



Patterns of recovery course in early intervention for FIRST episode non-affective psychosis patients: The role of timing

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ABSTRACT

Background: Prevention of symptom relapse and promotion of functional recovery are the two main goals of early intervention following a first episode of non-affective psychosis (FEP). The identification of patterns of recovery is important in developing and implementing recovery focused interventions at set time interval.

Method: Patterns of recovery course, in terms of symptomatic and functional remission, were explored at 1 and 3-year follow-up in a sample of 373 consecutive FEP patients. Relapses during this period were considered.

Results: Four patterns of recovery course were defined: good stable (26%), good unstable (21%), poor unstable (10%), poor stable (43%). Those who met criteria for good stable recovery were more likely have less severe baseline negative symptoms (OR = 2.092; 95% CI = 0.99–4.419) and to not be diagnosed with schizophrenia (OR = 2.242; 95% CI = 1.015–4.954). Short DUP (OR = 2.152; 95% CI = 0.879–5.27) and low premorbid IQ (OR = 2.281; 95% CI = 0.954–5.457) increased the likelihood of good unstable recovery. Less severe baseline negative symptoms (OR = 3.851; 95% CI = 1.422–10.435) and single status (OR = 4.307; 95% CI = 1.014–18.293) increased the likelihood of a poor unstable recovery. Poor unstable pattern was significantly associated with a high relapse rate (73%).

Conclusions: Our results shed light on identifying different recovery patterns in FEP. Despite evidence for early intervention effectiveness, we should explore ways to prevent relapse and improve long-term recovery, particularly in reference to the role of timing in the design of interventions.

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1. Introduction

Over the last two decades early intervention services (EIS) for first episode of psychosis have been widely implemented all over the world (McGorry, 2015). Evidence suggests that EIS may be effective on recovery, showing a positive impact on symptomatic and functional remission, and the prevention of relapse (Catts et al., 2010; Correll et al., 2018). Regretfully, in line with the literature, the changes in treatment options have not increased the proportion of recovered cases (Albert et al., 2011; Fusar-Poli et al., 2017; Jaaskelainen et al., 2013; Lally et al., 2017; Lappin et al., 2018). The median recovery rate for schizophrenia is 13.5% (Jaaskelainen et al., 2013) and only one out of seven patients recovers after a first episode of psychosis (FEP) despite psychiatric care

(Morin and Franck, 2017), mainly because many individuals with FEP remain socially isolated with poor functional outcomes (Santesteban-Echarri et al., 2017). Full recovery requires concurrent remission of positive and negative symptoms and adequate social/vocational functioning (fulfillment of age-appropriate role expectations, performance of daily living tasks without supervision, and engagement in social interactions). Although some patients with FEP can achieve sustained symptomatic and functional recovery, the overall rate of recovery is low (Robinson et al., 2004).

EIS have resulted in a higher rate of vocational recovery and improved quality of life, leading to the assumption that EIS is highly likely to be cost-effective when compared with standard care (Hastrup et al., 2013; McCrone et al., 2010). However, one shortcoming of EIS is the tendency to treat patients as a homogeneous group (Power, 2017). Rather than all individuals responding to intervention in the same way, recovery from a first episode of non-affective psychosis (FEP) is heterogeneous, consisting of subgroups with different baseline demographic

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and clinical characteristics, and different recovery pathways (Hodgekins et al., 2015). On the other hand, recovery concept is to certain extent insufficiently defined. Recovery demands change and adaptation, thus is not just a passive response to treatment, a simple remission of psychotic symptoms and return to premorbid functioning (Power, 2017). However, until the definition for recovery is further elucidated, factors such as symptom control and remission, and functional aspects of recovery such as improvements in cognition and social functioning, which are quantifiable, should be used as measures of treatment outcome and markers of recovery (Leucht and Lasser, 2006). Attempts to define and measure multidimensional outcomes and time for recovery are of value, particularly when done as objectively and stringently as possible (Bebbington et al., 2006; Jaaskelainen et al., 2013).

In order to assess the a priori hypothesis that FEP patients would show type and time heterogeneity in the recovery course, subgroups of recovery, in terms of symptoms and functional remission over a 3-year follow-up period, were explored. The objective was to examine the potential predictors of the different patterns of recovery.

2. Methods

This investigation was designed as an observational prospective study. Data were obtained from an ongoing epidemiological and three-year longitudinal intervention program of first-episode psychosis non-affective psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran et al., 2008). Our operational definition for a “first episode of psychosis” (FEP) included individuals with a non-affective psychosis who have not received previously antipsychotic treatment regardless of the duration of psychosis. In accordance with international standards for research ethics, this program, which is fully publicly funded by the regional Mental Health Services, was approved by the local institutional review board. Patients meeting inclusion criteria and their families provided written informed consent.

2.1. Subjects

All referrals to PAFIP between 2001 and 2010 were screened against the following inclusion criteria: being between 15 and 60 years old; living in the catchment area; experiencing their FEP; having no prior treatment with antipsychotic medication or, if previously treated, a total life time of adequate antipsychotic treatment of <6 weeks; meeting DSM-IV criteria (APA, 2000) for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. DSM-IV criteria for drug or alcohol dependence, intellectual disability and having a history of neurological disease or head injury were exclusion criteria.

Five hundred thirteen patients met the inclusion criteria and were therefore included in the PAFIP program over this period. Baseline sociodemographic and clinical information was recorded for the total sample. Diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1996), which was carried out by an experienced psychiatrist (BC-F) 6 months after the baseline visit. In particular, the baseline diagnoses of our FEP patients (i.e. 6 months after first contact) were as follows: schizophrenia ($N = 263$), schizophreniform disorder ($N = 147$), schizoaffective disorder ($N = 8$), brief psychotic disorder ($N = 55$), psychosis NOS ($N = 38$) and delusional disorder ($N = 2$).

2.2. Measures

Premorbid and sociodemographic information was recorded from interviews with patients, their relatives and from medical records on admission. Sex, age, age at psychosis onset (defined as the age when the emergence of the first continuous [present most of the time] psychotic symptom occurred), and duration of untreated psychosis (DUP, defined as the time from the first continuous [present most of the

time] psychotic symptom to initiation of adequate antipsychotic drug treatment), were collected.

Premorbid social adjustment was measured by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Premorbid IQ for first episode psychosis was estimated using the WAIS-III vocabulary subtest (Lezak, 1995).

Patients were screened for symptoms and functioning at baseline, 1 and 3-year follow-up. Clinical symptoms of psychosis were assessed by the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The severity scale of the Clinical Global Impression (CGI) Scale (Busner and Targum, 2007) was used to measure the overall severity of illness. Depressive symptoms severity was measured using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). Functional assessment was conducted with The Disability Assessment Scale (DAS) Spanish version (Mañá et al., 1998). General Cognitive Functioning (GCF) was calculated according to previous methodology (Reichenberg et al., 2008). The seven cognitive domains that are fundamentally impaired in psychosis were converted to z scores and averaged to obtain the GCF measure.

Information about number of relapses (Pelayo-Teran et al., 2017) and antipsychotic treatment, as mean chlorpromazine equivalent dosage (Gardner et al., 2010), were also considered in the present study. Relapse was defined as any of the following criteria that occurred during follow-up: (1) a rating of either 5 or above on any key BPRS symptom items, (2) CGI rating of ≥ 6 and a change score of CGI of “much worse” or “very much worse”, (3) hospitalization for psychotic psychopathology, or (4) completed suicide. The key BPRS symptoms were unusual thought content, hallucinations, suspiciousness, conceptual disorganization, and bizarre behaviour. Patients were considered to have a relapse if the re-emerged symptoms lasted for at least 1 week. Doses equivalent to 100 mg/day of chlorpromazine were 2 mg/day for risperidone, 5 mg/day for olanzapine, 75 mg/day for quetiapine, 60 mg/day for ziprasidone, and 7.5 mg/day for aripiprazole.

2.3. Recovery

As stated in our previous paper (Treen Calvo et al., 2017), a variable that counts both symptomatic and functional recovery criteria was created. Recovery was determined by scores of 2 or less in the corresponding items of the SANS and the SAPS scales, as established by the remission work group (Andreasen et al., 2005), and a score of 1 or less in the DAS scale. Recovery includes symptomatic remission and adequate psychosocial function at 1 and 3-year follow-up after a FEP. Both moments independently were considered to determine the pattern of recovery course.

Four patterns were defined according to the four possible courses of recovery: 1. Good Stable: patients recovered by the 1-year follow up that maintained recovery by the 3-year follow-up ($N = 98$; 26%); 2. Good Unstable: those patients not recovered by the 1 year-follow up but that achieved recovery between 1 and 3 years ($N = 77$; 21%); 3. Poor Unstable: patients recovered by the 1-year follow up that loss recovery between 1 and 3 years ($N = 37$; 10%); 4. Poor Stable: those patients that during the 3-year follow-up period neither achieved full remission of psychotic symptoms, nor functional recovery ($N = 161$; 43%).

2.4. Statistical analysis

Statistical analyses were done using SPSS, version 19.0. Univariate analyses of variance (ANOVA) were used to compare recovery patterns on sociodemographic, premorbid and baseline clinical variables. Using significant variables in baseline comparisons, a multinomial logistic regression was conducted to determine predictors of each pattern of recovery. Nagelkerke's R^2 , as a measure of the proportion of explained

variation in the logistic regression model, was investigated. In addition, the logistic regression analyses yielded odds ratios (ORs), which provided an additional measure of the strength of association.

In order to address longitudinal comparisons, repeated measure analysis of variance (ANOVA-r), adjusted for the covariates sex and age (and years of education for general cognitive function) were also conducted. Post-hoc multiple comparisons were Bonferroni corrected.

Finally, Kaplan-Meier survival analysis and the log-rank test were used to compare time to relapse by recovery patterns.

All statistical tests were two-tailed, and significance was determined at the 0.05 level.

3. Results

Out of the 513 patients enrolled in the program, a recovery measure was obtained for those with information at both 1 and 3-year follow-up assessments, totaling 373. A total of 113 (22%) patients abandoned the program, 56 before 1 year-follow up completion. First year retention rate was therefore 89%. In 25 cases, not 1-year but 3-year follow-up information was available; these 25 patients were not considered drop-outs, but nor were they included in the patterns of recovery classification.

Although there were no significant differences at baseline clinical severity between the group that completed follow ups and the dropout group, the dropout group presented significantly higher unemployment rates (51.9% vs. 39.7%; $p = 0.024$) and they were more frequently cannabis users (60.2% vs. 39.4%; $p < 0.001$). They were as well significantly younger at admission (30.3 ± 9.5 vs. 28.1 ± 8.7 ; $p = 0.029$), with lower education level (46.4% vs. 65.5% elementary education; $p < 0.001$) and were of a larger variety of races (97.6% vs. 85.8% Caucasian; $p < 0.001$). See Table 1.

Between recovery pattern subgroup differences

Comparisons on baseline characteristics of recovery pattern subgroups are presented in Table 2. Sex, education level, marital and occupational status, cannabis use, diagnosis, DUP, DUI, education, premorbid adjustment and level of functioning, negative global symptoms, negative and disorganized dimensions, and global cognitive functioning emerged as significant.

3.1. Predictors of the recovery patterns

A multinomial logistic regression model was used (Nagelkerke pseudo $R^2 = 32.8\%$; $\chi^2 = 92.39$, $p < 0.001$), with recovery pattern as the dependent variable (reference category = Poor Stable pattern) and baseline characteristics as independent variables. Our model showed that schizophrenia diagnoses (OR = 2.24; $p = 0.046$; CI = 1.02–4.95) and severe negative symptoms (OR = 2.09; $p = 0.053$; CI = 0.99–4.42) increased the likelihood of a Poor Stable pattern compared with a Good Stable pattern; those patients with long DUP (OR = 2.15; $p = 0.093$; CI = 0.88–5.27) and high estimated premorbid IQ (OR = 2.28; $p = 0.064$; CI = 0.95–5.46) were more likely to have a Poor Stable pattern compared with a Good Unstable pattern; severe negative symptoms (OR = 3.85; $p = 0.008$; CI = 1.42–10.44) and single status (OR = 4.31; $p = 0.048$; CI = 1.01–18.29) increased the likelihood of a Poor Stable pattern compared with a Poor Unstable pattern (see Table 3). The proportion predicted varied substantially: Good Stable was correctly predicted at 65.8%, Good Unstable at 25%, Poor Unstable at 13.3%, Poor Stable at 64.9%, and the total at 51%.

3.2. Significant measures over time by recovery pattern subgroups

The subgroup effect showed significant differences for the following outcome measures: positive and negative symptoms ($F = 70.11$; $p \leq 0.001$ and $F = 19.29$; $p \leq 0.001$ respectively), psychosocial and cognitive

Table 1
Demographic and clinical characteristics of completer and dropout groups.

	Completer (N = 373)		Dropout (N = 113)		Total (N = 486)		F(df = 1)	p
	Mean	SD	Mean	SD	Mean	SD		
Age at admission (years)	30.3	9.5	28.1	8.7	29.7	9.4	4.806	0.029*
Duration of illness (months)	23.3	37.8	19.6	35.9	22.5	37.4	0.808	0.369
Duration of psychosis (months)	12.9	29.5	11.1	23.2	12.5	28.1	0.322	0.571
	N	%	N	%	N	%	χ^2 (df = 1)	p
Diagnosis (schizophrenia)	200	53.6	56	49.6	256	52.7	0.574	0.449
Sex (male)	214	57.4	70	61.9	284	58.4	0.747	0.387
Race (Caucasian)	364	97.6	97	85.8	461	94.9	24.524	<0.001*
Education level (elementary)	173	46.4	72	65.5	245	50.7	12.365	<0.001*
Socioeconomic status of parents (Low)	192	51.6	62	59.0	254	53.2	1.818	0.178
Urban area (yes)	262	70.2	85	78.7	347	72.1	2.984	0.084
Living with parents (yes)	203	54.4	48	44.4	251	52.2	3.342	0.068
Living with family (yes)	274	73.5	73	67.6	347	72.1	1.434	0.231
Student (yes)	80	21.4	20	18.2	100	20.7	0.552	0.458
Single (yes)	281	75.3	81	73.6	362	74.9	0.131	0.718
Couple (yes)	63	16.9	24	21.8	87	18.0	1.397	0.237
Unemployed (yes)	148	39.7	56	51.9	204	42.4	5.082	0.024*
Occupational status (yes)	193	51.7	45	41.7	238	49.5	3.401	0.065
Family psychiatric history (yes)	92	24.7	24	21.4	116	23.9	0.496	0.481
Hospital status inpatient (yes)	256	68.6	80	70.8	336	69.1	0.190	0.663
Tobacco use (yes)	211	56.6	65	57.5	266	56.8	0.032	0.858
Cannabis use (yes)	147	39.4	68	60.2	215	44.2	15.162	<0.001*
Alcohol use (yes)	189	50.9	68	60.7	257	53.2	3.299	0.069
Baseline clinical assessment	Mean	SD	Mean	SD	Mean	SD	F(df = 1)	p
SAPS	13.7	4.4	13.7	4.5	13.7	4.4	0.002	0.962
SANS	6.8	6.2	6.5	6.1	6.7	6.1	0.143	0.706
Positive dimension	7.4	2.4	7.4	2.5	7.4	2.4	0.007	0.932
Disorganized dimension	6.2	3.5	6.3	3.7	6.3	3.5	0.014	0.905
Negative dimension	4.9	5.6	4.9	5.8	4.9	5.6	0.002	0.968
BPRS	62.8	13.4	63.3	14.5	62.9	13.6	0.085	0.771
CDSS	2.4	3.4	2.0	2.9	2.3	3.3	1.461	0.227

Abbreviations: SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia.

Table 2
Differences in baseline characteristics between subgroups of recovery trajectory.

Characteristics	Good stable		Good unstable		Poor unstable		Poor stable		Total		F(df = 3)	p	Post hoc
	(N = 98)		(N = 77)		(N = 37)		(N = 161)		(N = 373)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age at admission (years)	30.93	8.24	31.11	10.46	27.73	8.28	30.02	9.95	30.26	9.50	1.276	0.282	
Age at psychosis onset (years)	30.42	8.10	30.32	10.47	27.48	8.21	28.19	9.20	29.15	9.15	2.041	0.108	
Duration of illness (months)	10.84	16.11	23.39	31.39	17.38	21.35	33.06	49.66	23.49	37.96	7.512	<0.001	GS < PS
Duration of psychosis (months)	6.14	12.81	9.59	16.78	5.76	8.04	20.29	41.04	12.89	29.51	6.307	<0.001	GS < PS; GU < PS; PU < PS
Education (years)	11.27	3.56	10.56	2.99	9.78	2.80	9.75	3.14	10.32	3.25	5.083	0.002	GS < PS
Premorbid IQ	98.96	13.63	95.78	11.45	93.28	9.38	94.16	14.67	95.83	13.38	2.710	0.045	GS > PS
Premorbid adjustment (PAS)	1.63	0.91	2.22	1.17	2.25	1.23	2.67	1.52	2.26	1.34	12.910	<0.001	GS < GU; GS < PS
Level of functioning (DAS)	0.97	1.31	1.18	1.40	1.39	1.61	1.71	1.55	1.37	1.49	5.552	<0.001	GS < PS
Positive symptoms at admission (SAPS)	13.37	4.67	13.27	3.82	14.32	4.53	13.88	4.39	13.66	4.37	0.771	0.511	
Negative symptoms at admission (SANS)	4.95	5.18	7.43	5.37	4.86	4.44	8.02	7.01	6.78	6.16	6.812	<0.001	GS < GU; GS < PS; PU < PS
Psychotic dimension	6.95	2.44	7.23	2.45	7.19	2.37	7.84	2.42	7.42	2.44	3.096	0.027	GS < PS
Disorganized dimension	6.42	3.48	6.04	3.29	7.14	3.58	6.04	3.47	6.25	3.45	1.178	0.318	
Negative dimension	2.89	4.28	5.36	5.18	2.78	3.91	6.32	6.28	4.87	5.58	10.390	<0.001	GS < GU; GS < PS; PU < PS
Global cognitive functioning	1.13	0.76	1.64	0.95	1.48	0.82	1.67	1.05	1.48	0.95	6.000	<0.001	GS < GU; GS < PS; PU < PS
	N	%	N	%	N	%	N	%	N	%	χ^2 (df = 3)		
Diagnosis													
Schizophrenia	27	27.6	40	51.9	20	54.1	113	70.2	200	53.6	44.637	<0.001	GS < GU; GS < PU; GS < PS; GU < PS
Other schizophrenia spectrum diagnoses	71	72.4	37	48.1	17	45.9	48	29.8	173	46.4			
Education level (elementary)	35	35.7	32	41.6	18	48.6	88	54.7	173	46.4	9.716	0.021	GS < PS
Sex (male)	42	42.9	40	51.9	24	64.9	108	67.1	214	57.4	16.423	0.001	GS < PU; GS < PS; GU < PS
Socio-economic status of parents (Not/Low qualified worker)	44	44.9	39	51.3	18	48.6	91	56.5	192	51.6	3.456	0.327	
Urban area (yes)	73	74.5	61	79.2	25	67.6	103	64.0	262	70.2	6.967	0.073	
Living with family (yes)	72	73.5	60	77.9	27	73.0	115	71.4	274	73.5	1.132	0.769	
Single (yes)	63	64.3	60	77.9	27	73.0	131	81.4	281	75.3	9.980	0.019	GS < PS
Occupational status (employed/active)	61	62.2	38	49.4	22	59.5	72	44.7	193	51.7	8.567	0.036	GS > PS
Family psychiatric history (yes)	25	25.5	24	31.2	7	18.9	36	22.4	92	24.7	2.908	0.406	
Hospital status inpatient (yes)	66	67.3	54	70.1	20	54.1	115	71.4	255	68.4	4.360	0.225	
Tobacco use (yes)	55	56.1	40	51.9	26	70.3	90	55.9	211	56.6	3.534	0.316	
Cannabis use (yes)	34	34.7	28	36.4	22	59.5	63	39.1	147	39.4	7.446	0.059	GS < PU; GU < PU; PU > PS
Alcohol use (yes)	50	51.5	41	53.9	24	64.9	74	46.0	189	50.9	4.756	0.191	

functioning ($F = 105.24$; $p \leq 0.001$ and $F = 2.91$; $p = 0.037$ respectively) and mean chlorpromazine equivalent dose ($F = 22.08$; $p \leq 0.001$) (See Figs. 1 to 5).

3.3. Relapses

Number of relapses by recovery pattern showed significant differences ($\chi^2 = 37.936$; $p = 0.001$). No relapse occurred for 66% of Good Stable, 67% of Good Unstable, 27% of Poor Unstable, and 44% of Poor Stable. Similar relapse rates were found for Good Stable and Good Unstable subgroups, as well as for Poor Unstable and Poor Stable recovery patterns. However, significant differences emerged between Good Stable and Poor Unstable ($\chi^2 = 12.59$; $p = 0.001$), Good Stable and Poor Stable ($\chi^2 = 10.78$; $p = 0.001$), Good Unstable and Poor Unstable ($\chi^2 =$

12.504; $p = 0.001$), and Good Unstable and Poor Stable ($\chi^2 = 10.286$; $p = 0.001$), revealing Poor Unstable and Poor Stable with higher relapse rates.

Time to first relapse from entry into the study was entered in Kaplan-Meier survival analysis. Survival curves of the four recovery patterns were significantly different (log-rank [Mantel-Cox] $\chi^2 p = 25.13$; $p < 0.001$) (presented in Fig. 6). Similar relapse rates were observed between Good Unstable and Poor Unstable recovery subgroups during the first 600 days; after, relapse rates appeared to be about twice as high in the Poor Unstable recovery subgroup (log-rank [Mantel-Cox] $\chi^2 p = 13.28$; $p < 0.001$), and overtook the Poor Stable recovery subgroup; in the Good Stable recovery subgroup, after a high initial relapse rate, the curve approached that of the Good Stable recovery subgroup and came out on par at approximately the 2 year follow-up.

4. Discussion

This study explored the subtypes of recovery patterns of 373 FEP patients included in an EIS program that spanned 3 years. The results suggest that, controlling for clinical and functional remission, recovery from FEP is heterogeneous in rate and across time. Four recovery patterns were characterized and the evidence that distinct recovery subgroups exist is consistent, which may allow more subtle and precise classification. Each recovery pattern has a number of characterized and predictive variables.

There is a subgroup that presented a good and sustained recovery pattern, formed by FEP patients (26%) that achieve recovery during the first year of follow-up and maintain recovery by the 3-year follow-up. This subgroup has been conceptualized as early full recovery in

Table 3
Multivariate logit regression on factors for recovery trajectories in FEP patients.

	OR	P-value	95% CI	
			Lower	Upper
Good stable vs. Poor stable				
Negative symptoms	2.092	0.053	0.990	4.419
Diagnosis (other vs. schizophrenia)	2.242	0.046	1.015	4.954
Good unstable vs. Poor stable				
DUP (short vs. long)	2.152	0.093	0.879	5.270
Premorbid IQ (low vs. high)	2.281	0.064	0.954	5.457
Poor unstable vs. Poor stable				
Negative symptoms	3.851	0.008	1.422	10.435
Single	4.307	0.048	1.014	18.293

Nagelkerke pseudo $R^2 = 32.8\%$; $\chi^2 = 92.39$, $p < 0.001$.

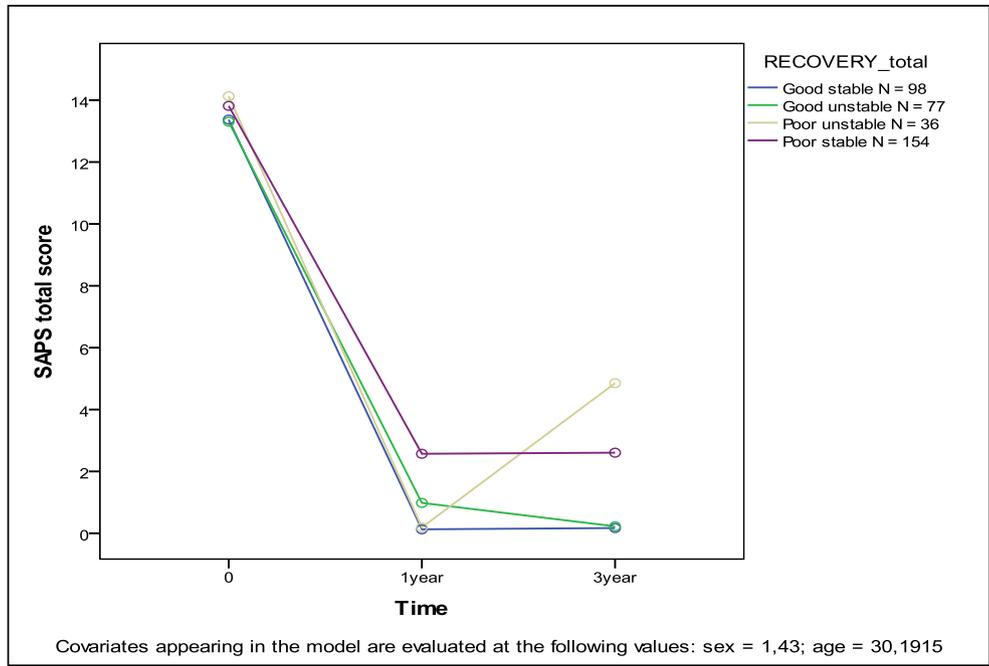


Fig. 1. Positive symptoms in the four recovery patterns.

early intervention and secondary prevention strategies at the time of a FEP (Fusar-Poli et al., 2017). Attending their baseline characteristics (active, female, married, cannabis non-users, not diagnosed with schizophrenia, short DUP, high level of education, good premorbid adjustment, high premorbid IQ, good baseline functioning, less severe negative and disorganized symptoms and high global cognitive functioning) one could say those are “the best” of the FEP patients presenting in clinical practice. Consequently, this subgroup also presented with a lower relapse rate (34%), and consequently a lower antipsychotic dose from the beginning to the end of the 3-year time span. In spite of this, as showed by Leucht et al. (2012), the risk of relapse after an FEP (26% in

their systematic review), even in medication maintenance patients, cannot be neglected.

There is a subgroup of FEP patients (21%) who, having not achieved clinical or functional recovery at 1-year follow-up, were found in full recovery parameters at 3-year follow-up. This that not correspond to the idea that for those patients completing the first year of treatment in EIS, approximately half achieve recovery (Whitehorn et al., 2002). DUP and estimated premorbid IQ emerged as predictors for those late and sustained recovery pattern subgroup. Interestingly, the role of DUP could be explained as a timing issue, meaning that those cases who receive treatment after a longer time with symptoms would need

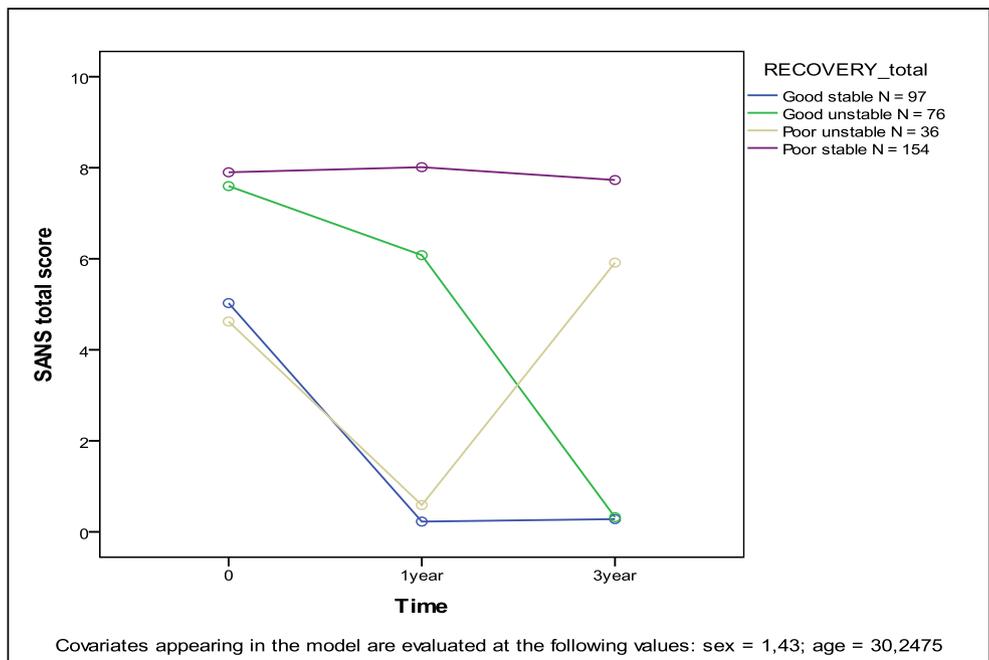


Fig. 2. Negative symptoms in the four recovery patterns.

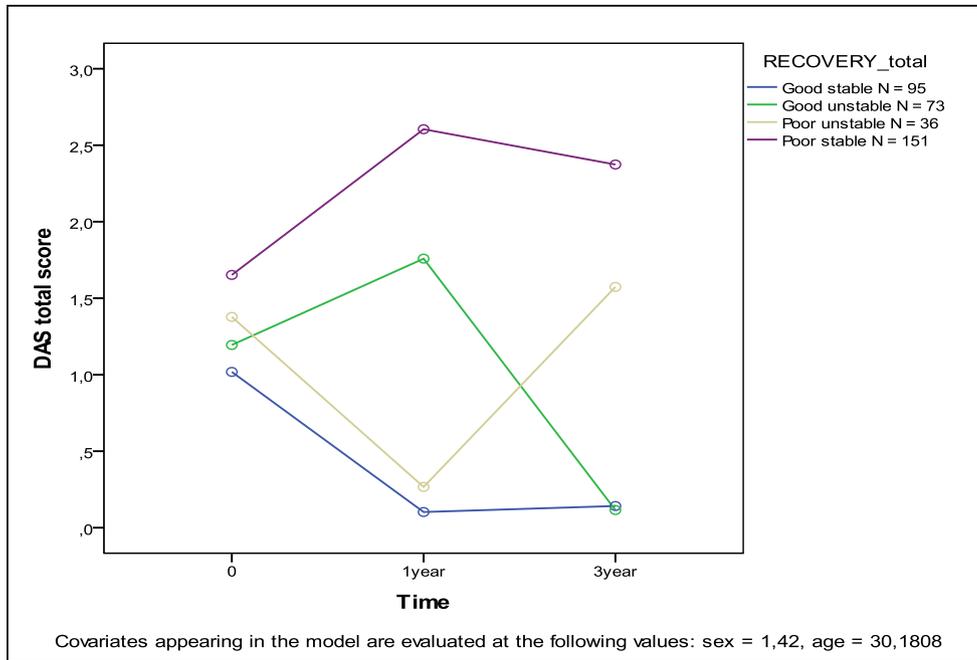


Fig. 3. Functioning in the four recovery patterns.

more time to achieve total recovery. Delaying treatment for psychosis may have a negative impact on its long-term course. The explanation given by Marshall et al. (2005) is that untreated psychotic symptoms may be toxic in terms of symptomatic recovery. These authors suggested that the chance of recovery is evenly distributed across time. EIS have been established to provide care soon after a diagnosis of psychosis has been recognized. But EIS should also include long-term follow-up, because in some cases benefits, such functional gain, only appeared during long term monitoring (Crumlish et al., 2009; Wunderink et al., 2013). Concerning IQ, our results suggest that early in the course of schizophrenia IQ is a sensitive and reliable predictor of recovery (Leeson et al., 2009). Studies focusing on IQ support the strong

association between low premorbid IQ and increased risk for schizophrenia (Woodberry et al., 2008). Higher estimated premorbid IQ has been associated with higher functioning on a variety of outcome measures (Ayesa-Arriola et al., 2017). This may reflect the buffering effects of reserve capacity or premorbid differences in age and IQ-related cognitive functioning (Green et al., 2008). Another factor to be considered that would be crucial for this subgroup, is the observed reduction in relapses and antipsychotic treatment. Survival analyses showed that after a first year of high relapse rate, relapses decrease to the point of equalization with relapses presented in the Good Stable recovery group (33% and 34% respectively). The flattening of the relapse rates was accompanied by significant antipsychotic dose reduction. This confirms that each

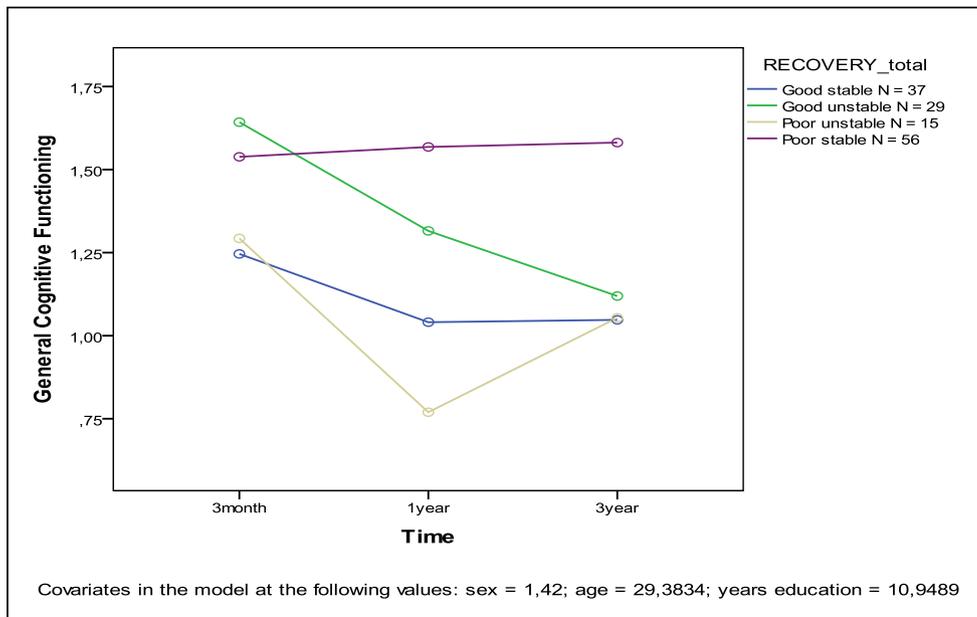


Fig. 4. General cognitive functioning in the four recovery patterns.

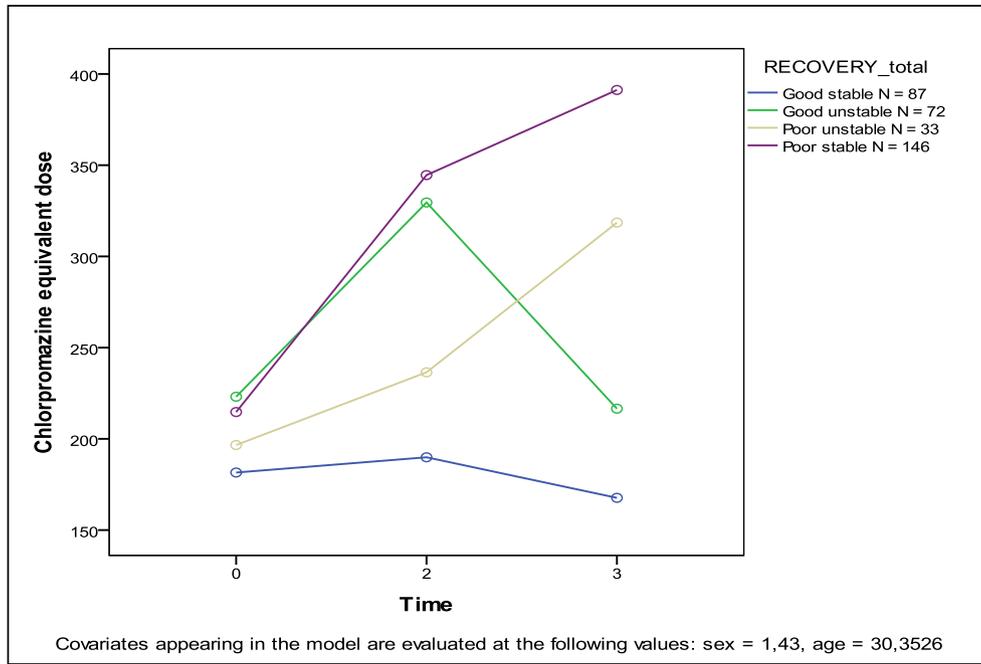


Fig. 5. Chlorpromazine equivalent dose in the four recovery patterns.

relapse is a traumatic experience associated with potentially serious psychosocial and functional consequences that are impacting the quality of life of the patient (Fusar-Poli et al., 2017).

There is a subgroup of FEP patients (10%) which presented an early but unsustainable pattern of recovery, predicted by presenting less severe negative symptoms and married status at baseline. This is a particular subgroup that during the first year achieved recovery but, unexpectedly at 3-year follow-up did not meet requirements of total recovery. A large

amount of literature supports the premise that negative symptoms are better predictors of concurrent and future socio-occupational functioning than positive symptoms (Rabinowitz et al., 2012). Hovington et al. (2012), found that those FEP patients who demonstrated negative symptoms at baseline showed significantly worse functioning when assessed again at 1-year in comparison to FEP patients without negative symptoms. Whitehorn et al. (2002) found that most of the symptom improvement occurred during the first 6 months of treatment.

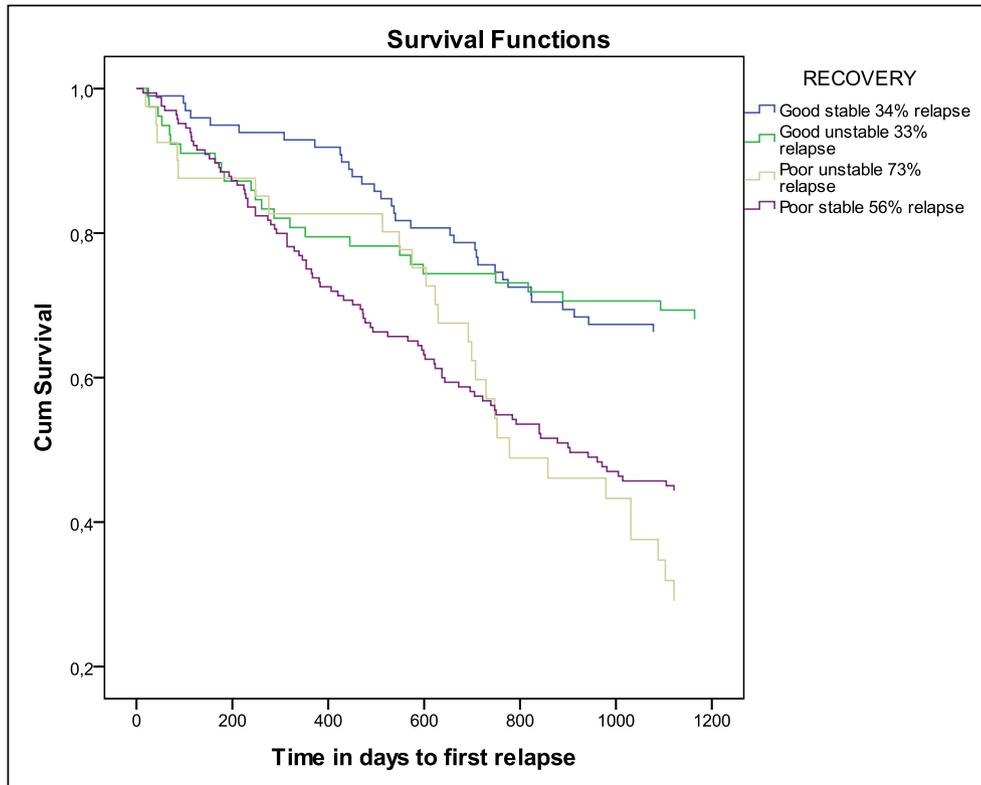


Fig. 6. Kaplan Meier survival estimates by recovery patterns.

However, as Sarkar et al. (2015) noted, negative symptoms are more difficult to treat than positive symptoms of schizophrenia, representing an unmet therapeutic need for a large numbers of patients. Little has been done to address the significant functional impairments in the disorder that are associated with negative symptoms. Negative symptoms and the resulting loss in productivity are responsible for much of the world-wide personal and economic burden of schizophrenia. Therefore, effectively treating negative symptoms could help to prevent long term disability in first episode patients with schizophrenia (Sarkar et al., 2015). We now turn to single status as a predictor of poor recovery. Patients with schizophrenia are not born into pre-determined ecological and social disadvantages; however, it is well known that they fall significantly behind controls in marriage or stable partnership (Murray et al., 2002). Messias et al. (2007) reported that individuals diagnosed with schizophrenia are more likely to be single than others, even as many as 20 years prior to diagnosis. Several studies show low marital rates for schizophrenic patients when compared with controls and other groups of mentally ill patients. Single patients present with a poor clinical course. Likewise, there are lower rates of single status among women than men, and lower socioeconomic status among the divorced, with clear evidence for selection of schizophrenia among those never married (Sharma et al., 2013). It is important to understand that sufferers of psychosis are often receivers of care from dedicated care givers, a fact that presents itself with many advantages. For example, receivers of care can be taught to recognize impending symptoms of relapse, helping them to avoid trigger situations. Care givers can also encourage patients to comply with treatments and to recognize early signs of serious treatment side effects. Persons who live alone, on the other hand, may lack medication supervision and have difficulty accessing medical care. In sum, lack of support might hinder persons with schizophrenia in achieving recovery. Certainly, an important aspect of this subgroup is their higher rate of relapse (73%) and the increase of doses of antipsychotics over time. Previous studies report a 41% relapse rate in FEP patients when taken as a homogeneous group (Kam et al., 2015), which is nearly half of the current subgroup's rate of relapse. Particularly note-worthy is that relapses increased after the first-year follow-up. This again places an emphasis on relapse prevention, specifically in the first year, and particularly for those who have experienced a previous relapse. This knowledge is necessary if strategies are to be developed that have the potential to improve and maintain hard won gains with intensive early intervention (Kam et al., 2015). It should be noted that recovery style changed over time, suggesting it was not a stable trait. The capacity for recovery raises the need for psychoeducation and other psychological interventions that could improve outcome (Thompson et al., 2003).

Finally, there is a subgroup within these FEP samples (43%) that did not achieve neither symptomatic nor functional remission. This non-recovery pattern was predicted by severity in negative symptoms and schizophrenia diagnoses. This may be seen as a tautological and circular explanation, since unfavorable illness courses, which encompass non-symptomatic and functional remission, are specific diagnostic criteria for schizophrenia, particularly in those cases with negative symptoms at baseline (Hovington et al., 2012). Schizophrenia features are strong predictors of poor long-term outcomes in FEP patients with odds ratios ranging from 5.70 to 5.86 (Austin et al., 2015). It has been suggested to exclude from treatment discontinuation/reduction strategies those FEP patients who have been diagnosed with schizophrenia at baseline (Alvarez-Jimenez et al., 2016). Not surprisingly, this subgroup presented a high (56%) and stable rate of relapse, with a higher antipsychotic dose that significantly increased over time. One again we remark on the importance of relapse on illness progression in predicting vulnerability to further episodes and risk of functional decline (Kam et al., 2015). Emsley et al. (2013) found that 80% of patients with schizophrenia were judged to have deteriorated over time in a 7-year follow-up study. The degree of deterioration in that study was significantly correlated with the number of relapses the patients experienced.

Individuals with recurrent relapses often do not achieve full symptomatic recovery, leading to a chronic course (Crumlish et al., 2009). Furthermore, treatment failure after relapse is evident in 16% of FEP and 14% of multi-episode samples (Emsley et al., 2013). However, to date there is limited empirical evidence to support illness progression after each relapse (Zipursky and Agid, 2015). In a previous study, we found poor adherence (OR 2.9) and schizophrenia diagnosis (OR 2.2) as the most robust predictors of a first relapse, which was also consequently associated with a higher risk of relapse at 3 years (OR 2.17) (Pelayo-Teran et al., 2017). Tools for the identification of a risk of relapse, such as the identification of such subgroups, can be especially useful at this early phase of illness (Tibbo et al., 2014). As previously mentioned by Tibbo et al. (2014), EIS have reported improvements in regular care, but there still remains a substantial barrier to recovery. Psychosocial rehabilitation interventions should be considered as evidence-based practices to promote recovery and need to become a major part of the standard treatment of the disease (Morin and Franck, 2017). Mental health professionals need to join with patients and their families in understanding that schizophrenia is not a malignant disease that inevitably deteriorates over time but rather one from which most people can achieve a substantial degree of recovery (Zipursky et al., 2013).

4.1. Limitations

All participants were EIS assigned, thus we did not conduct a randomized controlled trial for evaluating effectiveness of EIS in recovery. Some of the results presented confirm previous findings with shorter follow-up times. However, outcomes with a longer period should be considered. As stated by Wunderink et al. (2013) striking differences in recovery were seen at longer-term follow-up. The differences after 7 years did not appear in symptom remission or relapse rates but in functional remission and recovery. According to a systematic review by Menezes et al. (2006), 42% of people who have experienced a FEP presented a good outcome. However, treatment protocols are one size fits, while there is a wide spectrum of outcome. EISs should include recovery as their primary outcome and should include long-term follow-up because in many cases the benefits, such as functional gain, only appear during long term monitoring. Clearly, the length of treatment required in optimal EIS warrants further investigation. Finally, even though the approach to subgroup identification differed across studies, similar patient profiles have generally been identified (Jaeger et al., 2006). The question remains whether additional exploratory studies of this kind would increase our understanding of the patterns of recovery in FEP patients.

5. Conclusions

We consider the time-to-recovery findings presented in this paper to have important implications for EIS. Recovery focused interventions are a primary clinical goal, and need to be delivered over the long-term. We suggest that the identification of recovery patterns is useful in subgroups that appear consistent across cohorts and over time and differ on a number of key characteristics. The focus should be on robust identifiable and modifiable risk factors of poor recovery, such as shortening DUP, decreasing negative symptoms and preventing relapses. Taken together, the results have implications for EIS, timing and length of interventions in FEP.

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Contributors

All the authors have participated and have made substantial contributions to this paper.

Rosa Ayesa-Arriola: conception, design, statistical analysis, interpretations of data and drafting the article.

Jose María Pelayo Terán, Esther Setién-Suero and Karl Neergaard: statistical analysis, interpretations of data and revising the article.

Susana Ochoa, Mariluz Ramírez-Bonilla: interpretations of data and revising the article.

Rocio Pérez-Iglesias and Benedicto Crespo-Facorro: conception, desing and revising the article.

Conflict of interest

The authors have no conflict of interest to declare.

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