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Randomised controlled trial of cognitive-motivational therapy program for the initial phase of schizophrenia: a 6-month assessment

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ABSTRACT – *Background and Objectives:* The aim of this study is to investigate the relative effectiveness of routine care (RC) in addition to a specific early intervention program (PIPE) compared to routine care alone.

Methods: A total of 34 participants in the initial phase of schizophrenia took part in randomized, single-blind controlled trial. Participants were randomized to receive either routine care (RC; n = 13) or routine integrated with Cognitive-Motivational Therapy (PIPE; n = 21). PIPE comprised individual and family Cognitive-Motivational therapy plus routine care for 12 months. In this paper we present preliminary results at 6 months after the beginning of the intervention. Clinical assessments were carried out at pre-treatment, and in this manuscript the results at 3 and 6 months after starting the intervention by external raters are presented, using the Positive and Negative Syndrome Scale, Brief Psychiatry Rating Scale, the Clinical Global Impression Scale, the Global Assessment of Functioning scale, and relapses. Mann-Whitney test and MANOVAs analysis for variance effects were used for the statistical analysis.

Results: Significant greater clinical effects were observed in those patients treated in RC+PIPE at three months from baseline assessment and at six months in PANSS scale (Mann-Whitney test; $p < 0.000$). Other benefits of the program included increase in global activity, reduced relapse rates, and reduction of the pharmacological treatment.

Conclusions: These findings show the effectiveness of a program of routine care integrated with cognitive-motivational interventions (individual and family therapy) over routine psychiatric care alone for patients who are in the initial phase of schizophrenia.

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Introduction

Studies carried out to assess the effectiveness of cognitive-behavioral therapy (CBT) in the early phases of schizophrenia present very favorable results for symptomatic treatment[1-11]. A large body of recent research has arisen from the critical period hypothesis[12] investigating interventions at the prodromal stage of schizophrenia, at the acute phase and the late recovery phase.

In relation to the post-acute and posterior phase, studies comparing CBT with other therapeutic modalities show their superiority in reducing clinical symptoms in short periods of time[13-17].

Nowadays, many therapeutic programs use motivational interventions as a style and technical resource in the treatment of schizophrenia, like the treatment of associated substance use or programs addressed to promoting changes in behavior or attitudes towards intervention being two good examples[1,8,18,19].

It is important to consider the intrinsic motivation in patients with schizophrenia because of its effectiveness in psychotherapy programs. This could be explained because the effect of the motivation over the learning processes during the therapy. According to relevant authors intrinsic motivation should enhance learning outcomes[20,21]. Other authors found that intrinsic motivation strongly mediated the relationship between neurocognition and psychosocial functioning[22,23].

From this perspective, we designed an early intervention program for the initial phase of schizophrenia with the aim of assessing its effectiveness as an integrated (cognitive-motivational) psychological program versus the usual treatment of schizophrenia.

Materials and method

Design

A randomized, controlled, single-blind clinical trial was carried out. Patients and families were allocated either to the experimental intervention program plus routine care (PIPE) or to routine care alone (CG).

Abbreviations:
PIPE: (it) refers to integrated program with cognitive-motivational therapy plus routine care.
CG: (it) refers to control group.

Selection of patients and group allocation

In this trial, inclusion criteria were: (a) patients should be at the initial phase of schizophrenia (<3 years from first episode), according to DSM-IV criteria, excluding the diagnosis of schizoaffective disorder, severe mental retardation and language difficulties were not included in the trial[24]; (b) they should have used the Mataró's psychiatry service (Barcelona). Diagnoses were established by two experienced professionals based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[25] to improve reliability of diagnosis.

Participants were identified through a computerized database that collects all contacts with health services in a centralized manner regarding admissions into the Hospital of Mataró, visits to emergency services, outpatient consultations, visits to the Mental Health Centre, and admissions into the Day Hospital in Mataró. Patients and families were contacted and invited to participate in the study. Both patients and their family had to sign a consent form in order to be accepted into the trial. Patients and families were assessed by using different instruments: the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)[26], the Brief Psychiatric Rating Scale (BPRS)[27], the Clinical Global Impression Scale[28], and the Global Assessment of Functioning Scale (GAF)[29]. The assessment was carried out before being randomized to one of the two conditions in the clinical trial: (a) PIPE program plus routine care; and (b) only routine care. Randomization was carried out by an external researcher-epidemiologist through a computer program (SPSS.v.15) in charge of allocation.

Interventions

Integrated intervention program (PIPE)

The intervention program lasted for 12 months with a total number of 34 (weekly) sessions (of 45 minutes each), carried out in the Mental Health Centre. In this paper we only present preliminary results at 6 months after the beginning of the intervention.

The early intervention program PIPE combines three therapeutic components: psychoeducation, individual and family cognitive-motivational therapy. The PIPE program is described elsewhere[30].

Motivational Intervention (MI) was used to increase motivation for change, help patients solve their ambivalences, promote their adherence to both pharmacological and psychological treatment, change substance use habits (in the case of user patients), increase daily life activities, and maintain hygiene habits (in the case of patients with difficulties)[31].

Individual CBT were used to treat delirious ideas and hallucinations[32]. Family intervention aimed to promote communication attitudes that ensure an optimal family climate for the patient's recovery and the family's own adaptation to the illness. As in individual therapy, work with the family aimed to promote healthy and functional changes in accordance with MI style. The intervention program began with four psychoeducational sessions to provide the patient and family with information about the nature of the disease. The aim is to help the patient understand the illness by promoting his/her active participation in reducing the risk for relapses and the levels of social maladjustment. With regards to the family, the aim is to enhance their commitment to the patient's therapeutic process by avoiding blaming tendencies and reinforcing their motivation to help.

The individual cognitive intervention with a motivational style started during the third week of the program and lasted for 20 weeks approximately. Family therapy was carried out for 10 sessions. In some of them, the whole family (parents, siblings and patient) took part, whereas others involved family members only at the therapist's judgment.

Intervention was carried out by one therapist trained in the MI style and early psychological interventions to treat psychosis. Regular supervisions were carried out, some of them with audiovisual support.

Routine Care (RC)

The usual treatment for the initial phase of schizophrenia in the context of the Spanish Mental Health Care is pharmacological treatment as prescribed by the regular psychiatrist.

Assessment procedures and instruments

Assessments were carried out by a qualified external assessor in order to guarantee single-blinding and objectivity of results (a psychologist). They were carried out at three time periods: at pre-treatment (right before being allocated to one of the experimental conditions), 3 months after, and 6 months after baseline assessment.

The social and demographic characteristics of the patients and families were collected through a short questionnaire during the first interview.

Symptoms and Global Functioning

— Baseline assessment

To assess symptoms and global functioning, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression Scale, and the Global Assessment of Functioning Scale (GAF) were used.

— Assessments during the intervention (3 and 6 months after)

Three months after the beginning of the intervention, the BPRS was used in order to observe the patients' progress. Six months after, patients were assessed again using the baseline outcome measures relapse rates were also recorded during the study.

Relapses

Two strategies were used to record relapses aiming to avoid overlapping bias in the treatment of data.: (a) individual relapses which comprised (I) number and duration of inpatients admissions; (II) number and duration of outpatients admissions; (III) number of visits to emergency services due to deterioration of symptoms; and (IV) number and duration of deterioration of symptoms that require intervention by professionals (increase in/change of medication or non-scheduled visits; since de beginning of intervention to the follow up. If increase in medication is prescribed in the emergency room, both variables will be recorded. On the contrary, if the increase in medication is prescribed by the regular psychiatrist with the aim of preventing relapse in relation to current changes liable to affect the patient's status, then it will not be considered as a relapse. (b) Global relapses: if, in the context of a relapse, there is involvement of more than one of health care services listed above within the same period of time, this will be recorded as one single relapse (called "global"). The differentiation between the two strategies for this variable serves the purpose of avoiding bias in the treatment of the number of relapses. In the case that the patient shows a period of stability between the use of one service and another, they would be considered as two independent relapses.

Data analysis

Before the descriptive analysis of baseline, an analysis of scores was carried out, with statistical differences observed concerning the normal distribution of variables. For this reason, all analyses were carried out using non-parametrical procedures, including the analysis of covariance and Mann-Whitney U test (U) to compare both groups. Two-tailed tests of significance were used in all analyses. Multivariate analysis of Variance (MANOVAs) was used to compare differences in symptoms change between the PIPE and CG at 6 months follow-up. In order to control for the effect of psychotic symptoms, the PANSS baseline scores were used as a covariate in the MANOVAs. Doses of pharmacological treatment were converted to Chlorpromazine-equivalents doses (mg/day) in both groups and were also treated as a covariate[33].

Results

A total of 67 cases diagnosed with schizophrenic disorder meeting the inclusion criteria of this study were detected. During the enrollment process, 5 subjects moved out of area; 7 people could not be contacted; 19 did not agree to participate in the study because they did not think they had any mental illness; and 2 of them were false positives. The final sample of the study included by 34 patients allocated to the two experimental conditions: PIPE group (n = 21) and control group (n = 13) (see Figure 1). During the intervention, no patient dropped out. Data collection for the current results was completed two years after the first patient was included, because the sample inclusion was progressive during the program. The social, demographical and clinical characteristics were distributed homogeneously between groups (see Table 1).

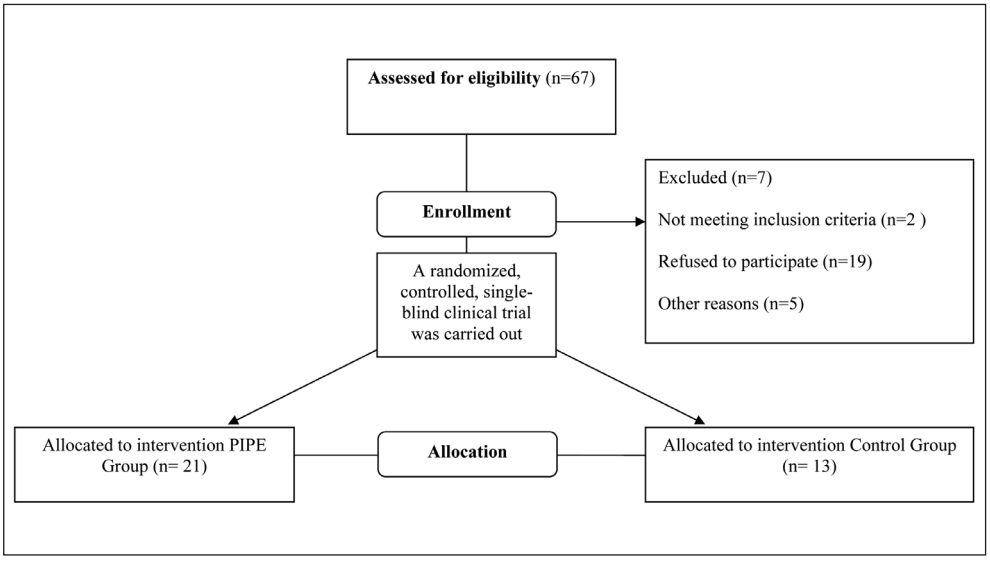

Figure 1. Sample enrollment and subject allocation.

Table 1
Clinical and demographical characteristics

	PIPE (n = 21)	Control (n = 13)	p
Gender	**n (%)**	**n (%)**	
Men	16 (76.2)	11 (84.6)	0.555
Women	5 (23.8)	2 (15.4)	
Age			
Mean	24	23.77	0.877
SD	4.347	3.961	
Study level	**n (%)**	**n (%)**	
Without studies	–	1 (7.7)	0.210
Primary studies	5 (23.8)	3 (23.1)	
Secondary studies	5 (23.8)	7 (53.8)	
Incomplete secondary studies	4 (19)	–	
University studies	4 (19)	1 (7.7)	
Incomplete university studies	3 (14.3)	1 (7.7)	
Housing status	**n (%)**	**n (%)**	
Family	14 (66.7)	10 (76.9)	0.795
Alone	4 (19)	1 (7.7)	
Own family	1 (4.8)	1 (7.7)	
Share flat	1 (4.8)	–	
Grandfathers	1 (4.8)	1 (7.7)	
Employment status	**n (%)**	**n (%)**	
Unemployed	7 (33.3)	4 (30.8)	
Part time	6 (28.6)	3 (23.1)	0.146
Full	–	1 (7.7)	
Retired	1 (4.8)	4 (30.8)	
Protect work	3 (14.3)	1 (7.7)	
Student	4 (14.3)	–	
Economic level	**n (%)**	**n (%)**	
Low	8 (40)	5 (41.7)	0.930
Medium-low	5 (25)	4 (33.3)	
Medium	5 (25)	2 (16.7)	
Medium-high	2 (10)	2 (8.3)	
Number of previous visits in emergencies service before the intervention			
Mean	3.56	3.33	0.530
SD	4.066	2.082	
Family history of psychosis	**n (%)**	**n (%)**	
No	6 (28.6)	5 (38.5)	
Yes	15 (71.4)	8 (61.8)	0.543
First grade	5 (23.8)	3 (23.1)	
Second grade	10 (47.6)	5 (38.5)	
Duration of Untreated Psychosis (DUP) weeks			
Mean	41.14	86.83	0.084
SD	57.493	90.020	

Symptoms and functioning

Table 2 shows scores in the clinical measures, global functioning and global clinical impression. An analysis of covariance was carried out with the scores of baseline assessment as covariables in order to compare two analyses: a) the effects between baseline assessments, 3 and 6 months after treatment; b) the effects between the groups of results with respect to baseline scores (see table 2 and 3).

Table 2
Comparison of results for intragroup clinical improvement 6 months after the beginning of early intervention

Measure	Integrated Care: PIPE Group (n = 21)				Routine Care Group (n = 13)			
	Baseline		6 months after beginning of treatment		Baseline		6 months after beginning of treatment	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PANSS Score								
Positive symptoms[a]	30.00	22.048	7.89	4.806	35.77	25.401	37.50	29.194
Negative symptoms[b]	32.11	23.823	19.74	11.239	38	.989	37.92	23.593
General Psycopathology[c]	23.42	20.416	6.58	5.015	39.23	34.086	44.17	33.086
Global Assessment of Funtioning Scale score[d]	48.95	12.865	65.79	10.706	45.38	13.301	45	17.321
Global Impression Scale score[e]	4.54	0.806	3.47	0.513	4.77	1.092	4.75	1.215

[a] Mann-Whitney test results of comparison between groups were U = 109.5. n.s. baseline; U = 50.5. p = 0.005 at six months.

[b] Mann-Whitney test results of comparison between groups were U = 113.5. n.s. baseline; U = 59. p = 0.025 at six months.

[c] Mann-Whitney test results of comparison between groups were U = 91.5. n.s. baseline; U = 33.5. p = 0.000 at six months.

[d] Mann-Whitney test results of comparison between groups were U = 106. n.s. baseline; U = 41.5. p = 0.002 at six months.

[e] Mann-Whitney test results of comparison between groups were U = 120.5. n.s. baseline; U = 39.5. p = 0.002 at six months.

Table 3
Comparison of results for intragroup clinical improvement at 3 and 6 months after the beginning of early intervention in the BPRS

Measure	Integrated Care: PIPE Group						Routine Care Group					
	Baseline (N = 19)		3 months after beginning of treatment (N = 19)		6 months after beginning of treatment (N = 19)		Baseline (N = 13)		3 months after beginning of treatment (N = 13)		6 months after beginning of treatment (N = 13)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Meam	SD	Mean	SD
BPRS[a]	39.74	6.756	28.58	5.048	28.95	6.843	43	12.30	42.08	12.280	46.25	14.536

[a] Mann-Whitney test results of comparison between groups were U = 112. n.s. baseline; U = 34. p = 0.001 at three months; U = 34. p = 0.001 at six months.

Significant improvement was observed in all PANSS scales between baseline and 6 months in the PIPE group.

1. Positive scale: there were remarkable differences between the intervention and control group with the former scoring lower compared to the latter (adjusted mean = 7.28, SE = 1.103, versus adjusted mean = 36.94, SE = 8.427) ($F = 7.436$, $df = 1$, $p < 0.011$).
2. Negative scale: adjusted mean = 19.5, SE = 2.578, versus adjusted mean = 37.69, SE = 6.811; ($F = 79.341$, $df = 1$, $p < 0.000$).
3. General psychopathology scale: adjusted mean = 5.74, SE = 1.15, versus adjusted mean = 43.52, SE = 9.551; ($F = 22.8$, $df = 1$, $p < 0.000$).

The main results of MANOVA analysis are shown in the Table 4. We included baseline assessments, pharmacological treatment and DUP into the variance model.

We observed heterogeneous values for DUP in both groups (PIPE mean = 41.14 weeks; RC mean = 86.83). No significant differences were found in bivariate analysis, but the clinical difference was evident and it was indicated to include the DUP values into de variance model to observe the effect in groups' evolution.

Table 4
MANOVAs analysis for variance effects

Measure PANSS Score	Baseline		12 months		F	p	η
	Mean	SD	Mean	SD			
Positive symptoms							
PIPE group	30.00	22.048	7.89	4.806	13.291	0.001	0.361
Control group	35.77	25.401	35.77	25.4			
Negative symptoms							
PIPE group	32.11	23.823	19.74	11.239	21.549	0.000	0.53
Control group	38	8.989	37.92	21.58			
General Psycopathology							
PIPE group	23.42	20.416	6.58	5.015	17.453	0.000	0.487
Control group	39.23	34.086	34.086	44.17			

The multivariate test showed a differential effect on the independent variable values in to design model (Lamda = 0.467; $F = 3$; $p = 0.000$; $\eta = 0.603$). The observed potency was 0.989. The effect size showed a 60% of the variance is explained by the group effect.

Global Functioning

High scores were detected by GAF scale in PIPE group, indicating an increase in activity, compared with the control group. Differences were significant at 6 months (adjusted mean = 66.43, SE = 2.456, versus adjusted mean = 45, SE = 5) ($F = 22.813$, $df = 1$, $p < 0.000$). Moreover, in the global clinical im-

pression assessments, the PIPE group scored significantly lower compared to the control group (adjusted mean = 3.47, SE = 0.118, versus adjusted mean = 4.72, SE = 0.351) ($F = 30.856$, $df = 1$, $p < 0.000$). Lower scores in that scale mean a better global clinical impression assessed by external rates.

Brief Psychiatric Rating Scale

Another interesting result is shown by the BPRS scores, as this scale allows us to obtain clinical improvement scores at 3 months (Table 3). Results are similar to those of PANSS scores, but their specific contribution is that they allow us to observe this significant improvement just 3 months after the beginning of intervention (adjusted mean = 28.39, SE = 1.57, versus adjusted mean = 46.11, SE = 4.196) ($F = 6.772$, $df = 1$, $p < 0.015$).

Relapses

After 6 months of treatment, 24% of patients in the control group were admitted into hospital in comparison to 10.5% of the group receiving early intervention; however this difference is not statistically significant ($\chi^2 = 0.922$; $p = 0.337$) (see Table 5).

There were no significant differences in the frequency of day hospital stays between the PIPE group and the CG. The same was observed when assessing frequency of non-scheduled visits to other services. The same frequency is observed for patients (n = 2) that go to the mental health centre in a non-scheduled manner. No significant differences ($\chi^2 = 2.264$; $p = 0.132$) were also observed in the frequency of visits to emergency services at 6 months between the PIPE group (21.1%) and the CG (46.2%).

Table 5
Comparison of relapses between groups at 6 months after the beginning of early intervention

Relapse rates at six months after starting the study

Groups	Integrated Care: PIPE Group (N = 19)			Routine Care Group (N = 13)		
Measure	Mean	SD	Medium Range	Mean	SD	Medium Range
Admissions[a]	0.11	0.315	14.97	0.67	1.231	17.63
Duration of admissions[b]	23	11.314	1.5	43.3	14.434	4
Non-scheduled visits[c]	0.11	0.315	15.58	0.25	0.622	16.67
Emergencies[d]	0.42	0.961	14.26	1.42	2.429	18.75
Increase in medication[e]	0.21	0.419	13.34	1.25	1.545	20.21
Global relapses[f]	0.21	0.419	13.37	1.17	1.403	20.17

[a] Mann-Whitney test results of comparison between groups were U = 94.5. p = 0.217.

[b] Mann-Whitney test results of comparison between groups were U = 0.000. p = 0.076.

[c] Mann-Whitney test results of comparison between groups were U = 106. p = 0.577.

[d] Mann-Whitney test results of comparison between groups were U = 81. p = 0.105.

[e] Mann-Whitney test results of comparison between groups were U = 63.5. p = 0.016*.

[f] Mann-Whitney test results of comparison between groups were U = 64. p = 0.022*.

However, significantly less participants in the PIPE group (21.1%) compared to the CG (53.8%) required increase in medication. This difference in frequencies is statistically significant ($\chi^2 = 3.680$; $p = 0.05$). In the PIPE group a 72% of the prescriptions were done by their regular psychiatrist and the 28% in emergency unit. On the other hand, we observed a 64% of the increase prescriptions in CG by emergency unit (the 36% was prescribed by their regular psychiatrist).

With regards to global relapses, there are highly significant differences between two groups ($\chi^2 = 5.398$; $p = 0.02$). 21.1% of patients in the PIPE group were recorded as having global relapses in contrast to the 61.5% in the control group. These data imply the presence of two or more of the outcome measures used in the register of relapses in the same period of time.

Discussion

Many studies conducting CBT at the initial phase of schizophrenia present similar results when comparing the experimental and control groups and their separate evolution with regards to positive symptoms and lower drop-out rates[9,15,34,35]. However, other studies do not find these significant differences in the improvement of positive symptoms[14,17] probably because their comparison groups are receiving, along with the regular treatment, problem-solving training or counseling interventions. Nevertheless, the three studies have pointed at the clinical improvement of the group receiving cognitive therapy in relation to other modalities.

In the present study, there are very favorable results just three months after the beginning confirming previous studies[9].

Findings showed an increase in global activity and global clinical impression in the PIPE group compared to the control group which supports the findings of previous clinical trials[1,8,36].

Remarkably, it is difficult to find studies conducting an intervention similar to the one presented here of a cognitive-motivational nature. In fact, we carried out a literature review to assess current opinions in this field. These issues make it clear that it is difficult to reach solid conclusions in this field due to the heterogeneity of the concept and the difficulty in writing manuals on this kind of intervention.

Nevertheless in Barrowclough's study[1] the MI proposed shares similar characteristics to the one presented here. However, the study design is different as her sample is not in the initial phase of the disease, and they have dual diagnoses.

The work carried out by Tarrier's group[10] shows assessments after 9 and 12 months of intervention with highly significant results also in all PANSS and global clinical impression scales. When assessing relapses in a short period of time such as 6 months, no significant differences are likely to be found in most of the measures explored. The results of our study show higher means in the control group in all the assessed measures. With regards to the number of hospital admissions, number of non-scheduled visits, visits to the emergency service, and duration of hospital stays. However, the frequency of global relapses and of the number of times when an increase in medication is needed shows statistically significant difference in the PIPE group in comparison to the control group; these results are similar to those of previous studies[14].

Something similar happens, as there is a lower number and less duration of hospital

stays in the group receiving CBT, although the levels of statistical significance do not reach such values as to reach more conclusive statements. Most studies applying CBT find this statistical significance in the longer term[1,37].

With regards to the limitations of this study, we have to state that the trial is carried out using a cognitive-motivational intervention, one of the most important ingredients of which is the therapist's style. This factor makes this study hardly comparable; in fact, there are few studies with such an intervention. Dr. Barrowclough and her team in Manchester show the effect of their psychological intervention in a very similar trial[1]. Nevertheless, the difficulty of both studies lies in being able to discern whether the improvement is due to the fact that adherence to treatment is enhanced or to the intervention as a whole.

On the other hand, the reduced size of the sample forces us to interpret results with some caution. Applying strict inclusion criteria in combination with the lack of insight reported by a significant number of potential participants resulted in loss of participants.

Furthermore, the reduced size of the sample has not allowed the dependent variables to meet normality criteria in a regular manner, and for this reason in the phase of statistical analysis some decisions were made in this respect, such as the use of non-parametrical tests.

In short, our study shows that the Early Intervention Program for Schizophrenia (PIPE) has a high impact on the clinical improvement and a mild impact on relapses after 6 months of intervention. In future studies, we will assess the impact of the intervention in the long term and during follow-up, as well as explore the relative efficiency of every component in the integrated interventions.

Conclusions

Results obtained in all outcome measures in our study show the positive impact that early intervention has at the initial stage of schizophrenia concerning clinical improvement, global impression, and global activity after three and six months of treatment. The findings of this study in relation to the rest of published works encourage us to wait. The assessment of relapses seems to require time sensitivity. Presenting results after six months of intervention limits this possibility and, therefore, this will be an aspect to be assessed in a later period.

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