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Effectiveness of Family Intervention for Preventing Relapse in First-Episode Psychosis Until 24 Months of Follow-up: A Systematic Review With Meta-analysis of Randomized Controlled Trials

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Background: **Relapse risk during the early years of first-episode psychosis (FEP) considerably increases the risk of chronicity. The effectiveness of family intervention for psychosis (FIp) for preventing relapse after FEP remains unknown. We assessed the effectiveness of FIp until 24 months of follow-up for preventing relapse and other relapse-related outcomes in patients following FEP.** ***Methods:*** **We searched the Cochrane, PubMed, PsycINFO, and ProQuest databases in June 2018. A systematic review with meta-analysis of randomized controlled trials (RCTs), sensitivity analyses, and publication bias were performed, comparing to treatment as usual (TAU) or TAU plus other psychosocial interventions. Outcomes assessed were relapse rates, duration of hospitalization, psychotic symptoms, and functionality. Risk ratios (RRs) and (standardized) mean differences (SMD; MD) were calculated.** ***Results:*** **Of the 2109 records retrieved, 14 (11 RCTs) were included. Pooled results showed that FIp was effective for preventing relapse (RR = 0.42; 95% CI = 0.29 to 0.61) compared to TAU and/or other psychosocial interventions. It also proved effective when compared to TAU alone (RR = 0.36) and TAU plus other psychosocial interventions (RR = 0.48). FIp showed benefits in reducing duration of hospitalization (TAU, MD = −3.31; other interventions, MD = −4.57) and psychotic symptoms (TAU, SMD = −0.68), and increased functionality (TAU, SMD = 1.36; other interventions, SMD = 1.41).** ***Conclusions:*** **These findings suggest that FIp is effective for reducing relapse rates, duration of hospitalization, and psychotic symptoms, and for increasing functionality in FEP patients up to 24 months. The study's main limitations were the inclusion of published research only; authors were not contacted for missing/additional data; and high heterogeneity regarding relapse definition was observed.**

Key words: family intervention/psychosis/relapse/randomized controlled trial/systematic review/meta-analysis

Introduction

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affective language, perception, and the sense of self. This condition can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies.[1] Schizophrenia affects more than 21 million people worldwide.[1] This mental disorder has a negative impact at a personal, family, and social level, resulting in neurological decline[2] accompanied by a range of cognitive deficits,[3] neurological soft signs,[4] and functional[5] and structural[6] brain alterations, which translate into a huge economic burden associated with disability and indirect costs due to lost productivity.[7]

Although antipsychotics have shown to significantly reduce positive symptoms of schizophrenia,[8] no substantial improvements in negative symptoms, cognitive deficits, or social functioning have been reported in earlier literature.[9] Furthermore, medication has some secondary effects which can cause low treatment adherence, thus increasing the risk of relapse.[10] Psychosocial interventions play a critical role in enhancing the patient's overall level of functioning, quality of life, and compliance with prescribed treatments that can help reduce the risk of relapse.[11,12]

A number of psychosocial interventions developed specifically for schizophrenia have received considerable empirical support. The most widely recommended psychosocial interventions are cognitive behavioral therapy (CBT) and family intervention for psychosis (FIp).[13]

Psychosocial interventions have shown to be an essential complement to pharmacological treatment in reducing psychotic symptoms[8]; in improving coping skills and psychosocial, emotional and behavioral adjustment[14]; and even in lessening the burden of family-related caregivers.[15]

The chronic course of schizophrenia emphasizes the need to implement interventions early on in this disorder.[16] First-episode psychosis (FEP) frequently occurs during adolescence and young adulthood; it is also associated with high stress levels, affective disorders, and suicide.[2] The first 5 years following FEP is seen as a critical period which entails increased cognitive decline,[17,18] and the risk of relapse is a predictive factor for the disease's trajectory.[17] It is estimated that 85% of patients relapse during the first few years of FEP, resulting in increased risk of chronicity and suicidal behaviors as well as impaired functional ability.[19] Hence, intervention soon after FEP is a useful strategy for preventing relapse and reducing disability due to schizophrenia.[2]

The role played by the relatives of patients with FEP is a topic of growing interest. The onset of FEP often manifests itself while the patient is still living at home with their parents.[20] Previous research has shown that FIp is effective for reducing relapse, improving social functioning, and mitigating the severity of psychotic symptoms and levels of expressed emotion in relatives at a more advanced stage of illness.[21,22] However, FIp's efficacy in preventing future relapses in the early stages remains unknown, and current evidence reports some inconsistencies[23] which preclude us from drawing firm conclusions.[10,24] Three previously published reviews assessed the efficacy of FIp when it comes to preventing future relapses: in a systematic review with no meta-analysis, the authors found FIp to be effective[24]; in a meta-analysis which included only one trial, efficacy was nonsignificant[10]; and in a review published in 2007, the authors observed how FIp may even be iatrogenic for patients with FEP.[23] However, a limited number of trials were included and identified in the aforementioned published reviews. Thus, further efficacy research is needed which includes more trials with meta-analysis to assesses FIp among patients with FEP in order to obtain evidence-based results on effectiveness.

The aim of this systematic review with meta-analysis is to assess the effectiveness of FIp for preventing second-episode psychosis (SEP) and other relapse-related outcomes until 24 months of follow-up in FEP patients within the first 5 years of onset compared to treatment as usual (TAU) and/or TAU plus other active psychosocial interventions including randomized controlled trials (RCTs) only.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[25] Please see supplementary material 1 for the PRISMA checklist.

Eligibility Criteria

We included studies that (a) published RCTs; (b) compared FIp delivered ≥6 months (The Schizophrenia Patient Outcomes Research Team [PORT] recommends that FIp should be delivered for at least 6 to 9 mo[26]) plus a pharmacotherapy condition according to individual study criteria (TAU) to either TAU or TAU plus non-FIp psychosocial interventions (eg, psychoeducation); (c) encompassed individuals with FEP <5 years; and (d) reported any post-intervention relapse (primary measure) or other relapse-related outcomes up to 24 months of follow-up. Secondary outcomes were duration of hospitalization, severity of psychotic symptoms, and functionality. TAU and relapse were defined as per criteria established in individual studies. Specifically, relapse was defined by authors when trials adopted pre-specified criteria or through rehospitalization due to exacerbated psychotic symptoms.

Search Strategy

Our primary search strategy was to conduct a database search of the Cochrane Library, PubMed, PsycINFO, and ProQuest; this was carried out on June 15, 2018. The following terms were searched and combined using the Boolean AND operator: ((“recent-onset” OR “early-onset” OR “first-episode” OR “early onset” OR “initial phase of” OR “early”) AND (“psychosis” OR “schizophrenia”) AND (“family intervention” OR “family therapy”) AND (“randomized controlled trial” OR “randomised controlled trial” OR “randomised-control trial” OR RCT)). The secondary strategy involved searching the reference list of included studies and relevant reviews. We only took into account articles published in English or Spanish.

Study Selection

The first author (M.C-G.) conducted the search. Once the database outputs were combined, all duplicate records were removed, and the titles and abstracts were screened (by M.C-G.). During the title and abstract review, we did not exclude any trials based on the outcome of interest (relapse or other relapse-related outcomes). Thus, we maximized the identification of relevant articles. This was because measures of relapse and other relapse-related outcomes are typically a secondary measure reported in primary studies, and are seldom mentioned in the title or abstract. Both authors (M.C-G. and P.C.) independently reviewed the full text and extracted data. They then came together to discuss all trials with study inclusion and data extraction inconsistencies. Decisions were made on these trials after consensus was reached. In total, 14 articles (11 RCTs) met full inclusion criteria. They were taken from 1622 initially screened records after excluding duplicates, of which 1575 were discarded.

Forty-seven articles were then full-text reviewed, resulting in 33 exclusions. Reasons for exclusion were as follows: 12 trials did not include patients with FEP; 10 trials did not deliver FIp; 4 trials did not assess relapse; 2 trials (3 articles) delivered FIp intervention <6 months; and 4 trials were excluded for other reasons (figure 1). Reasons for exclusion of full-text review references are presented in supplementary material 2.

Data Collection

The following data were collected: (a) sample size; (b) clinical and sociodemographic characteristics (age, patient type, diagnostic criteria); (c) type of FIp and comparison group delivered; (d) qualitative and quantitative results of primary and secondary measures; (e) quality assessment indicators; and (f) duration of follow-up.

Quality Assessment

Trial validity was measured using criteria from the Cochrane Collaboration's tool for assessing risk of bias.[27] This tool assesses potential sources of bias in RCTs, including (a) the adequate generation of allocation sequence; (b) the concealment of allocation to treatment conditions; (c) blinding of participants and personnel; (d) blinding of outcome assessors; (e) handling of incomplete data; (f) selective outcome reporting; and (g) other potential sources of bias. Participant and personnel blinding was assessed; however, it was not included in the general bias assessment given the difficulty in masking any condition groups for participants and personnel. FIp is inherently different from pharmacological conditions, and results may be biased for this domain. When it comes to multi-component therapies, relatives and even patients must receive training in intervention group assignment. Furthermore, the authors argue that they can easily identify the allocated arm. Both MCG and PC carried out the assessments. Ratings were cross-checked and any discrepancies was discussed and resolved.

Meta-analysis

Meta-analyses were performed for the 2 main comparisons: (a) FIp versus TAU and (b) FIp versus TAU plus alternative psychotherapy approaches. For the dichotomous variables, combined risk ratios (RRs) were estimated with 95% CIs. For the continuous variables, the mean difference (MD) was estimated when outcome measurements across all studies were made using the same scale. The standardized mean difference (SMD) was used when an outcome was measured using different

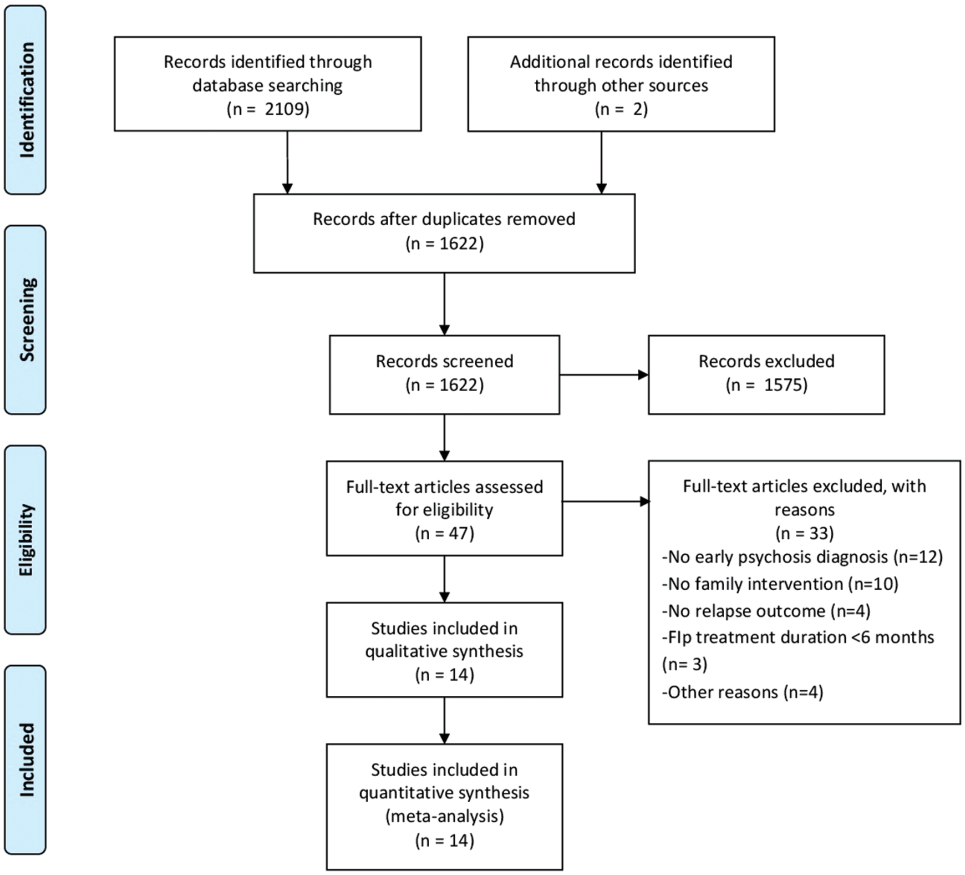

Fig. 1. PRISMA flowchart of literature search. For color, see the figure online.

quantitative scales.[28] Pooled estimates were assessed up to 24 months of follow-up.

We used random-effects meta-analyses to obtain pooled estimates, given that we observed between-study differences in several aspects, eg, (a) FIp content and methodology delivered to relatives; (b) duration of FIp delivered; (c) outcome measures and definition criteria; (d) follow-up assessments; and (e) clinical and sociodemographic characteristics (age, country, diagnostic criteria, and patient type).

To avoid unit of analysis problems, data from the Chien and Chan[29] (which delivered a design-two FIp arm and one TAU) were combined into a single group using each formula to obtain pooled means and SDs into a single sample size, respectively:

$$N = N_1 + N_2$$

$$M = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD = \sqrt{\frac{(N_1 - 1)\, SD_1^2 + (N_2 - 1)\, SD_2^2 + \frac{N_1 N_2}{N_1 + N_2} + (M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

Where N_x is the sample size, M_x is the mean, and SD_x is the standard deviation of each group 1 and 2, respectively.

Heterogeneity was assessed using the I^2 statistic. This test assesses the degree of heterogeneity, where a value of 0% to 40% indicates no observed heterogeneity; 30% to 60% shows moderate heterogeneity; 50% to 90% indicates substantial heterogeneity; and 75% to 100% shows considerable heterogeneity.[30]

We performed sensitivity analyses when substantial or considerable heterogeneity was detected for trials included in the meta-analyses. The following variables, except for the third criterion, were pre-specified in advance. They were considered moderating factors and, consequently, possible sources of heterogeneity. We excluded trials which were rated poor quality according to Agency for Healthcare Research and Quality (AHRQ) standards.[27,31] Poor quality was defined as one unmet criterion (eg, high risk of bias for one domain) or 2 unclear criteria, whose assessment was likely to have biased the outcome and pose important limitations that could invalidate the results, or 2 or more criteria with high or unclear risk of bias. We further excluded trials covering other psychosocial therapies in addition to FIp in the experimental group (multi-component integrated therapies). Finally, we discarded trials that adopted an instrument for assessing psychotic symptom severity and functionality that differs from most other trials. Studies classified as poor quality or at high risk of bias were included to improve understanding of any quality domain and transparency. However, we excluded them from our sensitivity analyses to determine whether or not methodological quality represented a source of heterogeneity.

Publication bias was assessed by inspecting the included trials through a funnel plot (scatterplot of treatment effect against a measure of study size).[32] In the absence of bias, the plot should resemble a symmetrical inverted funnel. An asymmetric funnel indicates a relationship between treatment effect and study size. This suggests the possibility of either publication bias or a systematic difference between smaller and larger studies. Namely, if publication bias exists, the largest published studies would likely report the smallest effects.[32]

Review Manager (RevMan) software was used to conduct all statistical analyses.[33]

Results

Characteristics of Included Studies

Eleven trials (14 articles)[29,34–49] met full inclusion criteria, encompassing a total of 1360 patients with FEP (table 1). Five trials were developed in Asia, 5 in Europe, and 1 in Australia. Patient ages across studies ranged from 16 to 40 years. Eight trials diagnosed mental disorder using DSM-IV criteria. Parents who participated in the study were the patients' main caregivers. The sample size of participating family members ranged from 1 to 15 per patient, the majority aged between 30 and 50 years. Both parents took part in most trials.

Of these 11 trials, 5 delivered FIp to relatives with the patient present. In 6 trials,[29,36,37,39,44,48,49] FIp was an adaptation of the manual published by other authors[50,51]; and in 3 trials FIp was administered by including individual and family multi-component integrated treatment, eg, cognitive behavioral therapy (CBT) and relapse prevention therapy (RPT).[41–43,48,49] Zhang et al[35] focused on educational and family group sessions plus antipsychotic medication. Chien et al[38] delivered a mutual support group centered around emotional expression, education, coping skills, and problem-solving; Chien[40] focused on psychoeducation and support group approaches; and Chien and Chan[29] held 2 FIp groups: (a) family-led mutual support groups; and (b) group psychoeducation for caregivers, both comprising 14 two-hour long group sessions. Seven trials compared FIp to TAU, and 3 trials compared FIp to TAU plus active psychotherapies other than FIp. In all trials that administered TAU plus other active psychotherapies as the comparison group, one trial administered TAU plus group psychoeducation for patients[38]; and 2 trials administered TAU plus individual or group education for patients or caregivers (the first delivered TAU plus individual education for patients[36] and the second TAU plus non-structured group intervention for caregivers and patients[44]).

In one trial, 2 comparison groups (TAU and TAU plus psychoeducation)[42] were extracted from the same sample, and no overall meta-analysis combining these groups was conducted when these trials were included in

Table 1. Characteristics of Included Studies

Study (y), Country	Patient Type	Diagnostic Criteria	Age (Mean)	Sample Size	Therapy Type	Comparison Group	Duration of Therapy	Follow-up	Adherence Rates
Zhang et al. (1994), China	FEP with schizophrenia	CMA	23.8	78	FIp focused on psychoeducation, mutual support and problem-solving + TAU	TAU (standard hospital out-patient service)	18 mo	18 mo	100%
Linzsen et al. (1996), The Netherlands	FEP with schizophrenia	DSM-IV	20.6	76	FIp based on manual (Falloon et al[50]): psychoeducation, communication skills and problem-solving + TAU	TAU + psychiatric management, individual education for patients and training in recognizing EWS of relapse	12 mo	12 mo	100%
Leavey et al. (2004), United Kingdom	FEP	ICD-10	No data	106	FIp based on manual (Falloon et al[50]): psychoeducation, communication skills and problem-solving + TAU	TAU (standard treatment from psychiatric services)	9 mo	9 mo	43%
Petersen et al. (2005); (Secher et al. 2015), Denmark	FEP	ICD-10	26.6	547	Assertive community treatment provided by multidisciplinary teams (1:10 caseload): social skill training, FIp (psychoeducational multi-family groups focusing on problem-solving procedures) and low-dose SGA	TAU (standard treatment at community mental health services, including contact with physician, nurse and social worker)	24 mo (FIp, 18 mo)	10 y	63%
Chien et al. (2006), Hong Kong	FEP with schizophrenia	DSM-IV	27.3	96	FIp focused on psychoeducation, mutual support and problem-solving + TAU	2 groups: TAU (hospital out-patient service); TAU + group psychoeducation for patients	6 mo	18 mo	78%
Chien & Wong (2007), Hong Kong	FEP with schizophrenia	DSM-IV	28.1	84	FIp based on manual (McFarlane et al[51]): structured psychoeducation and problem-solving + TAU	TAU (standard hospital out-patient service)	6 mo	12 mo	100%
Chien (2008), Hong Kong	FEP with schizophrenia	DSM-IV	25	68	FIp focused on psychoeducation and mutual support + TAU	TAU (standard hospital out-patient service)	8 mo	12 mo	94%
Gleeson et al. (2009, 2013), Australia	FEP	DSM-IV	20.1	81	Relapse prevention therapy: individual therapy and FIp (psychoeducation, problem-solving and relapse prevention) + TAU	TAU (standard treatment from EPPIC program)	9 mo	30 mo	72%
Palma-Sevillano et al. (2011), Spain	FEP with schizophrenia	DSM-IV	24	34	Motivational therapy: CBT and FIp (psychoeducation, communication skills and problem-solving) + TAU	TAU (standard treatment for the initial phase of schizophrenia)	12 mo	24 mo	94%

Table 1. Continued

Study (y), Country	Patient Type	Diagnostic Criteria	Age (Mean)	Sample Size	Therapy Type	Comparison Group	Duration of Therapy	Follow-up	Adherence Rates
Chien & Chan (2013), Hong Kong	FEP with schizophrenia	DSM-IV	24.3	135	2 FIp groups: (a) Family-led mutual support groups and (b) Group psychoeducation for caregivers (based on McFarlane et al[51]) +TAU	TAU (standard hospital out-patient service)	9 mo	24 mo	94%
Calvo et al. (2014, 2015), Spain	Adolescents with FEP	DSM-IV	16.1	55	FIp based on manual (McFarlane et al[51]): structured psychoeducation and problem-solving + TAU	TAU (individual psychiatric management) + non-structured group intervention for caregivers and patients	6mo	24mo	93%

Note: CBT, Cognitive behavioral therapy; CMA, Chinese Medical Association; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EWS, early warning signs; FEP, first-episode psychosis; FI, family intervention; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; TAU, treatment as usual.

the meta-analysis. This applied to duration of hospitalization. A study should contribute several independent comparisons, and the inclusion of multiple groups from a single study can create a unit-of-analysis error due to the unaddressed correlation between the estimated intervention effects from multiple comparisons.[28] As such, not including multiple groups from one study in a given meta-analysis is recommended.

Duration of FIp intervention ranged from 6 to 18 months. Post-treatment follow-up lasted between 6 and 24 months. Adherence, defined as the percentage of the sample who completed the FIp intervention, was ≥63% in most trials; adherence was <50% in only one trial.[37] Duration of hospitalization was measured as the number of days admitted to hospital following SEP. Patient functioning was assessed using the Specific Levels of Functioning Scale (SLOF)[52] and one trial adopted the Global Assessment of Functioning (GAF). Severity of psychotic symptoms was scored according to the Brief Psychiatric Rating Scale (BPRS)[53] and the Positive and Negative Syndrome Scale (PANSS).[54]

The authors' definitions of relapse were taken from 6 trials that considered relapse when assessing FIp efficacy. They were: (a) hospitalization in 4 trials; (b) ratings from 3 (mild) or below increasing to 6 or 7 (severe and very severe) on any of the following 3 BPRS items ((1) unusual thought content, (2) hallucinations, and (3) conceptual disorganization, meeting 1-wk duration criterion) in one trial[41,43]; and (c) the presence of all these 3 criteria: (1) recurrent or exacerbated psychotic symptoms explicitly recorded in psychiatric notes; (2) a significant increase in antipsychotic medication; and (3) psychotic symptoms persisting for at least 1 week in one trial[36] (table 2).

Risk of Bias Assessment

We assessed risk of bias across all domains of the Cochrane Collaboration's tool,[31] except for performance bias which has an inherent inability to mask individuals. Following assessment, the quality of included trials varied. Five trials reported adequate sequence generation; 7 trials reported adequate allocation concealment; 9 trials blinded relapse assessment; all trials reported attrition rates; only 2 trials reported enough outcomes; only one trial showed high risk of bias of other bias because the authors only included male subjects; and one trial reported an unclear risk of bias as the authors did not declare any funding sources (figure 2). Four trials met 5 good quality criteria, 4 trials met 4 criteria, 2 trials met 3 criteria, and just one trial met 2 criteria. According to AHRQ standards, 4 trials were rated good quality, 4 fair quality, and 3 poor quality.

Efficacy of Family Intervention for Preventing Relapses

Six comparisons were included in the meta-analysis (table 2 shows relapse rates during follow-up across all

Table 2. Relapse Rates of Studies Included in the Meta-analysis

Study	*N*º (FIG/CG)	Relapse Criteria	Relapse Rates *n*/*N* (%)	Decrease in Relapse
Zhang et al. (1994)	FIG: 32 CG: 31	Hospitalization	FIp: 5/32 (15.4%) CG: 17/31 (53.8%)	Significant
Linszent et al. (1996)	FIG: 37 CG: 39	Relapse defined as: (1) recurrent or exacerbated psychotic symptoms explicitly recorded in psychiatric notes; (2) a significant increase in antipsychotic medication; and (3) psychotic symptoms persisting for at least 1 wk. All 3 criteria must be present	FIp: 10/37 (27%) CG: 18/39 (50%)	Not significant
Leavey et al. (2004)	FIG: 57 CG: 49	Hospitalization	FIp: 6/57 (10.52%) CG: 6/49 (12.24%)	Not significant
Gleeson et al. (2010, 2013)	FIG: 41 CG: 40	Ratings from 3 (mild) or below increasing to 6 or 7 (severe and very severe) on any of the following 3 BPRS* items: (1) unusual thought content, (2) hallucinations, and (3) conceptual disorganization, meeting 1-wk duration criterion	7 mo, FIp: 2/34 (5.9%) CG: 8/37 (21.6%) 30 mo, FIp: 9/30 (30%) CG: 13/30 (43.3%)	Significant Not significant
Palma-Sevillano et al (2011)	FIG: 21 CG:13	Hospitalization	FIp: 4/21 (19%) CG: 9/13 (69.2%)	Not significant
Calvo et al (2014, 2015)	FIG: 27 CG: 25	Hospitalization	FIp: 4/27 (13%) CG: 12/25(50%)	Not significant

Note: BPRS, Brief Psychiatric Rating Scale; CG, comparison group; FIF, family intervention group; FIp, family intervention for psychosis.

trials included in the meta-analysis). In global terms, the meta-analysis showed significant reductions in relapse during follow-up in favor of FIp intervention up to 24 months of follow-up (RR = 0.42; 95% CI = 0.29 to 0.61) with no observed heterogeneity (I^2 = 1%). Subgroup analysis showed significant relapse reduction rates for FIp compared to TAU (RR = 0.36; 95% CI = 0.21 to 0.63) and other active interventions (RR = 0.48; 95% CI = 0.27 to 0.86), both with no observed heterogeneity (figure 3). Sensitivity analysis was not performed.

Efficacy of Family Intervention for Preventing Other Outcomes Related to Relapse

Duration of Hospitalization (Days). Eight FIp versus TAU comparisons on days of hospital readmission were included. Meta-analysis showed a significant mean reduction of 3.31 days in patients and relatives administered FIp compared to TAU at 24 months of follow-up (MD = −3.31; 95% CI = −6.48 to −0.14), with substantial heterogeneity (I^2 = 71%). When compared to other active interventions, a reduction of 4.57 days in favor of FIp (MD = −4.57; 95% CI = −7.49 to −1.65) was observed, indicating an absence of heterogeneity (supplementary material 3).

After conducting sensitivity analyses on trials excluding those that administered multi-component therapy,[41,43,48,49] we found reduced heterogeneity (I^2 = 39%), effective for fewer days of hospitalization when comparing FIp to TAU (MD = −4.80; 95% CI = −7.15 to −2.45). No reduction in heterogeneity was observed when we excluded low-quality studies[29,39,40] (supplementary material 6).

Psychotic Symptoms. Six comparisons were included in the meta-analysis. Patients with FEP subject to FIp intervention experienced a statistically significant reduction in psychotic symptoms compared to TAU at 24 months of follow-up (SMD = −0.68; 95% CI = −1.14 to −0.22), with substantial/considerable heterogeneity (I^2 = 76%). Sensitivity analyses excluding low-quality and high-risk-of-bias trials (I^2 = 76%),[29,35,39] trials that included other psychosocial therapies in addition to FIp (I^2 = 78%),[41–43] and the trial that assessed psychotic symptoms using the PANSS (I^2 = 80%)[42] showed no reductions in heterogeneity (supplementary material 6). Patients with FEP experienced nonsignificant reductions in psychotic symptoms compared to TAU plus other active interventions (SMD = −0.27; 95% CI = −0.82 to 0.28). Heterogeneity was not applicable (supplementary material 4).

Functionality. Six comparisons were included in the meta-analysis. FIp showed a statistically significant improvement in functionality level during follow-up compared to TAU at 24 months of follow-up (SMD = 1.36; 95% CI = 0.59 to 2.12) with considerable heterogeneity (I^2 = 94%), and to other active psychosocial interventions (SMD = 1.41; 95% CI = 0.87 to 1.96). Heterogeneity was not applicable (supplementary material 5).

Heterogeneity was not reduced after having performed sensitivity analyses on the functionality meta-analysis comparing FIp to TAU, when we excluded low-quality trials (I^2 = 96%),[29,39] excluding those trials that delivered multi-component therapy (I^2 = 73%)[48,49] and those that assessed functionality using the GAF scale (I^2 = 73%).[48,49] (supplementary material 6).

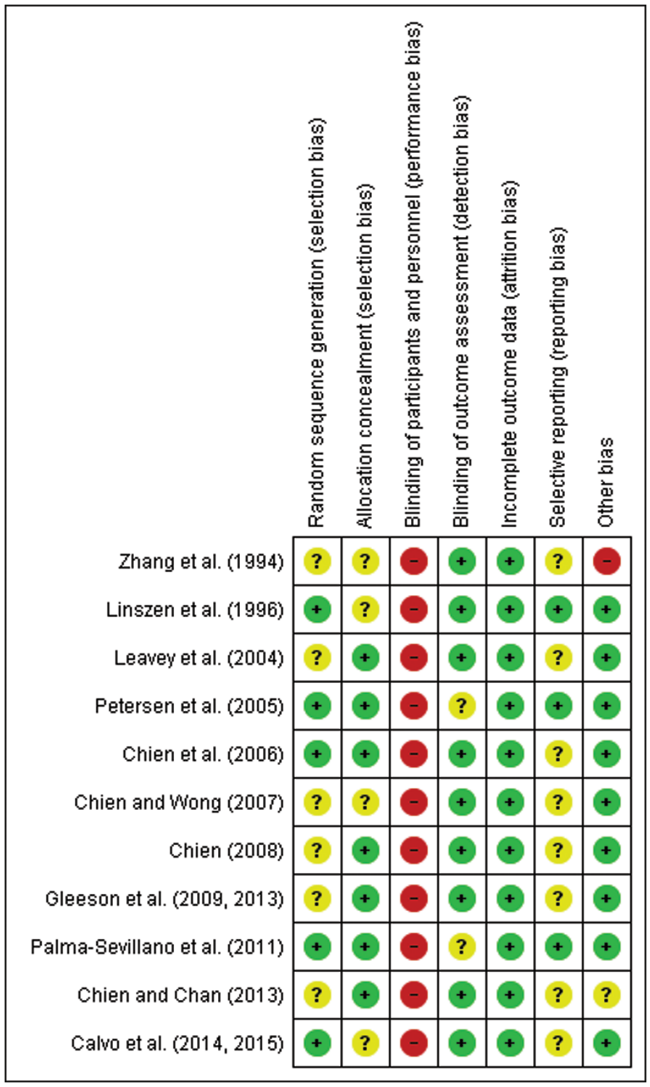

Fig. 2. Assessment of risk of bias in included studies. For color, see the figure online.

Publication Bias Analysis

There was no indication of asymmetry on the funnel plot for relapse rates, duration of hospitalization, or psychotic symptoms. For functionality, visual inspection suggests the presence of publication bias. This funnel plot suggest that positive results have more probability to be published than negative results (supplementary material 7). However, these results must be interpreted with caution given the limited number of trials included on the funnel plot.

Discussion

This meta-analysis examined the effectiveness of FIp for FEP on relapse, and on secondary relapse-related outcomes such as duration of hospitalization, severity of psychotic symptoms, and functionality up to 24 months. FIp was found to be more effective than TAU and TAU plus other psychosocial interventions. Psychoeducation and individual psychiatric management with education for patients and group education for caregivers and patients were compared at post-treatment in reducing relapse and duration of hospitalization, severity of psychotic symptoms, and in improving functionality in individuals with FEP up to 24 months post-treatment. Up to 24 months, estimated relative risk showed a 58% reduction in relapse risk; less days of hospitalization and reduced psychotic symptoms; and a significant improvement in functionality. These reductions were similar compared to TAU and TAU plus other active psychotherapies (in our meta-analysis, we identified trials that only delivered psychoeducation and individual or group psychiatric management with education for patients or caregivers plus TAU; no other interventions were compared), excepting for psychotic symptoms with nonsignificant results but only one comparison was included.

Our study offers new and useful insight into the effectiveness of FIp in patients with FEP for relapse and other relapse-related outcomes. For relapse, the effect size observed (RR = 0.42) compared to TAU or TAU plus psychoeducation was significant, encompassing 6 trials. A meta-analysis conducted in December 2008 and published in 2011 included only 2 trials and showed mixed results, concluding that further research is needed to determine FIp effectiveness among FEP patients.[10] Our study provides more evidence on the effectiveness of FIp for FEP compared to the aforementioned meta-analysis. Furthermore, although FIp has proved significantly effective for FEP, CBT has proved ineffective in patients with FEP[10] and schizophrenia[55] for reducing relapses, yet it is effective at mitigating the severity of psychotic symptoms according to 2 previous meta-analyses.[10,55] Thus, evidence suggests that FIp is a useful strategy for preventing relapse; however, other psychosocial interventions, including CBT, have shown to be effective at reducing psychotic symptoms. A likely useful prognosis-based approach for these patients would be multi-component integrated therapy which includes specific interventions that have demonstrated effectiveness for several outcomes. Regarding other relapse-related outcomes, no previous meta-analyses with pooled effect sizes in patients with FEP have been published. Yet authors have reported mixed results for reducing psychotic symptom severity in previous qualitative systematic reviews,[24,55,56] and argue that family intervention may be effective at improving social and interpersonal functionality.[21] In terms of duration of hospitalization, a lack of data provided little evidence of its effectiveness according to a previous systematic review.[10] Regardless, we found a clear benefit of FIp over pharmacology alone or alongside psychoeducation for individuals with FEP when it comes to duration of hospitalization, psychotic symptoms, and functionality, which previous systematic reviews did not report.

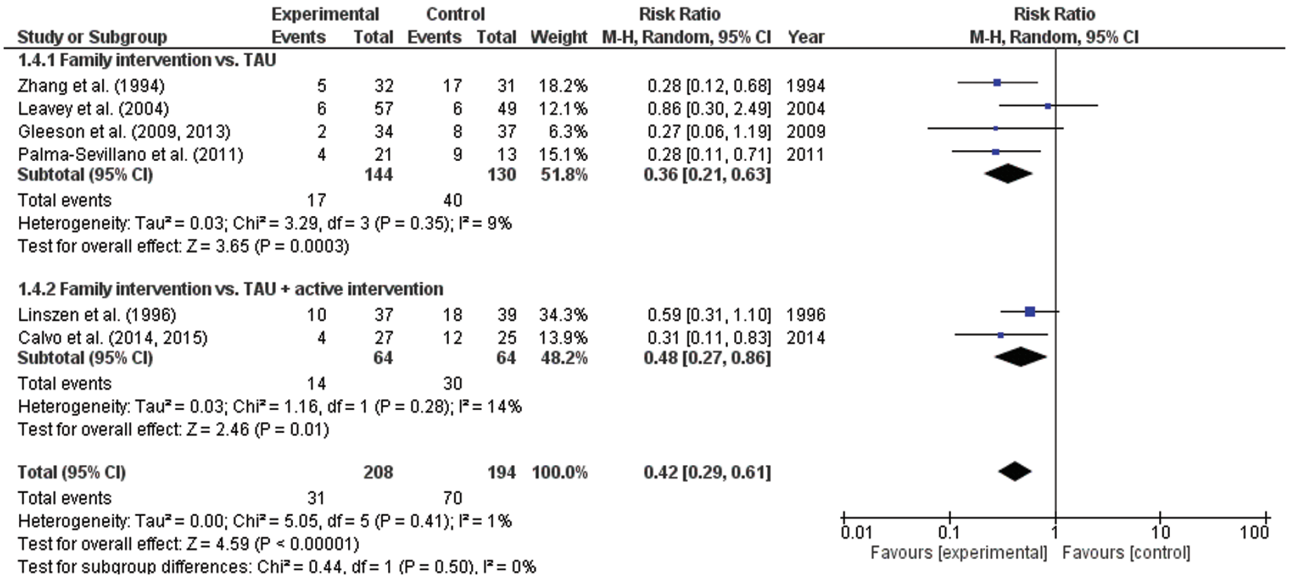

Fig. 3. Relapse-risk differences in first-episode psychosis (FEP) patients in studies comparing family intervention for psychosis (FIp) with treatment as usual (TAU) and/or TAU plus other active interventions. For color, see the figure online.

However, these results must be interpreted with caution. Despite the clinical benefits of FIp for FEP, these results only appear effective in the short to medium term (24 mo), and not in the long term (eg, 10 y) according to individual studies.[43,49] Furthermore, only 2 trials adopted a long-term approach, with one assessment at 30, 60, and 120 months, respectively. We identified only 3 trials that compared FIp to other psychosocial interventions; the key intervention component across all trials was educating about the illness. We found no trials comparing FIp to CBT. As such, further research is needed to compare other psychosocial interventions and their effectiveness. Lastly, and with the exception of relapse assessment, other meta-analyses showed substantial or considerable heterogeneity. Our results suggest that only whether the intervention encompasses multicomponent integrated therapy or not, may constitute sources of heterogeneity only for days of hospitalization. According to our results, study quality and the outcome assessment tool used were not a source of heterogeneity. Other non-assessed sources may include differences in availability and admission criteria for psychiatric hospitals across different regions and countries, and several TAU conditions have been observed in the included trials.

According to our study, FIp proved effective at reducing relapses in patients with FEP, which is also consistent with the effects observed in patients with schizophrenia.[21,22] Therefore, we recommend FIp intervention not only in schizophrenia but also at FEP. Evidence points to actively involving the relatives of patients with both recent psychosis onset and schizophrenia, thus contributing toward reducing relapse risk considerably. FIp may help relatives better understand this disorder and its impact on personal, social and interpersonal functioning, identify exacerbated psychotic symptoms, acquire problem-solving techniques during acute episodes, and gain awareness of the importance of treatment adherence.

Limitations

This study poses some limitations. First, the trials included in the meta-analysis varied substantially in terms of design and follow-up, the participants' clinical characteristics, the relapse criteria employed, and the outcome assessment instruments used. However, the pooled treatment effects across comparisons showed that all estimates were in the same direction before 24 months of follow-up; only one comparison in the duration of hospitalization meta-analysis took the opposite direction. This suggests that the RCT subgroups (eg, FIp programs alone or combined with other therapies) were clinically meaningful, and that comparisons were sufficiently homogeneous for obtaining summary effect estimates across subgroups.[28] Most relapse definitions included hospitalization only, whereas others covered additional specific criteria such as a significant increase in antipsychotic medication.[36] Some authors argue that other factors besides just hospitalization need to be taken into account to successfully define relapse; these include family functioning, support when leaving hospital, and adherence to treatment.[55] Thus, clinical consensus on defining relapse should be developed by clinicians and mental health professionals. Second, and as commented above, the duration of follow-up also varied across trials. While all trials included a follow-up of 6 to 24 months, studies differed with regard to the timing between baseline assessment and FIp intervention initiation, which may have influenced the relapse rates obtained. Moreover, given that previous research has found increased relapse rates over longer periods of time,[57] the findings from

the present meta-analysis can only be generalized to the first 2/3 years following treatment initiation. Third, only English and Spanish published trials were considered, meaning that relevant, other-language published trials were ruled out. Fourth, only a small number of trials were entered into the funnel plot to find evidence of publication bias. As such, we did not perform adequate formal testing for asymmetry, and our results for evidence of publication bias lacked robustness. Only in functionality assessment, results suggest that positive and significant and positive results are more likely to be published than nonsignificant and/or negative results. However, very few studies have been included in the funnel plot. Fifth, no previously published protocol of this systematic review was available. Sixth, only published studies were included in this systematic review. Missing data may have inflated our results, although having statistically significant results did not improve the chances of a study being published with leading biomedical journals.[58] Finally, the authors of the studies were not contacted to provide missing or additional data on patients with FEP or subsamples of schizophrenic patients who met inclusion criteria.

Clinical Implications

Evidence suggests that the first 5 years of FEP are crucial for the prognosis of psychotic disorder where deterioration occurs, doing so aggressively in the early years with more relapses, and that critical psychosocial influences, including family and psychological reactions to psychosis and psychiatric services, develop during this period.[17] Essentially, this period is marked by high relapse rates within 5 years of recovery, and this risk may decline with the maintenance of antipsychotic drug treatment[57] as well as with FIp, as our pooled results suggest.

Relapse in early phase psychosis increases chronicity[59] and suicide risk[60] and worsens psychosocial functioning[61] and family relationships.[62] Furthermore, economic analyses have indicated that the cost associated with treating psychosis relapse is 4 times that of stable psychosis.[63] Adolescents and youth who experience FEP usually still live at home, and family-based intervention can have positive effects on patients when it comes to preventing relapse and improving the course and development of psychotic disorder,[64] thus rendering it more cost-effective.[65]

Although intervention in early phase psychosis is considered clinically relevant, our systematic review is the only study to specifically assess FIp effectiveness early on. Our results echo the promising results from previous reviews[10,23,24] and replicate the obtained results at the more advanced stages of illness.[21,22]

Future Research

As commented above, FIp is effective in the short term to medium term (≤24 mo). As such, RCT trials with FIp delivered more than 6 months[26] and with relapse definition consensus reached by clinicians, reporting good, solid clinical psychometric properties[50,51,66] for improving comparability across studies and/or with more than 2 years' follow-up, are needed to establish FIp effectiveness. Sending reminders to the relatives of patients with FEP after treatment would likely be an appropriate strategy for preventing future relapses.

Furthermore, future FIp interventions should seek to identify symptoms relative to the period before a psychotic episode occurs and prevent risk factors to enhance their effectiveness. Before a psychotic episode, most patients experience impaired functional capacity alongside increasing negative symptoms, followed by positive symptoms which build in intensity, severity, and frequency as the psychotic episode approaches.[8] The overriding risk factors associated with a psychotic episode which should be prevented are non-adherence with medication, persistent substance use disorder, carers' criticism, and poorer premorbid adjustment.[67] Additionally, there is no evidence to suggest that FIp is more effective than CBT for relapses in patients with FEP given the lack of primary studies comparing the effectiveness of these interventions, and considering that no network meta-analyses featuring indirect comparisons have been published to date.

Finally, multi-component integrated therapies which encompass FIp plus other psychosocial therapies with evidence-based results on outcome efficacy are needed to improve the prognosis of patients with FEP. For example, CBT therapy has shown to be effective in improving psychotic symptoms,[24] whereas early intervention services are successful for tackling psychotic symptoms, adherence to treatment, relapse reduction, and school and work involvement.[68]

To conclude, the current study has shown that FIp for FEP is effective at reducing not only relapse but also episode severity in terms of duration of hospitalization, psychotic symptoms, and functionality up to 24 months after treatment initiation. The current findings also indicate that FIp is more effective than TAU and TAU plus other psychosocial interventions, as our meta-analysis suggests.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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