50.7%) (RR, 1.29; 95% CI, 1.07-1.55; $P = .007$; NNT, 5.7; 95% CI, 3.3-20.4; $P = .006$) and recovery in 3 studies among 640 patients (30.3% vs 27.6%) (RR, 1.24; 95% CI, 1.03-1.50; $P = .02$; NNT, 13.9; 95% CI, 5.6-27.5; $P = .19$) (eFigures 12, 13, and 14 in the Supplement).

Global Functioning and Involvement in School or Work

Global functioning in 7 studies among 1005 patients improved significantly more in EIS than in TAU (SMD, 0.21; 95% CI, 0.09-0.34; $P = .001$). The proportion of patients in school or employed in 6 studies among 1743 patients was significantly higher with EIS than with TAU (52.5% vs 45.3%) (RR, 1.13; 95% CI, 1.03-1.24; $P = .01$; NNT, 17.8; 95% CI, 9.8-100.0; $P = .02$) (Figure 2 and eTable 7, eFigure 15, and eFigure 16 in the Supplement). Effect sizes did not statistically differ in any subgroup analysis. In the meta-regression analyses, no significant moderators were identified (eTable 7 in the Supplement).

Quality of Life

Quality of life in 4 studies among 505 patients was significantly higher with EIS than with TAU (SMD, 0.23; 95% CI, 0.00-0.46; $P = .046$). Detailed results are shown in eFigure 17 in the Supplement.

Time Point Analyses

Superiority of EIS was consistent across almost all time points (6, 9-12, and 18-24 months of treatment). The exceptions were at 18 to 24 months for general symptom severity in 3 studies among 489 patients (SMD, −0.14; 95% CI, −0.32 to 0.04; $P = .12$) and for depressive symptom severity in 3 studies among 474 patients (SMD, −0.21; 95% CI, −0.51 to 0.08; $P = .16$) (Table 2).

Sensitivity Analyses

In the post hoc meta-regression analysis, the overall attrition rate and between-group attrition difference did not mediate any of the outcomes (eTable 6 and eTable 7 in the Supplement). The results of the post hoc subgroup analyses that excluded the 2 studies from Mexico essentially confirmed the findings of the entire available data set (eTable 8 in the Supplement).

Discussion

In this comprehensive meta-analysis of 10 RCTs (n = 2176), 6 to 24 months of EIS that consisted of 4 to 6 evidence-based[38] coordinated and integrated treatment components was associated with superior outcomes compared with TAU regarding all meta-analyzable outcomes. Our meta-analysis demonstrates that EIS programs, all of which comprised antipsychotic treatment and various psychosocial interventions, are associated with significant superiority to TAU across a wide range of clinically relevant outcomes, including hospitalization risk, bed-days, symptoms, and global functioning. The mean effect sizes were small for continuous outcomes, ranging from an SMD of −0.19 for depression symptom severity (for which patients were not selected) and an SMD of 0.21 for global functioning to an SMD of −0.32 for total symptom severity. Effect sizes were small to medium for categorical outcomes. For example, compared with TAU, participants in EIS had a 12.6% greater likelihood of being in school or employed (NNT, 17.8) and improved by 24% to 30% more than with TAU on other outcomes, such as remission (NNT, 5.7), relapse prevention (NNT, 10.0), hospitalization (NNT, 10.1), treatment engagement (NNT, 12.4), and recovery (NNT, 13.9).

The I^2 statistics describe the percentage of variation across studies that is due to heterogeneity rather than chance, all of which were less than 50% except for remission, for which I^2 was 68.9%, suggesting low outcome heterogeneity across studies. However, the respective 95% CIs imply some relevant heterogeneity of the treatment effect across the study populations, indicating that sources for this heterogeneity need to be identified that could help detect patient subgroups requiring a dynamic adaptation of EIS in terms of the intensity and duration of individual or combined EIS components.

Subgroup and meta-regression analyses were exploratory owing to the small number of studies. However, the results indicated robust findings across various potential sources of heterogeneity, such as study quality, observed case analyses, and lack of masking.

In the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study,[9] DUP less than 74 weeks (ie, the median) significantly increased effect sizes for the primary outcome of subjective quality of life from 0.31 to 0.54 and for total symptoms from −0.29 to −0.42. In contrast, in our meta-regression analysis, DUP did not significantly moderate the effectiveness of EIS. However, DUP data (provided by only 5 trials) varied greatly (mean, 9-194 weeks; median, 8-74 weeks). Only patient-level analyses can shed more light on the effect of DUP on the efficacy of EIS.

Superior involvement in school or work and global functioning were associated only with provision of vocational intervention and family therapy, respectively. These findings suggest that family involvement might independently improve symptomatic and functional outcomes, whereas educational or vocational rehabilitation succeeded in improving involvement in school and work. Both of these results should be investigated further.

The consistent significant advantage of EIS at the end of the intervention period in RCTs raises the question of generalizability of the findings to patients not captured in RCTs and of durability of the effects. Consistent with the treatment results in the meta-analyzed RCTs, the findings of a naturalistic, 10-year follow-up study[39] in Hong Kong using a matched historical control (n = 296) suggested that 2 years of EIS significantly reduced suicides and suicide attempts and resulted in fewer admissions (odds ratio [OR], 1.56; $P < .001$), shorter hospitalizations (OR, 1.29; $P = .04$), and longer employment tenure (OR, −0.28; $P < .001$). However, no differences emerged in psychotic symptoms, symptomatic remission, and functional recovery. In the German, naturalistic Integrated Care in Early Psychosis study[40] of EIS that included an early detection program, EIS (n = 120) was associated with better outcomes than a historical control (n = 105) at 1 year regarding remission, psychotic psychopathology, and global functioning. Although these superior findings may be driven by the addition of an early detection program, within the treated cohort, DUP did not appear to be predictive of the superior psychopathological and functional outcomes. However, as mentioned above, DUP was only reported in half of the studies and had a very heterogeneous distribution (weighted mean [SD], 79.9 [71.1] weeks), limiting the informative value of meta-regression analyses. Nevertheless, the addition of early detection elements as part of EIS that aim at reducing DUP could be considered in future studies. Moreover, studies should also include more minors to better represent the clinical sample of patients with early-phase psychosis.

Targeting the question of whether an extended duration of EIS would be superior to shorter intervention periods, an uncontrolled EIS study[41] reported that gains made at year 2 could be sustained or increased with EIS at a lower level for another 3 years. Two studies that randomized patients after 2 years of EIS to either extended EIS by 3 years vs TAU found beneficial effects at 5 years. The first study[42] found significant superiority of extended EIS for adherence, work alliance, and patient satisfaction, while the treatment effects remained stable in both groups. The second study[43] found a significant effect of EIS on the treatment duration and both positive and negative symptom remission. The treatment duration and treatment intensity had an independent effect on positive and negative symptoms and total symptoms, respectively. Another RCT[44] (n = 160) comparing extended EIS vs step-down treatment (even more intense than TAU) after 2 years of EIS indicated significant superiority of the 12-month extended EIS for several outcomes, such as negative and depressive symptoms, general psychopathology, global functioning, independent living skills, and work productivity. However, the fact that, in this study,[44] only 20% of patients achieved functional recovery (which included competitive employment) at year 3, as well as that supported employment and educational intervention outside of the context of EIS was successful in increasing vocational or educational attainment in first-episode psychosis,[45,46] suggests the need for greater focus on functional reintegration and employment or education.

Future research should focus on a better understanding of the sources of heterogeneity in treatment response. The research should seek to identify patient characteristics that determine the magnitude of gains overall and from individual EIS components, as well as their respective intensity and duration to achieve the targeted outcomes in the short term and in the long term. To allow comparability of the effects, EIS research studies and real-world programs should adhere to a set of treatment standards, although adaptations of EIS based on country and health care systems might be needed.[19] To allow meaningful comparisons of EIS across implementation sites and systems that will likely vary in their ability to improve different outcomes (probably reflecting their focus, priorities, and resources), EIS initiatives should also be oriented to a standard set of stakeholder-relevant outcomes (similar to the National Institute of Mental Health Early Psychosis Intervention Network[47]). In addition, information on the cost-effectiveness of specific EIS packages across variable treatment settings is needed.[45,46]

Given that schizophrenia is one of the disorders most associated with personal distress and societal cost,[1] sustaining gains achieved by EIS could be cost-effective.[48] Therefore, additional trials are needed that study different EIS extension vs step-down procedures for patient subgroups that can move between these

options based on identified needs. Such research is especially relevant because data from 3 programs suggest that 2 to 3 years,[49,50] 5 years,[49] 7 to 8 years,[51] or 10 years[52] after the discontinuation of EIS, the prior gains may largely be lost.

Limitations

Several limitations of this meta-analysis need to considered. Although we included 10 studies and 2176 patients (6 trials and 1554 patients more than the prior meta-analysis[10]), the numbers of trials and participants were modest, limiting the informative value of analyses regarding possible publication bias as well as subgroup and meta-regression analyses. Moreover, patient and treatment characteristics were heterogeneous in several dimensions, complicating the interpretation of independent effects of specific moderators and mediators, including the important variable of DUP, which is associated with the prognosis of psychosis in general and which also significantly moderated EIS outcomes.[9,53] In addition, the results for relapse, symptomatic remission, and recovery could be influenced by heterogeneous outcome definitions, although the same definitions were used for EIS and TAU in each individual study.

Furthermore, although 3 studies did not use masked assessors, this variable did not significantly moderate EIS superiority. Moreover, the only outcome potentially related to the variable of fidelity monitoring was a lower number of hospitalizations in EIS vs TAU in studies that reported fidelity monitoring outcomes.

Conversely, the TAU condition delivered by centers involved in an RCT may have consisted of care that is better and more comprehensive than real-world TAU, as indicated by the number of treatment elements and treatment intensity in TAU. If correct, this factor would have lowered effect sizes. Because the active treatment duration ranged from 6 to 24 months, we cannot comment on the efficacy of longer-term EIS interventions. Furthermore, the observed effect sizes were small to medium, and meta-analyzable cost-effectiveness data across variable settings and health care systems were lacking. Although each EIS program studied used 4 to 6 similar, evidence-based intervention components, differences in the choice and delivery of each component and in country-specific and setting-specific TAU conditions could be relevant. In addition, because each EIS program used 4 to 6 components, it was impossible to tease apart the effect of individual combinations of EIS elements. Finally, adherence to each of the treatments may have differed but was insufficiently reported.

Conclusions

Based on the results from this comprehensive meta-analysis, EIS was associated with better outcomes than TAU across many sources of variability. These findings should provide further impetus for the widespread implementation and funding of EIS in the United States and across the world, as has already begun.[54,55,56,57,58,59,60]

Notes

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eMethods 3. Overview Outcome Definitions and Scales

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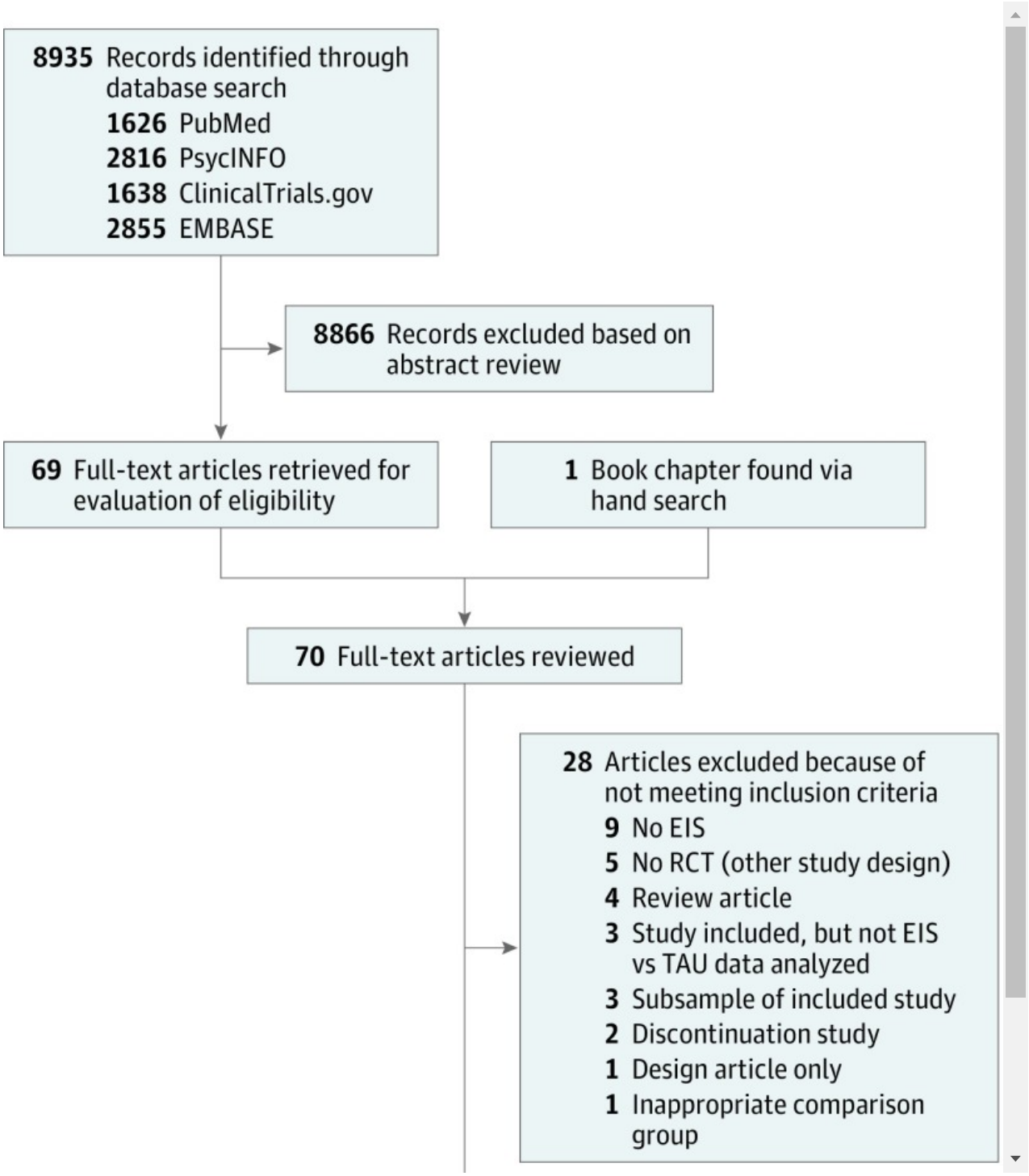
Figures and Tables

Figure 1.



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PRISMA Diagram of Included and Excluded Studies

EIS indicates early intervention services; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized clinical trial; and TAU, treatment as usual.

Table 1.

Study, Patient and Treatment Characteristics

Characteristic	Study Name					
	COAST[34]	JCEP[23]	LEO[35]	OPUS[36]	OTP[37]	PIANO[18]
Study Characteristics						
Duration, mo	9	24	18	24	24	9
No. of sites, location	1, South London/UK	1, Hong Kong	1, London/UK	5, Denmark	1, Norway	117, Italy
No. at baseline (EIS/TAU)	59 (32/27)	200 (100/100)	144 (71/73)	547 (275/272)	50 (30/20)	444 (272/172)
Inclusion criteria	1st Episode of any functional psychosis in past 5 y of contact	FEP according to *DSM IV*	≤2 Episodes of nonaffective PSY; SCZ; SzT; DEL	1st Episode SCZ spectrum d/o including DEL and SzT; ≤12 wk AP medication	Recent-onset SCZ (≤2 y since FEP), with more than 1 acute episode	1st Lifetime contact with the center fo any functio PSY
Early intervention services components	Medication review; vocational/ educational counseling; CBT; family PE/counseling; family therapy; crisis response team/crisis management	Medication review; vocational/ educational counseling; CBT; family PE/counseling; crisis response team/crisis management; SST	Medication review; vocational/ educational counseling; CBT; family PE/counseling	Medication review; family PE/counseling; family therapy; crisis response team/crisis management; SST	Medication review; CBT; family PE/counseling; family therapy; crisis response team/crisis management; SST	Medication review; CB family PE/counseli family thera
Patient Characteristics						
Age, mean (SD) [range]	28 (8) [8-65]	36.6 (8.7) [26-55]	26.3 (6.2) [16-40]	26.6 (6.4) [18-45]	25.4 (4.6) [18-35]	30.2 (9.6) [18-54]
Male, %	75	43	65	59	62	59

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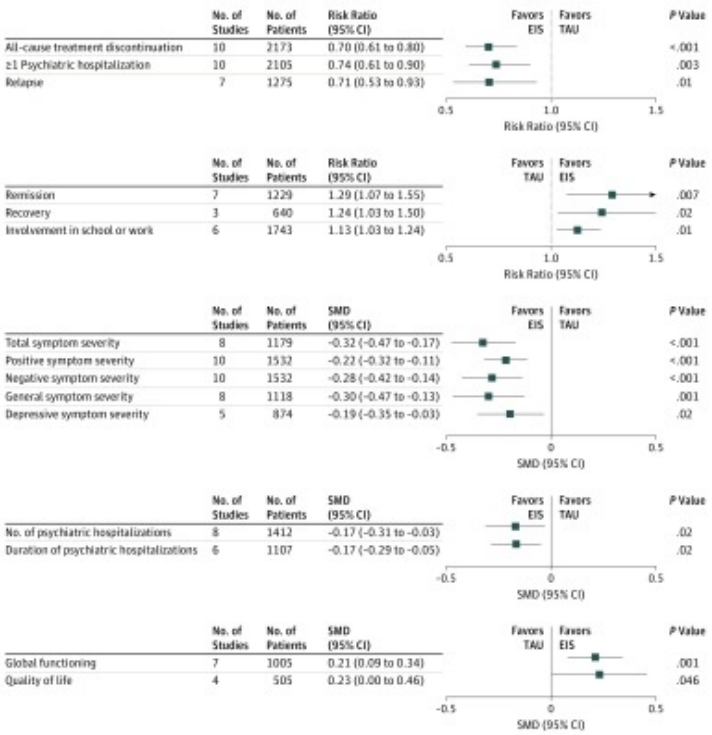
Abbreviations: AP, antipsychotic; BP, bipolar; CBT, cognitive behavioral therapy; COAST, Croydon Outreach and Assertive Support Team; DEL, delusional disorder; DUP, duration of untreated psychosis; EIS, early intervention services; FEP, first episode of psychosis; JCEP, Jockey Club Early Psychosis; LEO, Lambeth Early Onset; MDD, major depressive disorder; NOS, not otherwise specified; NR, not reported; OPUS, specialized assertive intervention; OTP, Optimal Treatment Project; PE, psychoeducation; PIANO, Psychosis: Early Intervention and Assessment of Needs and Outcome; PSY, psychosis; RAISE-ETP, Recovery After an Initial Schizophrenia Episode–Early Treatment

Program; SCZ, schizophrenia; SST, social skills training; STEP, Specialized Treatment Early in Psychosis; SzA, schizoaffective; SzA BP, schizoaffective bipolar; SzA DEP, SzA depressive; SzF, schizophreniform disorder; SzT, schizotypal disorder; TAU, treatment as usual.

Figure 2.



Summary of Pooled Results

EIS indicates early intervention services; SMD, standardized mean difference; and TAU, treatment as usual.

Table 2.

Outcomes at End Point and at Different Time Points[a]

Variable	Baseline to End Point					Short-term (6 mo)					Med
	No. of Studies (No. of Patients)	SMD (95% CI)	Result *P* Value	Heterogeneity *P* Value	Heterogeneity I^2	No. of Studies (No. of Patients)	SMD (95% CI)	Result *P* Value	Heterogeneity *P* Value	Heterogeneity I^2	No. Patie (No. Stud
Total symptom severity	8 (1179)	−0.322 (−0.474 to −0.170)	<.001	.18	31.7	4 (671)	−0.447 (−0.672 to −0.223)	<.001	.14	44.8	8 (11
Positive symptom severity	10 (1532)	−0.215 (−0.318 to −0.113)	<.001	.43	0.5	5 (695)	−0.306 (−0.497 to −0.116)	.002	.25	25.6	10 (153
Negative symptom severity	10 (1532)	−0.280 (−0.424 to −0.137)	<.001	.10	38.4	5 (695)	−0.333 (−0.527 to −0.139)	.001	.24	27.4	10 (153
General symptom severity	8 (1118)	−0.297 (−0.468 to −0.127)	.001	.11	40.2	5 (695)	−0.340 (−0.501 to −0.178)	<.001	.37	7.1	8 (11
Depressive symptom severity	5 (874)	−0.193 (−0.351 to −0.034)	.02	.30	17.9	3 (511)	−0.276 (−0.451 to −0.101)	.002	.58	0.0	5 (87
Global functioning[b]	7 (1005)	0.210 (0.085 to 0.336)	.001	.59	0	3 (286)	0.307 (0.026 to 0.589)	.03	.30	16.8	7 (10
Quality of life	4 (505)	0.230 (0.004 to	.046	.21	34.1	3 (544)	0.193 (0.024 to	.02	.51	0	2 (29

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Abbreviation: SMD, standardized mean difference.

[a]Negative SMD favored early intervention services when smaller values are better (psychopathology), and positive SMD favored early intervention services when larger values are better (global functioning and quality of life).
[b]Outcomes of 2 studies[20,22] were excluded from the analysis for being outliers, with effect sizes of greater than 2.4 favoring early intervention services.