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ORIGINAL PAPER

Rates and predictors of relapse in first-episode non-affective psychosis: a 3-year longitudinal study in a specialized intervention program (PAFIP)

José María Pelayo-Terán[1,2] · Virginia Gajardo Gajardo Galán[1,3] · Víctor de la Ortiz-García de la Foz[1,2] · Obdulia Martínez-García[1,2] · Rafael Tabarés-Seisdedos[2,4] · Benedicto Crespo-Facorro[1,2] · Rosa Ayesa-Arriola[1,2]

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Abstract Relapses may represent a critical hazard in schizophrenia spectrum disorders as they are associated with an increased risk of a clinical and functional deterioration. Preventing relapse after recovering from a first psychotic episode has become a major challenge due to its critical impact on lifelong functionality. This study explored the rate of first and second relapses and the predictors associated with these relapses in a large cohort of non-affective psychosis patients during a period of 3 years after the first break of the illness. From February 2001 to May 2014, sociodemographic and clinical data from an epidemiological cohort of 341 non-affective first-episode psychosis patients at risk of relapse were analysed at a specialized early intervention service. Logistic regression, Cox regression, and Kaplan–Meier survival analyses were performed to compare non-relapsed and relapsed patients. One hundred and sixty-six (48.7%) individuals relapsed at least once. Median time to relapse was 17.0 months in non-adherent patients and 40.0 months in adherent patients (log-rank χ^2: 51.36; $p < 0.001$). Non-adherence to medication (odds ratio-OR 2.979; $p < 0.001$), schizophrenia diagnosis (OR 2.173; $p = 0.002$), and age of onset (OR 1.020; $p = 0.033$) were the main predictors of the first relapse. Fifty-six subjects experienced a second relapse (33.73%) predicted by diagnosis (OR 1.975; $p = 0.074$), age of onset (OR 1.078; $p = 0.003$), and positive symptoms (OR 0.863; $p = 0.03$), but not adherence. Non-adherence is the main predictive factor of first relapse after a first episode of psychosis. Second relapses were not often and not related to modifiable factors, suggesting that multiple relapsed patients may comprise a subgroup with a higher biological risk.

Keywords First-episode psychosis · Schizophrenia · Relapse · Adherence · Longitudinal studies

Introduction

Relapses may represent a critical hazard in schizophrenia spectrum disorders as they are associated with an increased risk of a clinical and functional deterioration [1, 2]. The number of relapses has been associated with a greater risk of hospitalizations, chronicity and lack of clinical response [3, 4], brain tissue loss [5], suicide, or violence [6, 7], and it has suggested that they may lead to losses in clinical, social, and vocational recovery [8]. Even though this relationship has not been proven to be causal, it has been shown that relapses increase the economic cost, an enhanced burden for families and a higher stigma for patients [9, 10]. Despite early intensive interventions, as far as 82% of patients with a first episode of psychosis (FEP) may relapse during their first 5-years follow-up [11]. A recent systematic review revealed a rate of relapse of 77% in remitted first-episode patients during the first-year following antipsychotic discontinuation [12]. Likewise, in a previous report analysing a subsample of 140 individuals enrolled in PAFIP, we have described

José María Pelayo-Terán and Virginia Gajardo Gajardo Galán have contributed equally to this article.

✉ José María Pelayo-Terán
pelayoteran@gmail.com

1 Department of Medicine and Psychiatry, University Hospital Marques de Valdecilla, School of Medicine, University of Cantabria-IDIVAL, Santander, Spain

2 Centro Investigación Biomédica en Red Salud Mental (CIBERSAM), Santander, Spain

3 Complejo Hospitalario Universitario Infanta Cristina, Badajoz, Spain

4 Department of Medicine, Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain

a relapse rate of the 65% at 3 years after the first break of the illness and the only significant predictor for relapse was non-adherence to antipsychotic medication [13].

Preventing relapses in the early phases of the illness has been suggested to be crucial to achieve a better outcome [14, 15]. Therefore, the identification and, in turns, the modification of factors determining clinical relapses are timely and relevant topics of investigation. Clinical variables and general demographic variables appear to have little impact on relapse rates, whereas non-adherence to medication, persistent substance use disorder, carers criticism, and poorer premorbid adjustment significantly increase the risk of relapse in FEP [16]. Interestingly, the highest risk factor was the lack of treatment adherence (a fourfold risk). With regard to multiple relapses, there is a lack of information in the prevalence of subsequent relapses after a first relapse in the follow-up of patients experiencing a first episode of psychosis. Earlier studies suggest a similar rate of first and second relapses [11], but a lower rate of subsequent relapses may be expected by the implementation of preventive approaches within an early intervention service in selected patients after their first relapse [16]. Confirming this main association is important in order to develop effective preventive approaches that make an effort in improving modifiable factors such as non-adherence that may contribute to reduce relapses and associated costs. Mayoral and colleagues (2016) described that the rate of symptom recurrence over the 3-year period in functionally recovered FEP patients following the self-elected discontinuation of antipsychotic treatment is extremely high (67.4%). Remarkably, relapsed individuals had a greater severity of symptoms and lower functionality after 3 years compared to those patients who did not relapse during the follow-up [15].

Our hypotheses were that adherence to medication is the main predictor factor of having a relapse after a FEP and that the specific intervention programs may reduce the incidence of second relapses. In the present study, with an extended sample of 393 first-episode patients followed up in the longitudinal intervention program of first-episode psychosis, *Programa Asistencial de Fases Iniciales de Psicosis* (PAFIP), at the Marques de Valdecilla University Hospital (Santander, Spain) and using the previous definition for relapse [13], we investigated the rate of first and second relapses and the predictors of an increasing risk of relapse during the 3-year period after a first episode of psychosis.

Methods

Study setting

The participants in this study were drawn from an ongoing longitudinal intervention program of first-episode psychosis, PAFIP, University Hospital Marques de Valdecilla, Spain [17]. In conformance with international standards for research ethics, the local institutional review board approved this program. PAFIP is an early intervention service aimed to early detect and treat patients with a first episode of psychosis in the autonomous region of Cantabria. Patients meeting inclusion criteria, and their families provided written informed consent to be included in the PAFIP. As a clinical program, PAFIP includes inpatient and outpatient care, and provides specific and personalized clinical attention, cognitive behavioural psychotherapeutic interventions and psychopharmacological treatment of patients, and also family interventions, during the first 3 years after program intake. A more detailed description of the PAFIP program has been previously presented elsewhere [18].

Study design

The present study was a prospective observational study. Patients from the PAFIP study who had a good response to antipsychotic treatment and achieved clinical stability according to inclusion criteria were followed up for 3 years.

During the follow-up period, trained psychiatrists assessed clinical status of the patients and data on antipsychotic treatment (doses, concomitant medications and dropouts); the appearance of relapses (according to previous definition) was regularly recorded.

Subjects

From February 2001 to May 2014, all referrals to PAFIP meeting the inclusion criteria: (1) 15–60 years; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) no prior treatment with antipsychotic medication or if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; and (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder, were eligible. Referrals were excluded because of any of the following reasons: (1) meeting DSM-IV criteria for drug dependence excluding nicotine and caffeine, (2) meeting DSM-IV criteria for mental retardation (premorbid intelligence quotient scores were estimated from the Wechsler Adult Intelligent Scale-III vocabulary subtest), (3) having a history of neurological disease or head injury. Patients meeting these criteria and their families provided written informed consent to be included in the PAFIP. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID–I) [19], carried out at 6 months after the baseline visit.

Only PAFIP patients who achieved clinical improvement (CGI rating $\leq$4 and a decrease of at least 30% on BPRS

total score and all BPRS key symptom items, by being rated ≤3) for more than four consecutive weeks at some point during the first six months following program entry were included in the current investigation.

Clinical assessments

The severity scale of the Clinical Global Impression (CGI) Scale [20] was used to measure the overall severity of illness. Clinical symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) [21], the Scale for the Assessment of Positive symptoms (SAPS) [22], the Scale for the Assessment of Negative symptoms (SANS) [23], the Calgary Depression Scale for Schizophrenia (CDSS) [24], and the Young Mania Rating Scale (YMRS) [25].

Complete clinical evaluations (all clinical and side effect scales were used) were conducted at baseline, 6 weeks, 12 and 36 months. In addition, clinical visits were carried out approximately every month during the follow-up, with regular CGI assessments. Patients were followed in our outpatient clinic with rapid and easy access to a clinical appointment at any time, for any possible signs/symptoms of clinical exacerbation that might appear. If this would be the case, a thorough clinical assessment was performed to evaluate the severity of clinical symptomatology or criteria of relapse.

Definitions of predictor variables

The analysed variables included sociodemographic, clinical, and premorbid variables. Sociodemographic variables were recorded from patients, family members, and medical records: gender, marital status (1. Single or never married/conjugal; 2. Other status); living arrangements at psychosis onset (1. Living with relatives; 2. Living alone and other status); occupational status during the 2 years prior to the initial interview (1. Employment/student; 2. Unemployed); socio-economic status assessed by the Hollingshead and Redlich Scale [27] (1—high ≤ 3; 2—low ≥ 4); educational level (1—primary education; 2—10 years of education or higher); urbanicity (growing up and living most of the life in a city with more than 10,000 inhabitants). Clinical variables included: duration of untreated illness (DUI) defined as the time in months from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to the previous stable level of functioning) to the initiation of adequate antipsychotic drug treatment. The duration of untreated psychosis (DUP) is defined as the time from the first continuous (present most of the time) psychotic symptom to the initiation of adequate antipsychotic drug treatment. Initial symptom severity was assessed by total score of BPRS, SAPS, and SANS, and the psychotic, disorganized, and negative dimensions. Insight was assessed by the three dimensions of the abbreviated Scale to Assess Unawareness of Mental Disorder (SUMD) [28], and the dimensions were dichotomized into scores greater than 1 (good insight) or 1 (poor insight). Premorbid variables included the evaluation of history of cannabis use at baseline and three years with a semi-structured interview (1- sporadic or frequent use of cannabis, defined as 1 or more times a week for at least the last year; 2- non-cannabis use) and history of drug use at baseline (1- sporadic or frequent use of cocaine or other illicit drugs, defined as 1 or more times a week for at least the last year; 2- non-drug use). The first-degree family history of psychosis was based on the subject and family reports. Current family support was assessed with a 3-point rating (insufficient, fair and sufficient), based on material and emotional support, and scores of fair and insufficient were classified as poor family support. Finally, the premorbid functioning in childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years), and adulthood was measured by the Premorbid Adjustment Scale (PAS) [29] with the recommended modifications for first-episode psychosis patients [30]. A more detailed description of our predictor variables has been previously reported [13].

Adherence to antipsychotic drugs was assessed by gathering information about medication compliance from patients and close relatives putting together the information collected by different professionals involved in clinical follow-up (social workers, nurses, psychologists, and psychiatrists). For the present investigation, patients were dichotomized into having good (defined as patients regularly taking at least 90% of prescribed medication) and a poor adherence to medication during the observation period. This definition of adherence has been successfully used in previous reports from the PAFIP Cohort [13, 26]

Definition of relapse

Main outcome variables were relapse rates and time up to first relapse. According to our previous definition published elsewhere [13, 26], patients who achieved clinical improvement and stability (see above) were considered at risk of relapse over the 3-year period.

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 one week.

Data analysis

Data were analysed using SPSS (SPSS Inc., Chicago, IL, USA) version 17.0. The main objective of the analysis was to identify predictors of the first and second relapses after a first episode of non-affective psychosis.

A dichotomous variable was created which assigned a value of 1 once a patient experienced a relapse, 2 if the patient finished the follow-up without a relapse and 3 if the patient dropped out during follow-up (censored subjects). The included predictors were initially analysed with the univariate t-tests and Chi-square tests, depending on the nature of the variable, in order to compare characteristics of patients who relapsed with those who did not relapse after their first episode of psychosis.

Following univariate analyses, a backward logistic regression analysis was performed to predict relapse, including those predictor variables that were significantly associated with relapse (or a trend to significance with a $p < 0.075$) in the univariate analysis. Multiple Cox proportional hazards regression analysis was performed to confirm the robustness of the model and its association with time up to first relapse. Kaplan–Meier survival curves and a log-rank test were used to assess time to relapse and to compare median time to relapse between adherent and non-adherent patients. Patients who dropped out of the study or initiated an antipsychotic discontinuation strategy [15] were categorized as censored observations at the time of the occurring event.

Additionally, a second logistic regression model to predict second relapses in those patients who had a first relapse was performed with the same methodology.

Results

Description of study cohort

From 393 patients initially included in the PAFIP program, 341 achieved clinical improvement and stability accordingly to our previous definition. Clinical and sociodemographic characteristics of the sample, compared by relapse status at the end of the study are shown in Table 1. The overall dropout rate at three years was low ($N = 48$; 14.08%). Dropout reasons included the following: 21 patients due to own decision; 12 patients changed living catchment area; four died during follow-up and 11 dropouts were due to other reasons. Eight of these dropouts were after the first relapse (two patients died, four patients changed their living area and two more dropouts were due to other reasons). Figure 1 shows the trial profile.

From the 341 initial subjects, 243 (71.26%) were classified as adherent patients according to our definition, and 95 (27.86%) were non-adherent. In three subjects (0.88%), there was not enough information available to assess adherence.

Rates of relapse

Of the 341 patients, 166 (48.68%) experienced a relapse at least once over the 3-year period. The relapse rates along the three years were: 21.60% in the first year (70 relapses from 324 subject at risk); 14.84% in the second year (46 subjects relapsed from 310 subjects at risk; cumulative risk of first relapse: 36.02%); and 16.89% in the third year (40 relapsed from 296 subjects at risk; cumulative risk of first relapse: 48.68%). It must be noticed that the maximum follow-up was 1200 days: 3 years and 4 months.

Of the first 166 relapsed patients, 56 patients suffered a second relapsed (33.73% of the 166 patients at risk). Of these, 15 experienced a third relapse (26.79% of the 56 patients at risk of third relapse). Only six of these 15 patients had a fourth relapse, and just one of these subjects experienced a fifth relapse over the period.

Predictors of first and subsequent relapses

Differences in predictor variables between subjects with and without relapses during follow-up are analysed in Table 1. The only significant factors associated with relapse were non-adherence to medication, schizophrenia diagnosis, a younger age, and age of onset, and there was a trend in the association with a longer DUP. Given the high correlation between age at admission and age of onset, only this last variable was included in further analysis in order to avoid collinearity between variables. Differences between patients with one relapse and more than one relapse during follow-up are analysed in Table 1. The significant factors associated with more than one relapse were a younger age of illness onset and at study entry, a lower initial severity of positive symptoms (total score of SAPS) and a trend in the association with schizophrenia diagnosis.

The logistic regression analysis for the first relapse included adherence, diagnosis and duration of untreated psychosis, and none of them were excluded in the backward analysis. DUP was transformed into years in order to better understand the relationship between DUP and relapse. The model was statistically significant (Nagelkerke's $R^2 = 0.147$; $\chi^2 = 39.487$; $p < 0.001$). Odds ratio (OR) values and confidence intervals for the predictor variables are shown in Table 2.

Similarly, the Cox regression analysis with relapse by observation time as the dependant variable did not exclude any of the predictors in the backward analysis and was a statistically significant model ($\chi^2 = 64.060$; $p < 0.001$). Hazard ratios (HR) values and confidence intervals for the predictor variables are shown in Table 2. It is of note that

Table 1 Sample characteristics and univariate comparisons between relapsed and non-relapsed patients

Sample characteristics ($n = 341$)	Relapsed ($n = 166$)		Non-relapsed ($n = 175$)				1 relapse ($n = 110$)		>1 relapse ($n = 56$)			
	N	%	*N*	%	χ^2	*p*	*N*	%	*N*	%	χ^2	*p*
Gender (male)	99	60.0	97	55.1	0.832	0.382	65	59.6	34	60.7	0.018	1.000
Education level[a] (elementary)	80	48.5	79	45.1	0.450	0.515	51	47.2	29	51.8	0.307	0.623
Socio-economic status of parents[b] (not/low qualified worker)	90	54.5	85	49.7	0.788	0.384	60	55.0	30	53.6	0.320	0.870
Urban area[a] (yes)	121	73.3	128	73.6	0.002	1.000	82	75.2	39	69.9	0.590	0.462
Living with parents[c] (yes)	95	57.6	88	50.3	1.816	0.192	61	56.0	34	60.7	0.342	0.619
Single[c] (yes)	130	78.8	124	70.9	2.827	0.105	83	76.1	47	83.9	1.340	0.316
Occupational status[c] (unemployed/non-active)	88	53.3	87	49.7	0.445	0.517	62	55.5	26	46.4	1.624	0.249
Family psychiatric history (yes)	37	22.4	42	23.9	0.099	0.798	21	19.3	16	28.6	1.841	0.236
Hospital status inpatient (yes)	111	67.3	114	64.8	0.237	0.649	74	67.9	37	66.1	0.056	0.862
Tobacco use (yes)	98	59.4	103	58.5	0.027	0.927	70	64.2	28	50.0	3.102	0.095
Cannabis use (yes)	73	44.2	67	38.1	1.342	0.271	51	46.8	22	39.3	0.844	0.409
Alcohol use[c] (yes)	90	54.5	93	53.1	0.067	0.828	63	57.3	27	48.2	1.370	0.253
Diagnosis												
Schizophrenia	**105**	**63.6**	**84**	**47.7**	**8.724**	**0.003**	**64**	**58.7**	**41**	**73.2**	**3.207**	**0.067**
Other diagnoses	60	36.4	92	52.3			45	41.3	15	26.8		
Illness insight (SUMD)[d] (poor)	95	60.5	102	61.8	0.058	0.820	40	39.2	22	40.0	0.009	1.000
Adherence[e] (non-adherence)	**66**	**40.0**	**29**	**16.8**	**22.567**	**<0.001**	42	38.5	24	42.9	0.288	0.618

	Mean	SD	Mean	SD	*T*	*p*	Mean	SD	Mean	SD	*T*	*p*
Age at psychosis onset[c] (years)	**27.76**	**8.25**	**30.18**	**9.87**	**−2.433**	**0.015**	**28.94**	**8.43**	**25.50**	**7.47**	**2.578**	**0.011**
Age at admission (years)	**28.62**	**8.47**	**31.57**	**10.53**	**−2.858**	**0.005**	**29.74**	**7.47**	**26.42**	**7.66**	**2.421**	**0.017**
Duration of psychosis[c] (months)	**10.83**	**21.90**	**16.67**	**36.74**	**−1.794**	**0.074**	10.70	17.30	11.09	28.97	−0.107	0.915
Duration of illness[f] (months)	23.59	37.75	26.31	41.11	−0.627	0.531	25.07	39.47	20.69	34.31	0.698	0.486
Mean premorbid adjustment (PAS)[g]	2.20	1.28	2.29	1.40	−0.589	0.556	2.18	1.30	2.25	1.25	0.342	0.732
BPRS at admission	61.54	12.19	62.09	12.87	−0.395	0.693	62.29	12.68	60.07	11.13	1.109	0.269
SAPS at admission	13.44	3.90	13.47	4.51	−0.102	0.919	**13.91**	**3.93**	**12.52**	**3.71**	**2.192**	**0.030**
SANS at admission	6.64	5.68	7.08	6.38	−0.512	0.609	6.36	5.55	7.18	5.95	−0.878	0.381
Psychotic SANS SAPS dimension	7.35	2.33	7.28	2.46	0.335	0.738	7.58	2.35	6.91	2.27	1.750	0.082
Disorganized SANS SAPS dimension	6.08	3.21	6.18	3.55	−0.364	0.716	6.33	3.20	5.61	3.22	1.371	0.172
Negative SANS SAPS dimension	4.85	5.23	5.48	5.88	−0.907	0.365	4.56	5.03	5.41	5.61	−0.989	0.324

[a] $N = 339$, [b] $N = 336$, [c] $N = 340$, [d] $N = 322$, [e] $N = 338$, [f] $N = 329$, [g] $N = 315$

the main predictor for both relapse in the logistic regression analysis and relapse by time to relapse in the cox regression analysis was adherence to medication (OR 2.979 for relapses; HR 2.812 for relapses by observation time; both $p < 0.001$). None of the variables included in the models were significantly correlated.

The median time to relapse was 28.0 months (95% CI 25.7–33.0) (Fig. 2). It is of note that median time to relapse in non-adherent patients (17.0 months, 95% CI 12.96–21.04) was significantly lower than in the adherent patients (40.0 months; No CI given due to a high number of extreme values: 52% of the adherent patients survived 40 months). The Kaplan–Meier survival analysis showed that these differences in the median time to relapse between non-adherent and adherent patients were statistically significant (log-rank $\chi^2 = 51.356$; $p < 0.001$) (Fig. 3). This result was not significantly different when the sample was stratified by schizophrenia (log-rank $\chi^2 = 45.002$; $p < 0.001$) and other diagnoses (log-rank $\chi^2 = 6.659$; $p = 0.010$; comparison in the total sample, pooled results over the strata: log-rank $\chi^2 = 48.355$; $p < 0.001$).

The logistic regression analysis for second relapses included diagnosis, age of onset, and SAPS total initial score. The model was statistically significant (Nagelkerke's $R^2 = 0.151$; log-rank $\chi^2 = 18.956$; $p < 0.001$). Values and confidence intervals for the predictor variables are shown in Table 3. The forced addition of the variable "adherence" in a second block did not improve this model ($p = 0.925$), and it was not included as a significant independent predictor for second relapses (OR 0.967; $p = 0.924$).

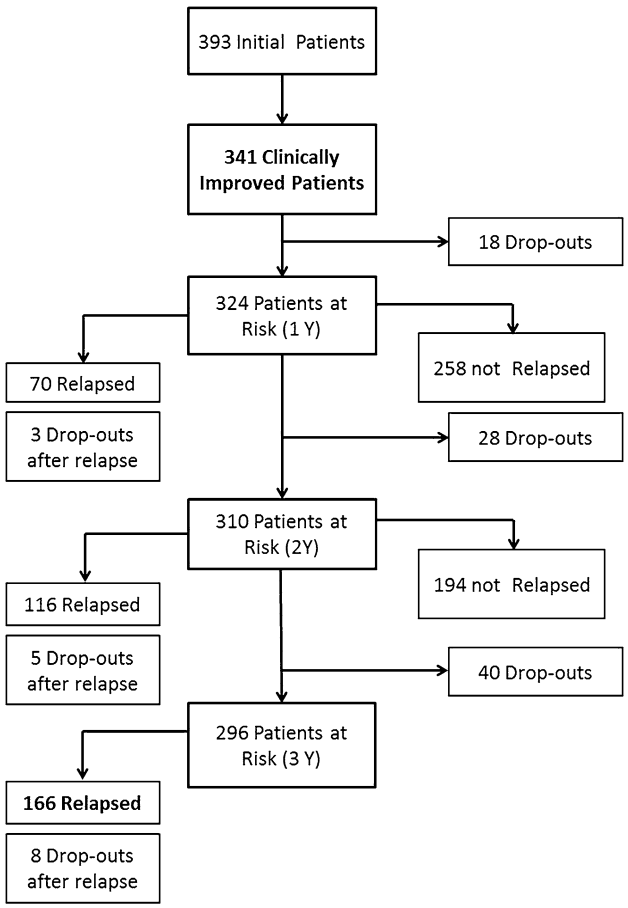

Fig. 1 Trial profile. In bold: Total initial number of subjects at risk of relapse (patients that clinically improved) and total number of subjects that relapsed at least once during follow-up

Discussion

The most relevant results that arose from our study were: (1) The rate of first relapse after a first episode of psychosis was 48.68% and out of them only 34% experienced a second relapse during the three-year follow-up (2) non-adherence to medication was the main relevant predictor of clinical relapses after a first episode of psychosis; and (3) only non-modifiable factors such as diagnosis and age of onset increased the risk of having a second relapse.

Almost half of the sample relapsed in the first 3 years after the break of the illness. Our current relapse rates are slightly lower than in our previous report of 65% over the period 2001–2005 [13] and other reported relapse rates after a first episode of psychosis [31]. Although a lower relapse rate could be expected in the context of an early intervention (EI) programme, similar rates have been reported in the context of EI, such as a 29.7% relapse rate at two years in the PEPP Canadian programme [32] or 30% relapse rate at 18 months in the LEO Lambeth programme [33]. Differences between reports might be explained by differences in definitions of relapse, lengths of follow-up, and diagnosis and characteristics of the setting (for instance, distribution of associated implied predictors). Thus, a recent meta-analysis revealed lower rates of relapses in EI services versus standard care settings and established mean relapse rates of 20 and 34% at 1- and 2-year follow-up for EI services [16]. With regard to second relapses, we found a much lower relapse rate compared to the first relapse. Our cumulative rate of second relapses (33.9%) is also in contrast with much higher rates such as

Table 2 Predictors associated with first relapse

Predictor	*B*	Wald	OR	95% CI	*p*
Logistic regression (dependant variable: relapse)					
Non-adherence	1.092	16.882	2.979	1.770–5.015	<0.001
Schizophrenia diagnosis	0.776	10.068	2.173	1.345–3.509	0.002
DUP (years)	0.141	5.508	1.151	1.023–1.295	0.019
Age of onset (years)	0.022	2.835	1.022	0.996–1.048	0.092
Predictor	*B*	Wald	HR	95% CI	*p*
Cox regression (dependant variable: relapse by observation time)					
Non-adherence	1.034	39.373	2.812	2.036–3.885	<0.001
Schizophrenia diagnosis	0.659	15.361	1.933	1.390–2.687	<0.001
DUP (years)	−0.076	2.921	1.079	0.989–1.177	0.087
Age of onset (years)	−0.020	4.549	1.020	1.002–1.038	0.033

Results from the logistic regression analysis and Cox regression for the predictor variables included in the models and odds ratio (OR) and hazard ratio (HR) values and 95% confidence intervals (CI)

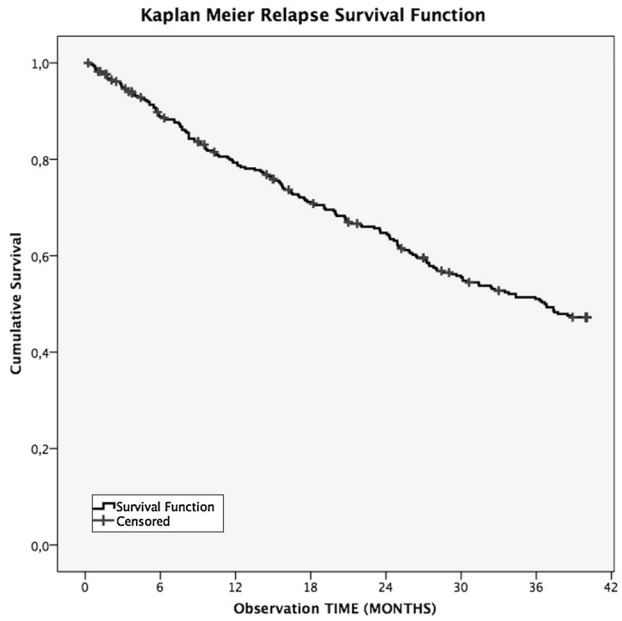

Fig. 2 Kaplan–Meier relapse survival function

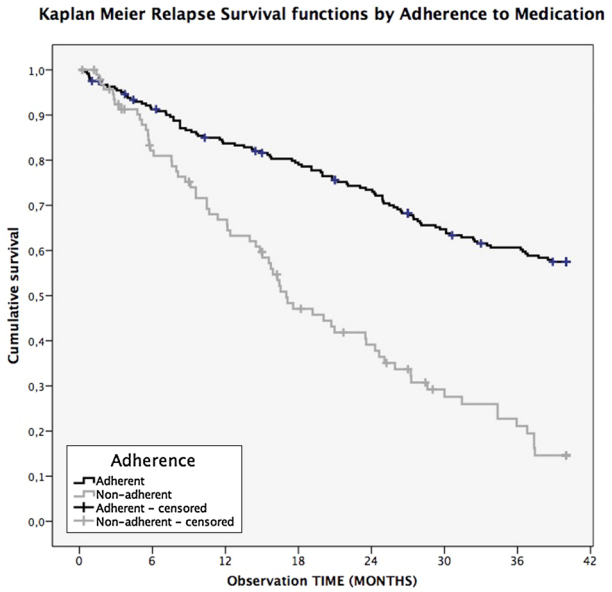

Fig. 3 Kaplan–Meier relapse survival functions by adherence to medication

the 56% reported by Robinson et al. [11]. The main independent predictor of first relapse and time to relapse in our sample was non-adherence to medication. Non-adherence to medication conferred an odds ratio of relapse near to 3 over the period. This result was concordant with our previous results and with other studies [31, 34, 35] including recent revisions and meta-analyses [16, 36] that showed

Table 3 Predictors associated with second relapses

Logistic regression (dependant variable: second relapse vs. one relapse)					
Predictor	*B*	Wald	OR	95%CI	*p*
Schizophrenia diagnosis	0.681	3.198	1.975	0.937–4.165	0.074
Age of onset (years)	−0.075	8.657	1.078	1.026–1.133	0.003
SAPS total initial score	−0.147	8.573	0.863	0.782–0.953	0.003

Results from the logistic regression analysis and variables included in the model for second relapses and odds ratio (OR) values and 95% confidence intervals (CI)

non-adherence as the most important predictor for relapse in psychosis. Accordingly, when patients were included in a treatment discontinuation strategy, twice as many relapses occurred compared to those patients who maintained antipsychotic treatment [15, 37].

The only additional predictors associated with relapse in our study were schizophrenia diagnosis and age of onset. With regard to diagnosis, only a few previous studies analysed this variable, some of them comparing affective versus non-affective diagnosis [16]. Our results here are in agreement with those studies that found that patient with schizophrenia and a younger age of onset tends to have more and earlier relapses [38]. In this regard, these patients may comprise a subgroup of individuals with a higher biological risk to relapse.

A key strength of this study has been to analyse second and subsequence relapses and their associated predictors. As expected in an early intervention programme, second and following relapses cumulative incidence were relatively low. As a difference with factors increasing the risk of having a first relapse, only non-modifiable factors such as diagnosis, age of onset, and initial positive symptom severity were significantly associated with these second relapses. Thus, first-episode subjects who achieve clinical improvement and stability with low adherence to antipsychotic treatment are in a higher risk of relapse, and therefore, preventive and intensive interventions are highly recommended to avoid this modifiable risk factor. In contrast, non-modifiable predictors (i.e. diagnosis or age of onset) seem to be significantly influencing the risk of having subsequent relapses. Additionally, as an unexpected finding, we observed that a lower initial severity of positive symptoms was associated with a higher risk of having a second relapse. We do not have an explanation for this finding, but it might be speculated that a lower initial psychotic severity could be associated with a more insidious course that might lead a higher risk of relapse.

Our results emphasize the potential relevance of two kinds of factors that may increase the risk of relapse: (1)

intrinsic established risk factors such as diagnosis or age of illness onset and (2) modifiable factors such as adherence to medication. Subjects with a first relapse and low adherence to antipsychotic treatment appear as a group of high risk of relapse in which a clinical effort in preventive and intensive interventions is highly recommended to avoid changeable risk factors and therefore to diminish the rate of second relapses.

Some limitations must be taken into account in the interpretation of the current investigation. First, in our study, assessors were not blinded to the patient's adherence status. The assessment of adherence and relapse by independent raters may have reduced this potential caveat. However, it has a high epidemiological and clinical validity in terms of representativeness, including usual clinical practice. A second limitation is the lack of an objective assessment for the adherence to treatment. We are fully aware that plasma levels and urine assays of the antipsychotic medication or its metabolite can provide the strongest evidence of medication usage, but they are expensive and invasive for the patient. Additionally, biological assays are not capable to tell us the real dosage of medication patients regularly take, given individual differences in the metabolism of medication. In our study, we followed a previous definition used for research, where adherence to medication was assessed gathering information from psychiatrists, nurses, and social workers involved in the treatment and follow-up of the patient and by taking into consideration information from patients and close relatives. Third, the lack of a control group is an additional limitation. Finally, although a large number of predictors have been included in the analysis, it is possible that other predictors could have been included with different results.

In conclusion, the recurrence of psychotic symptoms after having achieved clinical improvement and stability is a frequent event during early phases of the illness, being non-adherence to medication the best predictor of relapse after a first episode of psychosis. Clinicians should be fully aware of this risk and provide accurate information to patients about the risk of relapse if antipsychotics are discontinued. Therefore, systematic interventions to ensure proper understanding should be established in first-episode programs to enhance treatment compliance and to prevent uncontrolled treatment disengagement. The rate of subsequence relapses in an early intervention service is, as expected, less common than the rate of first relapse and do not seem to be related to adherence or other modifiable factors, suggesting that patients with multiple relapses may comprise a subgroup with a higher biological risk.

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Compliance with ethical standards

Conflict of interest Dr. José María Pelayo-Terán has received lecture honoraria and travel support form Janssen Johnson & Johnson, Lundbeck, Otsuka Pharmaceuticals, GlaxoSmithkline and EiLilly. Prof. Benedicto Crespo-Facorro has received honoraria for consulting/advisory boards from Otsuka Pharmaceuticals and lecture honoraria from Janssen Johnson & Johnson, Lundbeck, Roche and Otsuka Pharmaceuticals. Prof. Rafael Tabarés-Seisdedos has received grants from or acted as a consultant for the following companies: AstraZeneca, Janssen, Eli- Lilly, Lundbeck, Novartis, Pfizer, Sanofi-Aventis, and Wyeth that were deposited into research accounts at the University of Valencia. Dr.Virginia Gajardo Gajardo Galán, Víctor de la Ortiz-García de la Foz, Obdulia Martín-García and Dr. Rosa Ayesa-Arriola report no additional financial support or other relationship relevant to the subject of this article.

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