Predictors of Relapse and Functioning in First-Episode Psychosis: A Two-Year Follow-Up Study

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Objective: First-episode psychosis has an annual incidence rate of 24.6 to 40.9 per 100,000 population, and most individuals develop chronic disorders, such as schizophrenia or affective psychosis. The first two to five years are thought to be key determinants of long-term functional and clinical prognosis. This study aimed to determine the two-year course of illness in first-episode psychosis, including diagnosis, relapse, and functioning and factors related to these variables.

Methods: A total of 140 patients who experienced a first episode of psychosis were recruited and evaluated between 2008 and 2012 in a first-episode psychosis program in Barcelona, Spain. Regression models were used to determine factors predicting relapse and functioning.

Results: A general trend was noted toward improved functioning and less severe psychotic symptoms. However, after two years, one-third of the patients had a diagnosis of schizophrenia and more than 40% had a diagnosis of affective psychosis. Rates of relapse were 31% after one year and 43% at two years. Cannabis use after illness onset and poor insight were the best predictors of relapse. Being male and severity of negative symptoms at baseline predicted worse functioning at two years.

Conclusions: Patients with first-episode psychosis were found to have high relapse rates during the first years after illness onset. Further studies evaluating treatment strategies focused on reducing cannabis use and improving insight in first-episode psychosis should be encouraged.

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The annual incidence of first-episode psychosis (FEP) ranges from 24.6 to 40.9 per 100,000 inhabitants per year among persons ages 16 to 64 (1,2). Rates of progression to schizophrenia at five years are about 40% to 70% of all cases of FEP (3,4). Kraepelin described schizophrenia as a chronic disorder that drives most patients to limited functioning (5). A century later, the course of illness of schizophrenia still implies a strong trend toward social isolation and poor outcome (6). As a consequence, schizophrenia was the seventh cause of years lost due to disability (YLD) in 2000, which means a worldwide average of 15.4 per 100,000 years lived with disability (7,8).

Prospective longitudinal studies have highlighted a critical period after the onset of the illness that ranges from two to five years (9). Similarly, several authors have suggested that most cognitive and functional impairment occurs during this critical period and that treatment and therapeutic efforts should be especially intense during these years (10–12). Relapse rates are higher in this critical period than in other periods, ranging from 30% to 60% at two years (13) and up to 80% at five years after illness onset (14).

Studies that have focused on determining prognostic factors after a first episode of psychosis have described several predictors of progression to schizophrenia and worse outcome: being male and having greater clinical severity at onset, worse premorbid social adjustment, longer duration of untreated psychosis, and more negative symptoms at onset (3,15,16). Furthermore, patients with FEP have different characteristics and needs from those of patients with chronic illness. For example, they usually have not previously required health assistance and are thus disengaged from the health care system, which means that extra efforts may be required to ensure that they achieve adequate adherence to treatment and follow-up. They are at an age when relationships and academic and professional careers are under development and usually at a crucial point for their future. They may need special attention to cope with the onset of the illness and redirect their lifestyle expectations and may require social support for their professional or academic career; in addition, their relatives may benefit from specific interventions (17). Until now, specific FEP programs have yielded higher rates of remission, enhanced symptom control and treatment adherence, and

improved functionality and quality of life (10,17–19), compared with standard mental health programs. These outcomes have led governments around the world to implement FEP programs (20–22). However, there is still a need to increase remission rates and functionality in this population. A better understanding of the factors that influence outcomes might help achieve these goals. The aim of this study was to describe factors associated with clinical and functional outcomes at two years among patients with a first episode of psychosis in an FEP program.

METHODS

Setting

The Institute of Neuropsychiatry and Addictions–Parc de Salut Mar, Barcelona, Spain, has developed an FEP program with a set of coordinated inpatient and outpatient services that allows the efficient application of specific resources to all the patients in the program. The program started in 2008 and offers specific follow-up and immediate engagement after hospitalization, after an emergency department visit, or after referral by a general practitioner for a first episode of psychosis with a duration of no longer than two years. Other inclusion criteria were age between 18 and 35 years and estimated IQ higher than 80. Exclusion criteria were a medical history of neurological damage or head trauma and dependence on cocaine, stimulants, sedatives, or opioids (cannabis abuse or dependence was not an exclusion criterion).

All patients included in the study received psychiatric follow-up examinations according to general guidelines to ensure treatment with a second-generation antipsychotic drug at low to medium doses. When stabilization was achieved, patients were referred to the local outpatient service for treatment by a psychiatrist associated with the FEP program. Regular visits were scheduled once a week during the first month, once every two weeks in the second month, and once a month during further follow-up. More frequent visits were offered if needed. In accordance with U.S. and international recommendations (23,24) and studies of antipsychotic treatment discontinuation (25), patients who had experienced only a psychotic episode and who had been in clinical remission for more than one year (preferably two years) could discontinue antipsychotic medications but continue with follow-up appointments. All staff members of the FEP program met once a month. Patients reporting cannabis use were offered a specific psychological treatment for substance use, whereas patients who did not use cannabis were offered psychological assessment to help them cope with their illness. A structured program consisting of eight psychoeducation and informative sessions was offered to patients' relatives to provide them with needed information about FEP. To reinforce social reintegration, patients who described difficulties resuming their academic or job activities were given the opportunity to attend one-hour weekly group sessions led by a social worker and a psychologist. These professionals identified each patient's handicaps in order to help them find the appropriate social, academic, or work support. [More information about the program is included in an online supplement to this article.]

Assessments

Patients were evaluated with the Structured Clinical Interview for DSM-IV axis I disorders for diagnosis, the Positive and Negative Syndrome Scale (PANSS) (26) for psychotic symptoms, the Scale to Assess Unawareness of Mental Disorder (SUMD) (27) for insight, the Young Mania Rating Scale (28) for manic symptoms, the Calgary Depression Scale for Schizophrenia (29) for depression, the Global Assessment of Functioning (GAF) (30) for global functioning, and the Hamilton Anxiety Rating Scale (31) for anxiety. Information about substance use and presumed treatment adherence was collected from various sources (family, patient, and frequent urine drug tests). Suicide attempts and body mass index were also documented. These evaluations were performed at baseline (during hospital admission or first outpatient visit), two months, six months, one year, and two years or if relapse was suspected. Sociodemographic data and psychiatric family history were recorded at baseline. Program guidelines also included an extended neurocognitive battery and a brain MRI scan at two months and at two years.

Analysis

To determine factors predicting relapse, a Cox regression survival analysis with backward elimination modeling was carried out. Time to first relapse within the first two years of follow-up was the dependent variable, and it was defined as hospitalization for psychosis, which has been reported to be a good outcome measure (32), or a score higher than 4 on a PANSS positive item during a minimum period of one week (25,33). Sex, age at onset, cannabis use at baseline, average cannabis use since illness onset (joints per week), duration of untreated psychosis (days), GAF score just after the first episode (at two months of follow-up), scores on PANSS positive and negative subscale scores at baseline, SUMD score after the first episode (at two months of follow-up), and presumed treatment adherence during the entire follow-up period were the predictive variables.

To determine functional outcome, a linear regression model was developed with global functioning at two years as measured by the GAF as the dependent variable. The predictive variables were sex, age at onset, average cannabis use since illness onset (joints per week), duration of untreated psychosis (days), GAF score just after the first episode (at two months of follow-up), PANSS positive and negative subscale scores at baseline, insight after the first episode (at two months of follow-up) as measured by the SUMD, and apparent treatment adherence during the entire follow-up period. A backward elimination method was used to identify the best predictive model according to best R^2 value.

TABLE 1. Baseline characteristics of patients who experienced a first episode of psychosis

	All patients (N=140)		Completed 1-year follow-up (N=74)		Dropouts at 1 year (N=66)					
Variable	N	%	N	%	N	%	χ^2	t	df	p
Age (M±SD)	25.45±5.3		24.99±5.1		25.99±5.6			−1.10	136	.274
Male	81	58	45	61	36	55	.56		1	.454
Cannabis users (>1 joint per week)	64	49	35	48	29	50	.06		1	.815
Frequent cannabis users (>10 joints per week)	29	22	15	21	14	24	.24		1	.623
Duration of untreated psychosis (M±SD days)	93.35±184.6		75.09±98.7		117.64±246.3			−1.18	103	.240
PANSS score (M±SD)[a]										
Positive symptom score	25.49±6.3		26.21±5.6		24.65±7.0			1.28	103	.204
Negative symptom score	16.23±7.0		16.43±6.9		16.00±7.1			.31	103	.756
Total	85.4±19.0		86.59±20.3		84.04±17.5			.68	103	.496
Calgary score (M±SD)[b]	4.56±4.6		4.55±4.6		4.58±4.6			−.04	101	.967
SUMD global items score (M±SD)[c]	11.99±3.0		12.55±2.4		11.37±3.4			2.01	102	.047
YMRS score (M±SD)[d]	21.56±11.3		19.25±10.9		28.50±10.6			−1.48	102	.162
GAF score (M±SD)[e]	30.63±11.5		29.67±12.5		31.94±9.8			−1.05	114	.295
Born in Spain	54	69	35	75	19	61	1.52		1	.217

[a] Positive and Negative Syndrome Scale. Possible scores for positive and negative symptoms range from 7 to 49, with higher scores indicating more severe symptoms. Possible total scores range from 30 to 210, with higher scores indicating more and more severe symptoms.
[b] Calgary Depression Scale for Schizophrenia. Possible scores range from 0 to 27, with higher scores indicating more severe depressive symptoms.
[c] Initial 3 items of the Scale to Assess Unawareness of Mental Disorder. Possible scores on the 3 items range from 1 to 15, with higher scores indicating more severe lack of insight.
[d] Young Mania Rating Scale. Possible scores range from 0 to 60, with higher scores indicating more severe symptoms of mania.
[e] Global Assessment of Functioning scale. Possible scores range from 0 to 100, with higher scores indicating better functioning and less severe psychiatric symptoms.

On the basis of *DSM-IV* criteria at the two-month follow-up, patients were divided into two diagnostic groups: affective psychosis (bipolar disorder and schizoaffective disorder) and nonaffective psychosis (schizophreniform disorder, brief psychotic disorder, schizophrenia, drug-induced psychosis, and delusional disorder). Comparisons were made between groups in terms of GAF score at two years and time to relapse. Regression models were recomputed with diagnostic category as another independent variable.

RESULTS

A total of 140 patients were initially recruited to the FEP program from January 1, 2008, to July 1, 2013. A total of 133 patients completed the two-month follow-up assessment, 105 completed the six-month assessment, and 78 completed the one-year assessment. [A figure in the online supplement illustrates patient retention and dropout.] We compared the 66 patients who dropped out at any point over the one-year period with the 74 patients who continued in the program at one year in terms of sociodemographic and baseline clinical characteristics. As shown in Table 1, the only significant difference between groups was that patients who dropped out showed slightly better insight.

At baseline, 49% of the patients reported using cannabis at least once per week, whereas at one-year follow-up, only 16% of patients reported use at least once per week. The mean±SD number of joints per week reported by patients at follow-up was 3.3±4.5. At baseline, 74 patients (53%) reported light or moderate alcohol consumption, 55 (39%) reported no alcohol use, and 11 (8%) met criteria for alcohol abuse. Regarding cocaine use at baseline, 114 (81%) reported no use, 18 (13%) reported occasional use, and seven (5%) met abuse criteria. For amphetamine use at baseline, 123 (88%) reported no use, eight (6%) reported sporadic use, and eight (6%) met abuse criteria.

Diagnosis

The largest diagnostic group at baseline was psychosis not otherwise specified (N=63, 45%), followed by schizophreniform disorder (N=38, 27%); brief psychotic disorder (N=15, 11%); affective psychosis (N=12, 9%), including bipolar disorder with psychotic symptoms and schizoaffective disorder; schizophrenia (N=7, 5%); drug-induced psychosis N=4, 3%); and delusional disorder (N=1, 1%). At two-year follow-up, affective psychosis was the largest diagnostic group (N=19, 44%), followed by schizophrenia (N=15, 33%), schizophreniform disorder (N=5, 11%), and brief psychotic disorder (N=5, 11%). [A table presenting information on prescribed antipsychotic drugs at each time period is included in the online supplement.]

Relapse Rate

Cumulative rates of relapse, defined as any hospitalization for psychosis or any PANSS positive item score higher than 4, were 5% (N=7 of 133) at two-month follow-up, 26% (N=27 of 105) at six months, 31% (N=25 of 81) at one year, and 43% (N=27 of 62) at two years.

The backward elimination method to identify the best Cox regression model according to likelihood ratio criteria

TABLE 2. Significant predictors of functioning at two-year follow-up among patients who experienced a first episode of psychosis[a]

Step 5	B	SE	Beta	t	p
Constant term	94.22	7.53		12.51	<.001
Male	−14.88	6.07	−.38	−2.45	.020
PANSS negative score at baseline[b]	−.79	.38	−.32	−2.06	.049

[a] Only the final step in the linear regression model is shown. Model statistics: R=.536; R^2=.287; adjusted R^2=.24; SE of the estimate, 16.823, df=1 and 29. Because of missing data, not all patients followed for 2 years were included in the analyses.
[b] Positive and Negative Syndrome Scale

(seventh step, −2 log likelihood=187.48, χ^2=8.22, df=2, p=.016) showed that the best predictive variables for relapse were average cannabis use before relapse (B=.28, SE=.11, df=1, p=.01, Exp[B]=1.33) and lack of insight at two-month follow-up (B=.15, SE=.07, df=1, p=.04, Exp[B]=1.16).

Clinical Ratings and Global Functioning

Negative symptoms and gender were the best predictive variables of GAF score at two-years (Table 2). There were no significant differences between those with nonaffective psychosis and those with affective psychosis in terms of GAF score at two years (66.7±21.6 versus 80.1±12.8, respectively) or in terms of days until first relapse (337.6±275.8 versus 411.5±266.8, respectively). We added the diagnostic categories as a predictive variable in the two regression models. In the analysis to predict functioning, the variable diagnostic categories continued to be significant, along with negative symptoms and gender. [Results of this analysis are presented in a table in the online supplement.] However, the variable diagnostic categories was not significant in the Cox survival regression model to predict time to first relapse, and this variable did not change the resulting model (results not shown).

DISCUSSION

Since implementation of our FEP program, the overall relapse rate among patients was found to be 31% at one-year follow-up and 43% at two years. The GAF score of 70.1±20.6 at two years indicates that on average patients functioned fairly well. Cannabis use after illness onset and poor insight were the best predictors of relapse. Being male and having more negative symptoms at baseline were predictors of worse functioning at two years.

These relapse rates are similar to those observed in other FEP programs (34–36) and confirm that most FEP patients relapse at least once in the two to five years after illness onset. Our rates appear to be similar to those found in populations of immigrants with low incomes and in economically disadvantaged regions with high rates of immigration and unemployment (36,37).

Several follow-up studies have identified medication nonadherence and substance misuse, specifically cannabis use, as predictors of relapse and rehospitalization (34,38–41). In our sample, almost half of patients were cannabis users at baseline, whereas during the follow-up period, only a quarter of them kept smoking cannabis at least once a week. These rates are similar although slightly higher than those reported in other studies of FEP patients, in which cannabis use, abuse, or dependence ranged from 15% to 60% (40,42). The misuse criteria used might help explain these differences. Because some studies have reported a dose-response relationship between frequency of cannabis use and relapse (43), we decided to include all patients who smoked cannabis frequently, specifically weekly, instead of abuse or dependence criteria as in most previous studies (39,40). This allowed us to measure the effects of cannabis use itself rather than abuse or dependence.

Substance misuse has been related to treatment nonadherence (44), and treatment nonadherence may be interpreted as the sole underlying reason for relapse. However, in our study, as in others, we controlled for treatment adherence and reported the association of cannabis use with relapse (39,40). Nevertheless, with our study design, we cannot state that this association is causal.

We measured insight at two-month follow-up, and in line with other studies (45,46), we found that lack of insight after a first episode was independently associated with relapse. Because insight may be associated with positive symptoms, it may change during the acute phase, and it stabilizes with clinical response (47,48). Also, previous studies found that insight improvement within the first six months was a better predictor of clinical outcome than insight at baseline (46). Apart from cannabis use, treatment nonadherence is often another main factor predicting relapse (35), and its relationship with lack of insight has been widely reported (49). In our study, presumed treatment adherence did not remain a statistically significant predictor in the model, probably because of its strong association with insight and cannabis use, as discussed above. In addition, the fact that treatment adherence was only a clinical estimation may explain the lack of significant effect.

We found that negative symptoms at baseline and being male were independently associated with poor functional outcome. Male gender has been previously related to poor functional outcome in several studies of FEP and schizophrenia (50). Sex hormones and neurodevelopmental and psychosocial sex differences have been suggested as possible explanatory factors for these differences.

Negative symptoms have also been repeatedly shown to be associated with poor functioning in schizophrenia (51–53). Moreover, our study and others (54) have pointed out the predictive value of negative symptoms at illness onset for functioning one or two years later. Differences in negative symptoms at illness onset, when antipsychotics have not yet been prescribed, could be related more to primary negative symptoms than to secondary negative symptoms. It might be that only primary negative symptoms correlate with future poor functioning, whereas secondary negative symptoms represent a lower burden on functioning. Although our study does not solve this issue, other authors

have suggested that primary negative symptoms may have a different pathophysiology and different response to treatment (55,56).

Duration of untreated psychosis has been shown to be related to functional outcome (57–59), but we could not replicate these results. This relationship might represent an epiphenomenon, because an insidious onset of illness may cause both delayed treatment and poor outcome (58). Furthermore, an association between duration of untreated psychosis and negative symptoms has been described (60) and was found in our study (Pearson correlation=.30, p=.047). This may cause collinearity when both variables are introduced in a model to predict functioning, although we did not find any relevant collinearity in the model (results not shown).

We found that different variables predicted functioning and relapse. For instance, cannabis use predicted relapse but not functional outcome. Several studies have reported that patients with a dual diagnosis (mental and substance use disorders) are characterized by a better premorbid adjustment than patients without a dual diagnosis (61), which might attenuate the negative impact of psychotic relapse on social functioning.

Diagnostic categories were significant predictors in the regression model of functioning, with affective psychosis predicting better functioning. Previous literature has also pointed in this direction (62). However, diagnostic categories were not significant predictors in any of the regression models, which may suggest a lack of effect of diagnostic group in relation to functioning and relapse. Nevertheless, further studies that have larger samples and that include models with interaction between these variables would help to clarify this issue.

This study had some limitations. First, we did not control for premorbid adjustment. However, some studies have shown that the relationship between outcome and duration of untreated psychosis was not mediated by premorbid adjustment (63). Another limitation is the percentage of dropouts. Although the rate is similar to those in other studies, it may have reduced the predictive power of the variables assessed. Although our FEP program allows recruitment from either hospital or community settings, most of our patients required an initial hospitalization. This may introduce a sample bias compared with other FEP programs in which recruitment is only from the community. Notwithstanding, community programs may also fail to recruit patients who do not engage in outpatient settings but may be found in hospital settings.

Of note, this study had several strengths. It had a prospective design with frequent assessment that took into account several important variables that other studies have not included. For instance, we included current substance use instead of lifetime use, and frequent urine tests were conducted. We also included medication nonadherence, baseline measures, diagnostic influence, and insight.

CONCLUSIONS

Cannabis use, poor insight, male gender, and longer duration of untreated psychosis were the best outcome predictors in an FEP program. To improve outcomes in FEP, further studies should be encouraged to disentangle the pathophysiology underlying various outcomes and to test treatment strategies that focus on these predictors and that provide more intensive outpatient care.

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