Don’t blame psychosis, blame the lack of services. A message for Early Intervention

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Abstract

Background. Early Intervention Services (EIS) aim to reduce relapse rates and achieve better treatment and functional outcomes for first episode psychosis (FEP) patients. Reform of mental health services is underway in Greece and initial steps have been taken to shift standard care towards EIS.

Methods. We examined follow-up and relapse rates one year after initial treatment contact in the first longitudinal FEP study conducted in Greece. 225 patients were enrolled between 2015-2020. Sociodemographic, clinical and functional characteristics were assessed in association with follow-up and relapse rates.

Results. Within a treatment as usual follow-up setting, one year attrition rates were high. Only 87 patients (38,7%) retained contact with services after one year and within this time frame, 19 of them (21,8%) experienced a severe relapse requiring rehospitalization.

Conclusion. Both follow-up and one-year rehospitalization rates in our FEP sample, highlight the need for the implementation of early intervention services, that will aim at follow-up engagement maximization and relapse prevention. These indexes also provide a benchmark against which future early intervention services for psychosis in Greece will have to demonstrate superior efficacy.

Introduction

The importance of early intervention in psychosis has been well established [1, 2] and for this purpose Early Intervention Services (EIS) for psychosis have been developed throughout the world [3] aiming at achieving better outcomes and changing the course of the illness [4]. Current literature indicates that favorable long-term outcomes are predicted by achieving treatment remission and functional recovery at the first critical period of psychosis [5]. Researchers argue that relapses over time may not be due to psychosis per se but reflect poor access to mental health services or poor treatment adherence [6]. Principles of reducing duration of untreated psychosis and focusing on family education, supported employment and personalized medication management, are considered as highly important. EIS that are based on the above, have showed superiority comparing to usual Community Care [7].

In recent years, there has been a rising interest in developing such services in Greece [8, 9], based on the international principles of early intervention. For now, existing First-Episode Psychosis (FEP) services in Greece are mostly hospital-based outpatient services and not meeting EIS standards and for this reason a national strategic approach has been proposed in order to reform our country's Mental Health System and achieve better long-term benefits for the patients and their families [10]. Under the framework of implementing and organizing EIS, the Athens FEP Research study has been conducted to address further needs and treatment outcomes in FEP patients [11]. Conducting FEP studies in our country might elucidate current national mental health needs. The purpose of this study is to identify service engagement and relapse rates in FEP patients one year after first treatment contact as well as clinical and functional variables that may be related.

Methods

Participants:

The organizational framework of Athens FEP study has been extensively described elsewhere [11]. Between 2015-2020, 225 patients, from 5 different psychiatric hospitals across Athens, aged 16-45, have been enrolled and have provided inform consent. The inclusion criteria concern ICD-10 diagnosis of F1x.5, F20-F29, F30-F33 (WHO, 1992) in patients with first manifestation of psychosis, minimally exposed to antipsychotic medication (less than 2 weeks). Individuals with psychotic symptomatology due to organic causes or acute intoxication, IQ < 65, developmental disorders were excluded. After first episode psychosis, follow-up is routinely offered in an outpatient basis and information is gathered in one-year timepoint with a more comprehensive reassessment (by telephone or live).

Psychometric Measures and Definitions

A number of demographic and clinical variables were collected for analysis as potential predictors of follow-up (vs no follow-up) and relapse (vs no relapse). These included age (age of psychosis onset), gender, education (completed years), diagnosis, social and academic premorbid adjustment, DUP (Duration of Untreated Psychosis), lifetime cannabis use, cognition, presenting symptomatology and functionality both at baseline and one month later, type of hospitalization and length of admission and finally treatment adherence. These specific factors were chosen based both on previously identified predictors of service engagement and relapse [12, 13] as well as their availability in our medical records.

Service disengagement was defined as non-follow-up after multiple contact efforts within a time framework of three months, which is consistent with one of many definitions of service disengagement [12]. Hospitalization is a frequently used proxy for relapse when reporting in a naturalistic setting [14] and in our study relapse was defined by rehospitalization due to worsening of psychotic symptomatology during the first year. All subjects were screened using the diagnostic interview for psychosis [DIP] [15] and moreover a consensus diagnosis of two senior psychiatrists was implemented and diagnostic categories were determined [non-affective psychosis (F20-29), affective psychosis (F30-39) and drug-induced psychosis (F10-19)]. The Positive and Negative Symptom Scale [PANSS] [16] was used for the quantitative assessment of symptomatology and dimensions of total, positive, negative and general symptoms scores were assessed both at baseline and one month later. Global Assessment of Functioning [GAF] [17] scale was implemented to evaluate functionality at baseline and one month later. DUP was measured by NOS-DUP scale [18]. Premorbid Adjustment Scale [PAS] [19] was used to define premorbid social and academic adjustment till the age of 15 in order to ensure avoidance of prodromal symptomatology. Cannabis exposure was assessed with Cannabis Experience Questionnaire [CEQ] [20] and a binary variable was constructed by using the cut-off value of once or more per week during the lifetime period of most frequent use [21]. General intellectual capacity was estimated by full scale IQ score using the Greek version of Wechsler Adult Intelligence Scale-fourth edition (WAIS-IV GR) [22, 23]. The type of hospitalization was defined as a categorical carriable of voluntary hospitalization vs non-voluntary hospitalization vs outpatient visit, while the length of admission was measured as the duration

of hospitalization in days. Finally, adherence to medication during the first year was defined as reported by the patients (compliance vs no compliance).

Statistical Analysis

Descriptive statistics are presented for the overall population and stratified by one-year follow-up and moreover, those with 1-year follow up were categorized to those with or without a relapse. All continuous variables are presented with either mean and standard deviation (SD) or median and 1st, 3rd quartiles (Q1, Q3). The association of the one-year follow-up attendance and of relapse at 1st year with demographic, clinical, and functional characteristics was addressed in a univariate level; in case of a categorical variable the Pearson's chi-squared test was used, while for continuous variables a two-sample t-test or a Mann-Whitney test was applied. As exploratory analyses, the factors or covariates with a p-value less than 0.2 in the univariate level, as well as gender and age at onset, were considered for an inclusion in a multiple logistic regression model, from which the results were presented in terms of odds ratios (OR) and 95% confidence intervals (CI). All analyses were conducted using STATA v.14.2.

Results

Demographic, clinical and functional characteristics of our sample are presented in **table 1.** From the one-year follow-up assessment, only 87 individuals (38,7%) continued to use our FEP services. Univariate analyses did not indicate any association between service engagement at one year follow-up and basic demographic, preclinical, clinical, diagnostic or functional factors (**table 1**).

Table 1

Overall sample descriptive statistics and one-year follow-up (FU) stratification (1-year FU vs no FU) compared to demographic, clinical and functioning status at baseline and 1-month follow-up, adjusted for age, gender, educational level

	With 1-year FU	no FU		Overall
Demographics and Diagnosis	**N=87**	**N=138**	**p**	**N=225**
Age of onset according to dup	**N=81**	**N=134**		**N=215**
Median (Q1 - Q3)	23.0 (20.0-31.0)	23.0 (20.0-30.0)	0.844†	23.0 (20.0-31.0)
Gender, n (%)				
Male	53 (60.9%)	98 (71.0%)	0.117‡	151 (67.1%)
Female	34 (39.1%)	40 (29.0%)		74 (32.9%)
Education years	**N=85**	**N=137**		**N=222**
Mean (SD)	13.8 (2.2)	13.6 (2.7)	0.697	13.7 (2.5)
TRIPLE_DIAGNOSIS_F20F30F10, n (%)	**N=86**	**N=138**		**N=224**
1	72 (83.7%)	110 (79.7%)	0.151‡	182 (81.3%)
2	12 (14.0%)	16 (11.6%)		28 (12.5%)
3	2 (2.3%)	12 (8.7%)		14 (6.3%)
Full scale IQ	**N=79**	**N=110**		**N=189**
Mean (SD)	92.5 (13.0)	92.2 (11.5)	0.579	92.3 (12.1)
Length of admission in days	**N=74**	**N=109**		**N=183**
Median (Q1 - Q3)	33.0 (25.0-42.0)	30.0 (20.0-42.0)	0.147†	31.0 (21.0-42.0)
Type of hospitalization, n (%)	**N=87**	**N=136**		**N=223**
Voluntary hospitalization	45 (51.7%)	70 (51.5%)	0.485‡	115 (51.6%)
Unvoluntary hospitalization	32 (36.8%)	43 (31.6%)		75 (33.6%)
Outpatient	10 (11.5%)	23 (16.9%)		33 (14.8%)
Adherrence in medication	**N=61**	**N=14**		**N=75**
No	13 (21.3%)	1 (7.1%)	0.220‡	14 (18.7%)
Yes	48 (78.7%)	13 (92.9%)		61 (81.3%)
Lifetime_most _cannabis use	**N=85**	**N=133**		**N=218**
Less than one a week	62 (72.9%)	85 (63.9%)	0.165‡	147 (67.4%)
Once and more a week	23 (27.1%)	48 (36.1%)		71 (32.6%)
PANSS entrance positive symptoms,				

total scores				
Median (Q1 - Q3)	29.0 (24.0-33.0)	27.5 (23.0-32.0)	0.198†	28.0 (23.0-33.0)
PANSS entrance negative symptoms, total scores	**N=87**	**N=137**		**N=224**
Median (Q1 - Q3)	20.0 (14.0-25.0)	18.0 (13.0-26.0)	0.432†	19.0 (13.5-25.0)
PANSS entrance general symptoms, total scores				
Median (Q1 - Q3)	50.0 (43.0-57.0)	46.0 (37.0-58.0)	0.033†	48.0 (39.0-57.0)
PANSS entrance total	**N=87**	**N=137**		**N=224**
Median (Q1 - Q3)	99.0 (87.0-114.0)	92.0 (76.0-115.0)	0.055†	94.0 (81.0-114.0)
PANSS month positive symptoms, total scores	**N=87**	**N=136**		**N=223**
Median (Q1 - Q3)	13.0 (10.0-16.0)	13.0 (11.0-17.5)	0.312†	13.0 (10.0-17.0)
PANSS month negative symptoms, total scores	**N=87**	**N=136**		**N=223**
Median (Q1 - Q3)	13.0 (9.0-19.0)	12.0 (9.0-18.0)	0.755†	13.0 (9.0-18.0)
PANSS month general symptoms, total scores	**N=87**	**N=136**		**N=223**
Median (Q1 - Q3)	29.0 (23.0-34.0)	28.0 (24.0-34.5)	0.621†	28.0 (23.0-34.0)
PANSS month total	**N=87**	**N=136**		**N=223**
Median (Q1 - Q3)	54.0 (45.0-68.0)	56.0 (46.0-67.5)	0.525†	55.0 (45.0-68.0)
Nottingham DUP (in weeks)	**N=85**	**N=138**		**N=223**
Median (Q1 - Q3)	10.0 (4.0-28.0)	11.0 (5.0-26.0)	0.519†	10.0 (5.0-28.0)
GAF entrance	**N=82**	**N=126**		**N=208**
Median (Q1 - Q3)	40.0 (30.0-52.0)	35.0 (30.0-50.0)	0.169†	40.0 (30.0-50.0)
GAF month	**N=80**	**N=123**		**N=203**
Mean (SD)	60.6 (13.9)	59.6 (13.7)	0.620	60.0 (13.7)

PAS Academic	N=80	N=120		N=200
Median (Q1 - Q3)	0.2 (0.1-0.4)	0.3 (0.1-0.4)	0.470†	0.2 (0.1-0.4)
PAS Social	**N=80**	**N=110**		**N=190**
Median (Q1 - Q3)	0.2 (0.1-0.4)	0.2 (0.0-0.3)	0.178†	0.2 (0.0-0.3)

†Mann- Whitney test. ‡Pearson's chi-square test. two-sample t-test with equal variances.

FU: Follow-up; PANSS: The Positive and Negative Symptom Scale; GAF: The Global Assessment of Functioning scale; DUP: Duration of Untreated Psychosis; PAS: Premorbid Adjustment Scale

At a second level, potential factors from univariate analyses (i.e., p<0.2) were included in a multiple regression model, as well as gender and age, regardless of univariate analyses results. GAF at entrance and PAS Social were excluded due to collinearity with PANSS score. From the exploratory analyses, no association was found between service engagement at one year follow-up and potential factors (**table 2**).

Table 2

Multiple regression model of one-year follow-up vs no follow-up and clinical factors from univariate analyses (i.e., p<0.2), adjusted for gender and age.

	Univariate analyses		Multiple logistic (N=170)	
no FU vs. 1yr FU	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Gender (female vs. male)	0.64 (0.36, 1.12)	0.118	0.71 (0.34, 1.48)	0.364
Age on onset (years)	0.99 (0.96, 1.03)	0.748	1.00 (0.96, 1.05)	0.948
TRIPLE DIAGNOSIS				
2 vs. 1	0.87 (0.39, 1.95)	0.740	1.03 (0.37, 2.85)	0.953
3 vs. 1	3.93 (0.85, 18.1)	0.079	3.81 (0.43, 33.7)	0.230
cannabis use (≥1 wk vs. (<1 wk))	1.52 (0.84, 2.76)	0.166	1.21 (0.59, 2.48)	0.605
Length of admission in days	0.99 (0.97, 1.01)	0.172	0.99 (0.97, 1.01)	0.465
PANSS entrance total	0.99 (0.98, 1.00)	0.150	1.00 (0.98, 1.01)	0.786

CI: Confidence interval

A total 19 of 87 who attended at follow-up (25%) had experienced relapse with required rehospitalization. Univariate analyses did not indicate any association between relapse rates and factors related to PANSS subscales' score and functionality (at baseline and one-month), diagnosis, DUP, academic and social premorbid adjustment, full scale IQ, cannabis lifetime use, duration and type of hospitalization, with the exception of treatment adherence (**table 3**).

Table 3

Associations between relapse at first year (relapse vs no relapse) and demographic, clinical and functioning status at baseline and 1-month follow-up, adjusted for age, gender, educational level.

	Not-relapsed	Relapsed	
Patients with 1 year follow-up	**N=68**	**N=19**	**p**
Demographics and Diagnosis			
Age of onset according to dup	**N=62**	**N=19**	
Median (Q1 - Q3)	23.0 (21.0-31.0)	21.0 (18.0-28.0)	0.276†
Gender, n (%)			
Male	41 (60.3%)	12 (63.2%)	0.821‡
Female	27 (39.7%)	7 (36.8%)	
Education years	**N=67**	**N=18**	
Mean (SD)	13.9 (2.2)	13.1 (2.3)	0.164
TRIPLE_DIAGNOSIS_F20F30F10, n (%)	**N=67**	**N=19**	
1	56 (83.6%)	16 (84.2%)	0.731‡
2	9 (13.4%)	3 (15.8%)	
3	2 (3.0%)	0 (0.0%)	
Full scale IQ	**N=62**	**N=17**	
Mean (SD)	92.2 (13.5)	93.7 (11.2)	0.679
Length of admission in days	**N=57**	**N=17**	
Median (Q1 - Q3)	34.0 (26.0-41.0)	29.0 (20.0-45.0)	0.782†
Type of hospitalization, n (%)			
Voluntary hospitalization	33 (48.5%)	12 (63.2%)	0.507‡
Unvoluntary hospitalization	27 (39.7%)	5 (26.3%)	
Outpatient	8 (11.8%)	2 (10.5%)	
Adherrence in medication	**N=47**	**N=14**	
No	4 (8.5%)	9 (64.3%)	**<0.001**‡
Yes	43 (91.5%)	5 (35.7%)	
Lifetime_most _cannabis use	**N=66**	**N=19**	
Less than one a week	50 (75.8%)	12 (63.2%)	0.276‡
Once and more a week	16 (24.2%)	7 (36.8%)	
PANSS entrance positive symptoms, total scores			

Mean (SD)	29.1 (6.5)	29.6 (7.3)	0.749
PANSS entrance negative symptoms, total scores			
Mean (SD)	20.9 (8.0)	19.6 (6.9)	0.524
PANSS entrance general symptoms, total scores			
Median (Q1 - Q3)	50.0 (42.5-57.0)	50.0 (43.0-57.0)	0.727†
PANSS entrance total			
Median (Q1 - Q3)	99.5 (88.5-114.5)	98.0 (86.0-110.0)	0.615†
PANSS month positive symptoms, total scores			
Median (Q1 - Q3)	13.0 (10.0-15.5)	12.0 (10.0-18.0)	0.516†
PANSS month negative symptoms, total scores			
Median (Q1 - Q3)	13.0 (8.5-19.0)	13.0 (9.0-18.0)	0.984†
PANSS month general symptoms, total scores			
Median (Q1 - Q3)	28.5 (23.0-34.0)	30.0 (24.0-35.0)	0.419†
PANSS month total			
Median (Q1 - Q3)	52.5 (45.0-67.5)	56.0 (45.0-71.0)	0.565†
Nottingham DUP (in weeks)	**N=66**	**N=19**	
Median (Q1 - Q3)	9.5 (4.0-28.0)	10.0 (4.0-29.0)	0.958†
GAF entrance	**N=63**	**N=19**	
Median (Q1 - Q3)	40.0 (30.0-55.0)	45.0 (35.0-51.0)	0.223†
GAF month	**N=61**	**N=19**	
Mean (SD)	60.6 (14.2)	60.6 (13.2)	0.984
PAS Academic	**N=62**	**N=18**	
Median (Q1 - Q3)	0.2 (0.1-0.3)	0.3 (0.1-0.5)	0.462†
PAS Social	**N=63**	**N=17**	
Median (Q1 - Q3)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.548†

†Mann- Whitney test. ‡Pearson's chi-square test. two-sample t-test with equal variances. CI: Confidence interval; PANSS: The Positive and Negative Symptom Scale; GAF: The Global Assessment of Functioning scale; DUP: Duration of Untreated Psychosis; PAS: Premorbid Adjustment Scale

At a second level, potential factors from univariate analyses (i.e., $p<0.2$) were included in a multiple regression model, as well as gender and age, regardless of univariate analyses results. From the

exploratory analyses, only medication adherence was significantly associated with relapse (**table 4**).

Table 4

Multiple regression model of relapse vs no relapse and clinical, demographic factors from univariate analyses (i.e., p<0.2), adjusted for gender and age.

	Univariate analyses		**Multiple logistic (N=55)**	
Relapse vs. no relapse	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Gender (female vs. male)	0.89 (0.31, 2.53)	0.821	1.70 (0.31, 9.21)	0.539
Age on onset (years)	1.00 (0.94, 1.07)	0.998	0.94 (0.84, 1.05)	0.266
Education (years)	0.84 (0.65, 1.08)	0.166	1.05 (0.71, 1.55)	0.814
Adherence (yes vs. no)	0.05 (0.01, 0.23)	**<0.001**	0.03 (0.004, 0.26)	**0.001**

CI: Confidence interval

Discussion

FEP treatment programs are far from well implemented and established in our country. In this longitudinal study of FEP patients, the first conducted in Greece, we report rates of relapse within a year from first psychosis manifestation. Moreover, low follow-up adherence raises concerns for the efficacy of available FEP Programs and emphasize the need for keeping up with international standards of Service models and the perspectives of Early Intervention.

In our study, patients who retained contact at one year follow-up time point did not differ in terms of baseline characteristics from FEP patients that refused follow-up, thus they could be considered a representative sample to report relapse rates. Furthermore, this indicates that basic demographic differences or illness-related characteristics are unlikely to explain the high attrition rates observed within a year of first contact. Relapse within a year was defined stringently by hospital readmission. Relapse rates of 25% are consistent with the literature regarding 1st year relapse rates in FEP patients [13]. Moreover, DUP, clinical diagnosis, symptomatology and functionality were not associated with relapse, as previously reported [4]. The small sample of patients that experienced relapse could be a study limitation and a plausible explanation for the above results. Research evidence suggests that a number of risk factors, predominantly medication non-adherence, substance use disorder and poorer premorbid adjustment have been associated with increased relapse rates [13]. These factors were not found to be related with relapse rates in our analysis with the exception of medication non-adherence, as expected [24]. However, another limitation in this study is that treatment discontinuation could not be distinguished from partial non adherence.

Low follow-up rates in our study raise skepticism concerning existing FEP services. While service disengagement is considered a negative prognostic factor [25], the majority of our FEP patients refused

continuation of outpatient treatment, as provided by our hospital-based FEP settings. Service disengagement is a heterogenous concept and rates of a range of 6–60% [26] and of 12–53% [27] are reported, however recent studies, emphasizing on Early Intervention Services, report a more favorable outcome of 15,6% on 2 years follow-up average [12] and 32% within the first 12 months after enrollment [28]. In the era of early intervention, disengagement rates have declined and the cause is not clear partly due to methodological variation, but due to provided multidimensional treatment [12]. In our study attrition at first year has been 62%, in contrast with reported disengagement rates of studies concerning EIS. It is plausible to assume that these high attrition rates could be due to provided treatment, as 4 out of 5 clinical settings across Athens offer treatment as usual as standard follow-up (clinical follow-up without specific psychological or psychosocial interventions), while the only operating Early Intervention Outpatient Service in Athens does not operate within a clear catchment area, reducing the chance of following FEP patients due to outreach issues [8]. Moreover, substance use, contact with the criminal justice system, medication non-adherence, lower symptom severity are reported amongst robust predictors of disengagement [12]. In our analysis, we were not able to explore criminal records or other than cannabis substance use and lack of family support [27] as factors for service disengagement, however, demographic, clinical- and functionality-related factors were not related with follow-up adherence. Given that the greatest challenge for this study is the high drop-out rate, it is hard to determine whether the results present an accurate description of the course of illness among people using FEP services in Greece, however the negative association for psychosis-related factors explored might offer an explanation that other non-specific, non-clinical factors such as the lack of mental health service sectorization or traumatic experiences related to hospitalization or antipsychotic medication might be a reason for not choosing the same clinical setting for follow-up. Engaging a person with the service and building a relationship from which therapy and treatment can be facilitated, is a major contributor for improving outcomes [29]. To address patients' multidimensional needs, community-based, recovery-oriented, non-stigmatizing assertive programs, such as EIS, might maximize follow-up engagement. Current gaps in provided standard of care highlight the need for specific, FEP-oriented EIS.

While intervention in primary psychosis remains challenging [30, 31], filling the therapeutic gap for FEP patients offering optimized, community-based, multi-disciplinary approaches should be a priority. EIS have a clear benefit for patients and their families [32, 33] and moreover are cost-effective for Mental Health Care Systems [34]. Quality in Mental Health Services Is pivotal for the effectiveness and efficiency of mental healthcare systems [35]. By reporting relapse and follow-up rates, the Athens FEP study underlines the present need for the implementation of EIS in our country providing also a benchmark against which future EIS for psychosis in Greece will have to demonstrate superior efficacy. While scarce financial support and lack of government recognition of EIS importance are reported as key barriers for implementation of EIS services [36], a recent government legislation setting the legal framework for the establishment of EIS in Greece (Official Government Gazette of the Hellenic Republic, A 256–23.12.2020) within the National Health System has been an important, but still a first, initial step. Even though there is still much to be done, such advances raise justified optimism for a new era of treating psychosis by implementing fundamental principles of early intervention.

Declarations

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Authors' contributions

SD analyzed the participant data and was a major contributor in writing the manuscript. PS, IV, MS, LAX, IR, RFS, NN, IK, LM and SF collected and analyzed participant data. NS and CK were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Research Ethics committee of the Eginition hospital (protocol 644Y46Ψ8N2-ΓΚΣ). All methods were performed in accordance with the relevant guidelines and regulations. Every subject feasible to participate in the study provided a signed informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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