

## Special Article - Schizophrenia &amp; Psychosis

# Meta-Review of Systematic and Meta-Analytic Reviews on Family Psychoeducation for Schizophrenia

Petretto DR\*, Lussu C, Zuddas C, Pistis I, Piras P, Preti A and Masala C

Department of Education, Psychology, Philosophy,  
University of Cagliari, Italy

\*Corresponding author: Donatella Rita Petretto,  
Department of Education, Psychology, Philosophy,  
University of Cagliari, Italy

Received: March 27, 2017; Accepted: May 05, 2017;

Published: May 23, 2017

## Abstract

The purpose of family psychoeducation is to increase patients' and their families' knowledge and understanding of their illness and treatment. Improved knowledge of schizophrenia is expected to enable people to cope better with their illness. The aim of this review is to summarize and appraise evidence from published systematic and meta-analytic reviews on family psychoeducation in schizophrenia. Thorough search and analysis of reviews on efficacy of family psychoeducation in schizophrenia were carried out in PubMed/Medline (1987-2015), Ovid/Psych Info (1987-2015), and the Cochrane Database of Systematic Reviews. We included only reviews reporting quantitative summary statistics on studies carried out in patients with schizophrenia and written in English. Review methodology was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. Double check by two independent assessors was applied. Nine reviews meeting inclusion/exclusion criteria were included in the meta-review. Risk of relapse was reduced in protocols that included family members, whether conducted in single family or in multifamily group sessions. However, effectiveness seems not to be maintained at follow-up. Hospital admission/re-hospitalization was less influenced by family psychoeducation, and no reproducible effect on compliance/medication adherence was found. Overall, quality of evidence on the effectiveness of family psychoeducation in schizophrenia is poor.

**Keywords:** Schizophrenia; Psychoeducation; Family; Interventions; Meta-analysis; Meta-review

## Introduction

Schizophrenia and related psychoses are severe mental disorders with a high impact in terms of disability and poor quality of life. The clinical course of schizophrenia is typically one of highly recurrent acute episodes with chronic impairment of social, vocational and personal wellbeing [1-3]. The costs for patients, their families and society are huge, and largely generated by the direct cost of care, especially hospitalization [4-6].

Currently, pharmacotherapy is the most important therapeutic intervention in the treatment of schizophrenia-spectrum psychoses. However, response rate is limited to 60% of treated patients, and about 1 in 3 people have an illness with a "treatment resistant" course [7,8].

Many educational programs have been aimed at improving knowledge of the disorder, its symptoms, course and outcome, and the availability of treatment, and have focused specifically on the patients and their families [9-14].

The purpose of family psychoeducation is to increase patients' and their families' knowledge and understanding of their illness and treatment. Improved knowledge of schizophrenia is expected to enable people to cope better with their illness [9,15,16]. Studies on the effectiveness of these programs have found medium-sized protective effects against the risk of relapse and the probability of readmission [12,14]. Overall, evidence on the effectiveness of

family psychoeducation in schizophrenia is sparse, and it is unclear what specific outcomes are affected and how. The aim of this review is to summarize and appraise evidence from published systematic and meta-analytic reviews on family psychoeducation in schizophrenia.

## Methods

Search was based on the following electronic databases: PubMed/Medline (1987-2015), Ovid/Psych INFO (1987-2015), and Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2016). A combination of the following keywords was used: (1) type of paper: systematic review or meta-analysis; (2) population: psychosis or schizophrenia; (3) intervention: family psychoeducation. Only published studies in English were included: there is evidence that "systematic reviews that are based on a search of English language literature that is accessible in the major bibliographic databases will often produce results that are close to those obtained from reviews based on more comprehensive searches that are free of language restrictions" [17]. The so-called "gray" literature was excluded, since selection bias in unpublished literature searches was found to be higher than in published literature [17,18].

Retrieved abstracts were scanned for relevance, and the full paper was retrieved only for the studies matching the inclusion criteria. The reference list of the retrieved reviews was examined, too, to identify potential additional studies. We included only reviews reporting summary statistics on family psychoeducation from studies carried out in patients with schizophrenia.

**Table 1:** Characteristics of reviews which met the inclusion criteria.

	Author(s) (Year)	Professional field of the reviewers	Type of review	Topic of review	No. of reviewed studies	Year range of the studies	Total no. of subjects	Outcome variables
1	[24]	Psychiatry	Systematic review	Psychoeducation in schizophrenia	k=15	1966-1993	1341	- relapse
2	[39]	Psychiatry	Systematic review	Psychosocial treatment in schizophrenia	k= 16	1978-1995	4099	- relapse
3	[40]	Psychiatry	Meta-analysis	Family Interventions in Schizophrenia	k=25	1977-1997	2.692	- relapse
4	[23]	Psychiatry	Systematic review & meta-analysis	Schizophrenia or related serious mental illness	k=10	1966-1999	1125	- relapse - rehospitalisation
5	[27]	Psychiatry	Systematic review & meta analysis	Family intervention and cognitive behaviour therapy in schizophrenia or related disorder	k=18	1980-1999	1467	- relapse - readmission
6	[41]	Psychiatry	Systematic review	Psychosocial interventions for improving medication adherence in schizophrenia	Psychoeducation k=12	1980-2000	1409 (cal- culated)	- medication adherence
7	[28]	Psychiatry	Systematic review & meta analysis	Family psychosocial interventions in schizophrenia or schizophrenia-like conditions	k=53	1978-2008	4444	- relapse
8	[12]	Psychology	Meta-analysis	Psychoeducation in psychotic disorders (schizophrenia)	k=18	1982-2005	1534	- relapse - rehospitalization - medication adherence
9	[14]	Psychiatry	Systematic review & meta analysis	Family psychoeducation (FPE)	k= 44	1988 - 2009	5142	- relapse - readmission - compliance

Two authors assessed all the retrieved articles for inclusion, on the basis of their titles and abstracts. Two more authors (DRP and CL) independently assessed the selected records again and inspected the full article for inclusion criteria. Two authors extracted the data, and disagreements were solved by discussion. Two authors, other than those who extracted the data, assessed the quality of the reviews independently using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist [19]. The tool consists of 11 items and was proved to possess good face, reliability and content validity for measuring the methodological quality of systematic reviews [20]. Disagreements were solved by discussion.

Grading of evidence was estimated according to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which takes into account how the evidence was achieved (RCTs versus observational trials or case reports), inconsistency of results (which is inferred by significant heterogeneity of the study results), indirectness of evidence (which is inferred by the use of approximate population level measures), imprecision (which pertains to wide confidence intervals [CI], continuous data with CI>0.5, and binary and correlation data with CI>0.25 in either direction), and the risk of bias in the trials [21,22]. Three additional factors (large magnitude of effect, dose-response, and confounders) may lead to rating up the quality of evidence.

## Results

The search strategy identified 9 systematic or meta-analytic reviews (see Flowchart Diagram).

Excluded reviews (n=24) did not report quantitative summary statistics on the reviewed studies, or were on samples other than patients diagnosed with schizophrenia, or were not focused on the topic of interest.

The main characteristics of the included reviews are summarized

in Table 1.

There was a wide variability in the year range of the studies considered in the reviews, and this corresponded to a wide variability in the number of included studies. Eight out of nine reviews incorporated a meta-analysis of the findings, which is summarized in Table 2.

### Target outcomes in the reviews

The main outcomes considered in the reviews were frequency of relapse, number of re-hospitalizations, and medication adherence/compliance. Only two reviews considered suicide or total mortality, and just one review summarized data on clinical global response and on service utilization. In the subsequent analyses we focused on hard indicators of effectiveness: relapse, re-hospitalization and medication adherence/compliance.

### Sample characteristics

Most reviews focused on patients diagnosed with schizophrenia, but some of the included reviews also included heterogeneous samples of patients with serious mental illness or psychoses related to schizophrenia. In general, no detail was offered on how the diagnosis of schizophrenia was done, and information on gender and age composition of the samples was rarely provided. Overall sample size of the meta-analyses was always above 1000 participants, but the single studies had a sample size below 100 participants on average.

### Study overlap

To have a grasp of the extent of overlap of primary studies among the reviews, we compared the samples of the oldest and of the most recent reviews, and calculated the rate of reviewed articles' overlap between the two reviews; we applied the same calculation to quantify the degree of overlap between the oldest and the most recent reviews among those that we judged to have the best quality [12,23].

There was no overlap between the oldest review [13] and the most

**Table 2:** Summary of results extracted from included systematic reviews and meta-analyses.

Study	Outcome	k	n patients	Effect Size
[24]	Relapse	11	693	1. <i>Six crisis-oriented, brief weekly sessions vs. Medium- and low-dose medication:</i> Significantly lower relapses in family crisis intervention 2. <i>Behavioral family therapy vs. Supportive individual psychotherapy with brief family counselling:</i> Significantly fewer relapses in family treatment group 3. <i>Education of relatives vs. Regular hospital follow-up, little family contact:</i> Significantly reduced relapses for family treatment group 4. <i>Education and discussion in patient-only and relative-only groups vs. Standard aftercare:</i> No differences in relapse 5. <i>Education, discussion, communication, and problem-solving training vs. Day hospital alone, social skills training:</i> Family treatment significantly reduced relapse 6. <i>Behavioral program vs. Education only:</i> Family treatment significantly reduced relapse 7. <i>Education, discussion, family therapy in the home vs. Education plus relatives' support group:</i> No significant differences between the groups in relapse 8. <i>10-week program for relative oriented to building alliance and problem solving vs. Standard outpatient care:</i> No difference in relapse 9. <i>Clinic-based behavioral family management developed by Falloon vs. Standard services:</i> Treatment group had significantly fewer relapses 10. <i>Psychoeducational multifamily group vs. psychoeducational single-family therapy, dynamic multifamily therapy:</i> Psychoeducational multifamily group had significantly less relapses 11. <i>Psychoeducational multifamily group vs. Psychoeducational single-family group:</i> Significantly fewer relapses in multifamily group Family intervention equal to standard care: k = 2 Family intervention better than standard care: k = 7 Cannot answer: k = 3
[42]	Relapse	12	3732	Family intervention equal to standard care: k = 2 Family intervention better than standard care: k = 7 Cannot answer: k = 3
[41]	Relapse	12	874	Comparison I: family intervention vs. usual care effect size: $I^2 = 0.20$ [0.14-0.27]
	Relapse	5	523	Comparison II: family intervention + patient intervention vs. usual care effect size: $I^2 = 0.18$ [0.09-0.26]
[23]	Relapse	6	720	Any form of psychoeducation vs. standard care With or without readmission – over 9-18 months RR= 0.80 [0.70, 0.92]
	Relapse	3	385	Any form of psychoeducation vs. standard care - Without readmission RR=1.05 [0.84, 1.31]
	Relapse	2	303	Any form of psychoeducation vs. standard care - By 1 year 1.16 [0.92, 1.46]
	Relapse	1	82	Any form of psychoeducation vs. standard care - By 18 months RR= 0.5 [0.23, 1.11]
	Re-hospitalisation	1	82	Any form of psychoeducation vs. standard care - By 18 months RR=0.56 [0.28, 1.12]
	Relapse	2	114	Standard length group psychoeducation vs. standard care - Without readmission RR=0.58 [0.34, 0.99]
	Relapse	1	32	Standard length group psychoeducation vs. standard care - By 9 months RR= 0.7 [0.36, 1.37]
	Relapse	1	82	Standard length group psychoeducation vs. standard care -By 18 months: RR=0.5 [0.23, 1.11]
	Re-hospitalisation	1	82	Standard length group psychoeducation vs. standard care -By 18 months: RR=0.56 [0.28, 1.12]
[27]	Relapse	11	729	1st 12 months v. all other treatments Fixed effects odds ratio/ effect size= 0.63 [0.46 – 0.86] Random effects odds ratio/ effect size= 0.52 [0.31 – 0.89]
	Relapse	6	355	1st 12 months v. standard care Fixed effects odds ratio/ effect size= 0.37 [0.23 – 0.59] Random effects odds ratio/ effect size =0.37 [0.23 – 0.60]
	Relapse	5	357	1st 12 months v. active treatments Fixed effects odds ratio/ effect size= 0.89 [0.59 – 1.38] Random effects odds ratio/ effect size = 1.67 [0.71 – 0.31]
	Relapse	6	264	1-2 years v. all other treatments Fixed effects odds ratio/ effect size= 0.74 [0.44 – 1.25] Random effects odds ratio/ effect size = 0.57 [0.18 – 1.32]

[27]	Relapse	5	148	1-2 years Single family treatments v. all other treatments Fixed effects odds ratio/ effect size= 0.40 [0.19-0.84] Random effects odds ratio/ effect size = 0.42 [0.11 – 1.64]
	Relapse	4	228	Follow-up 4-15 months Single family treatments v. standard care Fixed effects odds ratio/ effect size= 0.79 [0.46 – 1.37] Random effects odds ratio/ effect size = 0.70 [0.27 – 1.76]
	Readmission	4	242	1st 12 months v. all other treatments Fixed effects odds ratio/ effect size= 0.57 [0.33 – 1.00] Random effects odds ratio/ effect size = 0.38 [0.10 – 1.40]
	Readmission	3	193	1st 12 months v. standard care Fixed effects odds ratio/ effect size= 0.69 [0.37 – 1.27] Random effects odds ratio/ effect size = 0.43 [0.08 – 2.28]
	Readmission	3	143	1st 12 months Single family treatments v. all other treatments Fixed effects odds ratio/ effect size= 0.21 [0.09 - 0.49] Random effects odds ratio/ effect size = 0.22 [0.09 – 0.51]
	Readmission	6	638	1st 2 years v. All other treatments Fixed effects odds ratio/ effect size = 0.60 [0.43 – 0.84] Random effects odds ratio/ effect size = 0.47 [0.23 – 0.96]
	Readmission	4	286	1st 2 years v. Standard care Fixed effects odds ratio/ effect size= 0.51 [0.31 – 0.84] Random effects odds ratio/ effect size = 0.39 [0.11 – 1.34]
	Readmission	3	187	1st 2 years Single family interventions v. Standard care Fixed effects odds ratio/ effect size= 0.23 [0.11 – 0.46] Random effects odds ratio/ effect size = 0.24 [0.12 – 0.47]
	Readmission	4	253	Follow-up up to 2 years after v. Standard care Fixed effects odds ratio/ effect size= 1.08 [0.64 – 1.81] Random effects odds ratio/ effect size = 1.08 [0.64 – 1.83]
[41]	Medication adherence	14	1435	Intervention group > comparison group: 3 Intervention group = comparison group: 11
[28]	Relapse	3	213	Any family-based interventions vs. standard care 0-6 months: RR = 0.71 [0.46 - 1.09]
	Relapse	32	2981	Any family-based interventions vs. standard care 7 - 12 months: RR = 0.55 [0.48 - 0.62]
	Relapse	3	181	Any family-based interventions vs. standard care 13 -18 months: RR = 0.64 [0.47 - 0.88]
	Relapse	13	1019	Any family-based interventions vs. standard care 19- 24 months: RR = 0.64 [0.55 - 0.75]
	Relapse	4	497	Any family-based interventions vs. standard care 25- 36 months: RR = 0.89 [0.72 - 1.10]
	Relapse	1	63	Any family-based interventions vs. standard care 5 years: RR = 0.88 [0.70 - 1.11]
[12]	Relapse/ Rehospitalization	5	452	Any family-based interventions vs. standard care 8 years: RR = 0.86 [0.71 - 1.05] Post-assessment effect size (Hedges' g) =0.53 [0.12 – 0.95]
	Medication adherence	2	171	Post-assessment effect size (Hedges' g) = -0.25 [-1.25 – 0.75]
	Relapse/ Rehospitalization	4	387	Follow-up ≤6 months effect size (Hedges' g) =0.35 [0.14 – 0.55]
	Relapse/ Rehospitalization	7	362	Follow-up 7–12 months effect size (Hedges' g) =0.48 [0.15 – 0.82]
[14]	Relapse/ Rehospitalization	3	144	Follow-up >12 months effect size (Hedges' g) = 0.21 [-0.07 – 0.49]
	Relapse (for any reason)	11	1214	Medium term: RR=0.70 [0.61 - 0.81]
	Relapse (for any reason)	11	1214	Long term: RR=0.73 [0.62 - 0.85]
	Relapse (for any reason)	11	1214	Long term (5 years): RR=0.89 [ 0.73, 1.08 ]
	Relapse (for any reason)	11	1214	Long term (7 years): RR=0.62 [0.42 0.92]
	Relapse (with readmission )	11	206	Medium term: RR= 0.77 [ 0.56, 1.07 ]
	Relapse (with readmission )	11	206	Long term: RR = 0.71 [ 0.56, 0.89 ]
	Compliance with medication/ non-compliance	10	1400	Short term: RR= 0.52 [0.40 - 0.67] Medium term: RR= 0.36 [0.27 – 0.49]
	Compliance with medication/ non-compliance	6	781	
Compliance with medication- non compliance	3	282	Long term: RR= 0.48[0.31-0.75]	

[14]	Compliance with medication - partial compliance	3	472	Short term: RR= 0.64 [0.49, 0.85]
	Compliance with medication - partial compliance	1	118	Medium term: RR =0.68 [0.39, 1.18]

recent one [24], with just one study in common [25]. All other studies were specific to the review, 15 and 29 respectively (Table 3).

Regarding the reviews that we scored as having the best quality, seven studies were in common, corresponding to 26% of the Pekkala, et al. 2002 review and to 33% of the Lincoln, et al. 2007 review [12,23].

The modest degree of overlap between reviews limits comparability of findings across reviews and undermines the judgment about the quality of evidence.

### Quality assessment

Quality assessment ratings for each included review is summarized in Table 4.

For comparison, we also reported the quality rating concerning the four systematic reviews or meta-analyses on family psychoeducation covered in the Taylor, et al. 2009 meta-review on institutional care for people with long-term mental health problems [26].

In our scoring, one review only obtained a score below 50% of maximum score. Five out of nine included reviews scored above 80% of the maximum score, indicating good quality of the review. The scoring of the reviews also covered in the Taylor, et al. 2009 meta-review was similar to the present scoring, thus supporting the reliability of the judgment [26].

**Evidence of relapse:** Relapse as an outcome was covered in eight reviews out of nine, but collapsed the information with that on re-hospitalization [12,14]. Risk of relapse was reported to be reduced in protocols that included family members, but not in interventions focussing on patients only. Family psychoeducation was reported to be effective whether conducted in single family or in multifamily group sessions [13]. Effectiveness seems not to be maintained at follow-up [27,28]. When relapse was considered together with re-hospitalization as an outcome, some evidence in favour of maintenance of effectiveness at follow-up was reported [12,14].

**Evidence of hospital admission/re-hospitalization:** Evidence of hospital admission/re-hospitalization was covered in four reviews out of nine. No evidence of a decrease of hospital admission/re-hospitalization was reported in three reviews out of four. Xia, et al. 2011 reported a reduction of the risk of relapse with readmission in the long term (RR = 0.71 [0.56, 0.89])[14].

**Evidence of compliance/medication adherence:** Compliance/medication adherence was covered in three reviews out of nine. Two reviews found no effectiveness of family psychoeducation on compliance/medication adherence. Xia, et al. 2011 reported an improvement in the short, medium and long term, drawing evidence from ten, six and three independent studies, respectively [14]. The effects in the longterm were appreciable but with a wide (>0.25) confidence interval (RR= 0.48[0.31-0.75]).

**Overall quality of evidence:** Overall, quality of evidence on the effectiveness of family psychoeducation in schizophrenia is poor. There was limited overlap between the reviews of the included studies.

It is therefore difficult to compare the findings of one review with another. The AMSTAR score was reasonably good for most reviews, but the risk of bias of the included studies was estimated in six reviews only.

In some reviews it was not clear whether RCTs only were included; in some reviews qualitatively different outcomes (e.g., relapse and re-hospitalization) were collapsed to produce an overall estimate of effectiveness. Most findings were doomed by imprecision (wide confidence intervals), or derived by less than 10 independent trials, which limits estimation of heterogeneity and bias in publication. Magnitude of effect, when present, was in the medium-to-low effect size, no dose-response could be established, and confounders were not properly addressed.

Our evaluation agrees with that reported by Xia, et al. 2011 in their reviews, in which they judged the available evidence on the effectiveness of family psychoeducation to be low to very low [14].

### Discussion

We reviewed the available evidence on the effectiveness of family psychoeducation in schizophrenia. Systematic reviews and meta-analyses only were considered, since they are expected to convey the highest level of evidence in describing the strength of the results measured in a clinical trial or research study. Quality of evidence was assessed by both considering the adherence of each review to the current standard of review methodology, and taking into account studies' findings and the degree of confidence in their estimates.

We found that in the shortterm (at post treatment or shortly after) family psychoeducation was related to a consistent reduction of relapse into acute psychosis. The effect was mainly produced by protocols that included family members in the session, whether applied to a single family or to a multifamily group. This result did not translate into a consistent reduction of hospital admission/re-hospitalization over the medium/long-term and was not stable at follow-up. No evidence was found of an effect of family psychoeducation on compliance or medication adherence.

As already noted by Lincoln, et al. 2007, the heterogeneity of studies and the low numbers for most outcome categories produced effects with large confidence intervals, which hampers confidence on these estimates [12]. Overall, the low quality score that can be attributed to the grade of current evidence on the effectiveness of family psychoeducation suggests that further research is very likely to change both these estimates and the confidence that can be assigned to them.

Scarce or null effect on medication adherence discounts one of the explanations that were advanced to explain potential effectiveness of family psychoeducation, which was suggested to reduce relapse by increasing adherence to therapies. Alternative explanations on the effectiveness of psychoeducation purport a positive influence on family climate, by a lenient impact on expressed emotion [29], and improved problem-solving and coping skills in the patients and their

**Table 3:** Degree of overlap between representative meta-analyses.

<b>A. Latest versus oldest meta-analysis</b>			
	Xia, et al. (2011)	Dixon, et al. (1995)	
List of included studies			
1	Barrowclough, et al. (1990)	Falloon, et al. (1982)*	Common =1
2	Bäumli, et al. (1996)*	Falloon, et al. (1985)	
3	Bäumli, et al. (2007)	Glick, et al. (1985)*	Specific to Dixon, et al., 1995 =15
4	Buchkremer, et al. (1997)	Goldstein, et al. (1978)*	Specific to Xia, et al., 2011 = 29
5	Chabannes, et al. (2005)*	Hogarty, et al. (1986)*	
6	Chabannes, et al. (2008)	Hogarty, et al. (1991)	
7	Chan, et al. (2007)*	Kottgen, et al. (1984)*	
8	Chen, et al. (2005)*	Leff, et al. (1982)*	
9	Dai, et al. (2007)*	Leff, et al. (1985)	
10	Dong, et al. (2006)*	Leff, et al. (1989)*	
11	Feldmann, et al. (2000)	Levene, et al. (1989)*	
12	He, et al. (2008) *	McFarlane, et al. (1994)*	
13	Herz, et al. (1996)	McFarlane, et al. (1995)*	
14	Herz, et al. (2000)*	Randolph, et al. (1994) *	
15	Hornung, et al. (1993)	Schooler (1995)*	
16	Hornung, et al. (1995) *	Tarrier, et al. (1988)*	
17	Hornung, et al. (1996)	Vaughan, et al. (1992)*	
18	Hornung, et al. (1998)	Zastowny, et al. (1992)*	
19	Hornung, et al. (1998b)		
20	Hornung, et al. (1999)		
21	Hornung, et al. (1999b)		
22	Jiang, et al. (2004)*		
23	Kissling, et al. (1999)		
24	Klingberg, et al. (1999)		
25	Li, et al. (2004)*		
26	Li, et al. (2005)*		
27	Li, et al. (2008)*		
28	Liu, et al. (2004)*		
29	Merinder, et al. (1999)		
30	Merinder, et al. (1998)		
31	Merinder, et al. (1998b)		
32	Merinder, et al. (2000)*		
33	Pitschel-Walz, et al. (1993)		
34	Pitschel-Walz, et al. (1995)		
35	Pitschel-Walz, et al. (1997)		
36	Pitschel-Walz, et al. (2006)		
37	Razali, et al. (1995)*		
38	Razali, et al. (1997)		
39	Sun, et al. (2005)*		
40	Tarrier, et al. (1988)*		
41	Tarrier, et al. (1989)		
42	Tarrier, et al. (1990)		

43	Wang, et al. (2008)*		
44	Wang, et al. (2008b)*		
45	Xie, et al. (2006)*		
46	Zeng, et al. (2003)*		
47	Zhang, et al. (2003)*		
48	Zhang, et al. (2006)*		
49	Zhang, et al. (2007)*		
50	Zhang, et al. (2007b)*		
51	Zhang, et al. (2008)*		
52	Zhao, et al. (2007)*		
53	Zhou, et al. (2005) *		

**B. Latest versus oldest meta-analysis among those with highest AMSTAR score**

	Pekkala, et al. (2002)	Lincoln, et al. (2007)	
List of included studies			
1	Barrowclough, et al. (1990)	Atkinson, et al.(1996)*	Common = 7
2	Bauml, et al. (1996)*	Bäumli, et al. (1996)*	Specific to Pekkala, et al., 2002= 6
3	Buchkremer, et al. (1997)	Browne, et al. (1996)*	Specific to Lincoln, et al., 2007= 18
4	Feldmann, et al. (2000)	Chien, et al.(2004)*	
5	Herz, et al. (1996)	Chien, et al.(2005)	
6	Herz, et al. (2000)*	Fries, et al. (2003)*	
7	Hornung, et al. (1993)	Herz, et al. (2000)*	
8	Hornung, et al. (1995)*	Hornung, et al. (1995)*	
9	Hornung, et al. (1996)	Hornung, et al. (1999a)	
10	Hornung, et al. (1998)	Hornung, et al. (1999b)	
11	Hornung, et al. (1998b)	Leavy, et al. (2004)*	
12	Hornung, et al. (1999)	Leff, et al. (1982)*	
13	Hornung, et al. (1999b)	Li and Arthur (2005)*	
14	Kissling, et al. (1999)	Merinder, et al. (1999)*	
15	Klingberg, et al. (1999)	Posner, et al. (1992)*	
16	Merinder, et al. (1998)	Ran, et al. (2003)*	
17	Merinder, et al. (1998b)	Rund, et al. (1994)*	
18	Merinder, et al. (1999)	Shin and Lukens (2002)*	
19	Merinder, et al. (2000)*	Tarrier, et al. (1988)*	
20	Pitschel-Walz, et al. (1993)	Tomaras, et al. (2000) *	
21	Pitschel-Walz, et al. (1995)	Xiong, et al. (1994)*	
22	Pitschel-Walz, et al. (1997)		
23	Razali, et al. (1995)*		
24	Razali, et al. (1997)		
25	Tarrier, et al. (1988)*		
26	Tarrier, et al. (1989)		
27	Tarrier, et al. (1990)		

Notes to the table.

Asterisk (\*) indicates studies whose results were entered in the meta-analysis.

Common studies are in bold.

**Table 4:** AMSTAR evaluation.

	Dixon (1995)	Penn (2001)	Pitschel-Walz (2001)	Pekkala (2002)	Pilling (2002)	Zygmunt (2002)	Pharoah (2006)	Lincoln (2007)	Xia (2011)
1. Was an 'a priori' design provided?	YES	YES	YES	YES	YES	YES	YES	YES	YES
2. Was there duplicate study selection and data extraction?	YES	NO	YES	YES	YES	YES	YES	YES	YES
3. Was a comprehensive literature search performed?	YES	NO	NO	YES	YES	YES	NO	YES	NO
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	YES	NO	YES	Cannot answer	YES	YES	Cannot answer	YES	Cannot answer
5. Was a list of studies (included and excluded) provided?	YES	NO	NO	YES	YES	NO	YES	NO	YES
6. Were the characteristics of the included studies provided?	YES	YES	YES	YES	YES	YES	YES	YES	YES
7. Was the scientific quality of the included studies assessed and documented?	YES	Cannot answer	YES	YES	YES	YES	YES	YES	YES
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	YES	YES	YES	YES	YES	YES	YES	YES	YES
9. Were the methods used to combine the findings of studies appropriate?	NO	Cannot answer	YES	YES	YES	NO	YES	YES	YES
10. Was the likelihood of publication bias assessed?	NO	NO	YES	YES	YES	NO	YES	YES	YES
11. Was the conflict of interest stated?	NO	NO	Cannot answer	YES	Cannot answer	YES	YES	YES	YES
Tot YES	8/11 (72%)	3/11 (27%)	8/11 (72%)	10/11 (91%)	10/11 (91%)	8/11 (72%)	9/11 (81%)	10/11 (91%)	9/11 (81%)
Taylor (2009) Quality Assessment			12/14 (85%)	14/14 (100%)	14/14 (100%)		14/14 (100%)		

relatives in the face of new psychopathological crises [10]. Whether one of these explanations or both are grounded is still undetermined.

Poor maintenance of the effects in the medium/long-term follow-up suggests that family psychoeducation does not translate into a stable change in family functioning. It can be advanced that family psychoeducation works as a form of supportive intervention, enabling families facing difficult situations to cope with them and receive emotional and practical support. Alternatively, it can be hypothesized that family psychoeducation produces adaptations that work in the current situation but do not generalize to new types of crisis. Either way, family psychoeducation would be effective when provided on a recurrent basis, without any expectation of any magical effects beyond its administration. Patients that discontinue drugs have a hugely enhanced risk of relapse into active psychosis [30]. Some psychosocial interventions should similarly require continuous administration to provide benefit. In planning such kind of interventions, costs of administration in terms of staff, time and location should be weighed against savings following reduction of relapse and, possibly, of re-hospitalization.

In the wake of the current financial cuts in the healthcare sector, it is encouraging that multifamily groups have a comparable effectiveness to single-family interventions. Preliminary evidence suggests that brief psychoeducational interventions-expected to be less expensive in terms of time and staff-can reduce relapse in the medium term when provided to people with severe mental illness, and favor medication compliance in the short term [31]. It is not clear how this evidence can generalize to family psychoeducation applied to people with schizophrenia, since quality of evidence was rated low [31].

It is worth mentioning that multimodal protocols of care addressing first-episode psychosis within the framework of the “early intervention” paradigm were able to produce measurable effects in the short term, which also translated into considerable cost curbing

following lower hospitalization rates [32,33]. These positive effects tend to disappear after termination of the intervention [34,35].

Early intervention services usually include individual and family psychoeducation, cognitive behavioral therapy, and a wide range of both structured and unstructured psychosocial interventions (i.e., skills training group, school and professional training). These interventions are likely to contribute the most in the short term to the superiority of these protocols of care over treatment as usual (TAU). When these interventions cease, and pharmacotherapy remains the principal tool to treat patients with chronic schizophrenia, differences with TAU disappear [34].

An unexpected finding of this meta-review is the scarce overlap of primary studies among the reviews. It appears that different authors promote different criteria to include a study into a systematic review or a meta-analysis. When more stringent criteria are applied, evidence of the effectiveness of family psychoeducation for schizophrenia is attenuated in a range of outcomes [14]. The appraisal of these differences across reviews is important for stakeholders, particularly in long-term organizational decisions, such as those that derive from the inclusion of a recommendation in guidelines. Future systematic reviews are expected to be transparent in the definition of inclusion and exclusion criteria of the studies to be reviewed.

## Conclusion

Narrative reviews are greatly more optimistic on the real effectiveness of family psychoeducation interventions [16], and on the basis of these optimistic reviews family psychoeducation is recommended as evidence-based practice in several guidelines for schizophrenia or severe mental illness [36-38]. The evidence drawn from meta-analyses is more conservative, and so far effects have been reported in the moderate-to-small range for risk of relapse [12,14], with small effects on psychosocial functioning [39]. It must be stressed that the expression “family psychoeducation” covers

several approaches, which differ in their theoretical orientation, modality, and duration [39]. Conflating different models to the aim of quantitative analysis might obscure relevant aspects of the single intervention.

As a matter of fact, patients with psychosis often live in close contact with their relatives, who give them informal care and support. High levels of family burden and family stress (i.e., expressed emotion) result from the impact of the disorder on close relatives [29]. Despite this, the provision of family interventions is limited [40].

The results of this meta-review indicate the necessity of further studies on the effectiveness of family psychoeducation, to address inconsistencies in the literature and identify specific processes involved in the efficacy of the intervention (impact on family climate versus improved coping, and problem-solving versus promotion of adherence to pharmacotherapy) [41].

## Acknowledgment

This study is supported by the Italian Medicines Agency (Agenzia Italia del Farmaco) – grant for SPERA-S Study on Psychoeducation Enhancing Results of Adherence in Schizophrenia (FARM892ZXE). DRP is the principal investigator and grant holder of the SPERA-S study and is - together with CM - speaker of the SPERA-S research network. DRP, AP, CM, CZ, CL, IP, PP all contributed to the design of the study. DRP, CL and AP contributed to the study with qualitative data analysis. DRP, AP, CM, CZ, CL, IP, PP drafted the paper. All the authors have revised the paper and have approved the final manuscript. Dr C. L. is the recipient of a Grant from the Regione Sardegna, Italy (Grant n. PRR-MAB-A2011-19250, “Programma Master & Back 2010/2011 - Percorsi di Rientro”). DRP, CM, AP design the study.

## References

- Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull.* 1998; 24: 75-85.
- Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatr Scand.* 2007; 116: 317-333.
- Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry.* 2007; 64: 1123-1131.
- Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. *Schizophr Bull.* 2004; 30: 279-293.
- McEvoy JP. The costs of schizophrenia. *J Clin Psychiatry.* 2007; 14: 4-7.
- Millier A, Schmidt U, Angermeyer MC, Chauhan D, Murthy V, Toumi M, et al. Humanistic burden in schizophrenia: a literature review. *J Psychiatr Res.* 2014; 54: 85-93.
- Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. *Curr Med Res Opin.* 1997; 14: 1-20.
- Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry.* 2012; 13: 318-378.
- Falloon IRH, Fadden G. *Integrated Mental Health Care: A Comprehensive, Community-based Approach.* Cambridge: Cambridge University Press. 1993.
- Falloon IR, Montero I, Sungur M, Mastroeni A, Malm U, Economou M, et al. Implementation of evidence-based treatment for schizophrenic disorders: two-year outcome of an international field trial of optimal treatment. *World Psychiatry* 2004; 3: 104-109.
- Bäumli J, Pitschel-Walz G, Volz A, Engel RR, Kessler W. Psychoeducation in schizophrenia: seven-year follow-up concerning rehospitalization and days in hospital in the Munich psychosis information project study. *J Clin Psychiatry.* 2007; 68: 854-861.
- Lincoln TM, Wilhelm K, Nestoriuc Y. Effectiveness of psychoeducation for relapse, symptoms, knowledge, adherence and functioning in psychotic disorders: a meta-analysis. *Schizophr Res.* 2007; 96: 232-245.
- Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, et al. Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull.* 2010; 36: 48-70.
- Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. *Cochrane Database Syst Rev.* 2011; : CD002831.
- Falloon IR, Boyd JL, McGill CW, Williamson M, Razani J, Moss HB, et al. Family management in the prevention of morbidity of schizophrenia: clinical outcome of a two-year longitudinal study. *Arch Gen Psychiatry* 1985; 42:887-896.
- Lucksted A, McFarlane W, Downing D, Dixon L. Recent developments in family psychoeducation as an evidence-based practice. *J Marital Fam Ther.* 2012; 38: 101-121.
- Enger M, Juni P, Bartlett C, Hohenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? *Health Technol Assess.* 2003; 7: 1-76.
- Ferguson CJ, Brannick MT. Publication bias in psychological science: prevalence, methods for identifying and controlling, and implications for the use of meta-analyses. *Psychol Methods.* 2012; 17: 120-128.
- Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007; 15: 10.
- Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* 2009; 62: 1013-1020.
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924-926.
- Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction--GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011; 64: 383-394.
- Pekkala E, Merinder L. Psychoeducation for schizophrenia. *Cochrane Database Syst Rev.* 2002; CD002831.
- Dixon LB, Lehman AF. Family interventions for schizophrenia. *Schizophr Bull.* 1995; 21: 631-643.
- Tarrier N, Barrowclough C, Vaughn C, Bamrah JS, Porceddu K, Watts S, et al. Community management schizophrenia: a controlled trial of behavioral interventions with families to reduce relapse. *Br J Psychiatry.* 1988; 153: 532-542.
- Taylor TL, Killaspy H, Wright C, Turton P, White S, Kallert TW, et al. A systematic review of the international published literature relating to quality of institutional care for people with longer term mental health problems. *BMC Psychiatry.* 2009; 9: 55.
- Pilling S, Bebbington P, Kuipers E, Garety P, Geddes J, Orbach G, et al. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychological Medicine.* 2002; 32: 763-782.
- Pharoah F, Mari JJ, Rathbone J, Wong W. Family intervention for schizophrenia. *The Cochrane Collaboration.* 2010; CD000088.
- Casacchia M, Roncone R. Italian families and family interventions. *J Nerv Ment Dis.* 2014; 202: 487-497.

30. Cañas F, Alptekin K, Azorin JM, Dubois V, Emsley R, García AG, et al. Improving treatment adherence in your patients with schizophrenia: the STAY initiative. *Clin Drug Investig*. 2013; 33: 97-107.
31. Zhao S, Sampson S, Xia J, Jayaram MB. Psychoeducation (brief) for people with serious mental illness. *Cochrane Database Syst Rev*. 2015; : CD010823.
32. Mihalopoulos C, Harris M, Henry L, Harrigan S, McGorry P. Is early intervention in psychosis cost-effective over the long term? *Schizophr Bull*. 2009; 35: 909-918.
33. Cocchi A, Mapelli V, Meneghelli A, Preti A. Cost-effectiveness of treating first-episode psychosis: five-year follow-up results from an Italian early intervention programme. *Early Interv Psychiatry*. 2011; 5: 203-211.
34. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Øhlenschlaeger J, Le Quach P, et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Arch Gen Psychiatry* 2008; 65: 762-771.
35. Marshall M, Rathbone J. Early intervention for psychosis. *Cochrane Database Syst Rev* 2011; 15: CD004718.
36. Hogan MF. The President's New Freedom Commission: Recommendations to reform mental health care in America. *Psychiatric Services*. 2003; 54: 1467-1474.
37. Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, et al. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2010; 36: 48-70.
38. Substance Abuse and Mental Health Services Administration (SAMHSA). Family psychoeducation: How to use the evidence-based practices KITs. HHS Pub. No. SMA-09-4422. Rockville, MD: Center for Mental Health Services, Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services 2009, available at 1-877-726-4727 or Retrieved September 13, 2011.
39. Mueser KT, Deavers F, Penn DL, Cassisi JE. Psychosocial treatments for schizophrenia. *Annu Rev Clin Psychol*. 2013; 9: 465-497.
40. Magliano L, Marasco C, Fiorillo A, Malangone C, Guarneri M, Maj M, Working Group of the Italian National Study on Families of Persons With Schizophrenia. The impact of professional and social network support on the burden of families of patients with schizophrenia in Italy. *Acta Psychiatr Scand*. 2002; 106: 291-298.
41. Petretto DR, Preti A, Zuddas C, Veltro F, Rocchi MB, Sisti D, et al. Study on psychoeducation enhancing results of adherence in patients with schizophrenia (SPERA-S): study protocol for a randomized controlled trial. *Trials*. 2013; 14: 323.