Psychiatria Danubina, 2019; Vol. 31, Suppl. 2, pp S171-180 *Conference paper*

EFFICACY OF CENTER FOR INTEGRATIVE PSYCHIATRY MULTIMODAL EARLY INTERVENTION SERVICES IN EARLY-PHASE PSYCHOSIS ON HOSPITAL READMISSION

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SUMMARY

Background: *Growing body of evidence has opened new opportunities to enhance treatment outcomes during early-phase psychosis (EPP). The objective of this study was to evaluate the effect of the Centre for integrative psychiatry (CIP) multimodal Early Intervention Services (EIS) on time to relapse in the patients with early-phase psychosis (EPP) during 12 and 24 month period.*

Subject and methods*: We performed a retrospective cohort study on the sample of 454 EPP patients (duration of the diagnosed disorder ≤5 years) admitted to Psychiatric Hospital "Sveti Ivan", Zagreb Croatia, from January 2, 2015, to December 5, 2018, for the acute treatment of EPP. The end of follow up was March 5, 2019. The primary outcome was the time to rehospitalization because of relapse during the 12 months from the hospital discharge. Independent variable was the EIS.*

Results*: We analyzed 454 EPP patients, 260 in EIS group and 194 in no EIS group. After the adjustment for twenty possible confounding factors using the Cox proportional hazard regression, patients who received EIS had significantly and clinically relevantly lower hazard for rehospitalization because of relapse during the first 12 months (HR=0.39; $CI_{95\%}$ 0.21-0.61; p<0.001), and during the first 24 months from the hospital discharge (HR=0.56; $CI_{95\%}$ 0.39-0.80; p=0.003; sequential Holm-Bonferroni corrected p_{corr}=0.004).*

Conclusions: *Our study indicated efficacy of the CIP multimodal EIS in patients with EPP demonstrated through the time to the hospital readmission because of relapse during the 12 and 24 months from the hospital discharge. These results strongly support the need for implementation of multimodal EIS in all patients with EPP.*

Key words: *schizophrenia spectrum disorder - early intervention services - early-phase psychosis - schizophrenia*

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INTRODUCTION

The early-phase psychosis (EPP) is a period that potentially offers important opportunities for secondary prevention (Birchwood et al. 1998). The main goals of treatment in the EPP are to start with the effective treatment as early as possible, to accelerate remission through effective biological and psychosocial interventions, minimize the patient's adverse reactions to the experience of psychosis and to maximize social and work functioning, and to prevent relapse and treatment resistance (Spencer et al. 2001).

The appropriate use of antipsychotics in patients with first-episode psychosis (FEP) has a crucial impact on the course and outcome of the illness, and on shaping patients attitude toward their illness (Gaebel et al. 2014). The majority of FEP have high rates of response to antipsychotic treatment (Lieberman et al. 2003). While relapse rate is relatively low in the first year of illness, 81.9% of the FEP experience relapse within 5 years. Non-adherence in FEP is one of the most important risk factors for relapse (Robinson et al. 1999, Alvarez-Jimenez et al. 2012, Coldham et al. 2002). Long-acting injectable (LAI) antipsychotics are related to better adherence in FEP patients (Titus-Lay et al. 2018), and are substantially superior compared to oral antipsychotics in preventing hospitalization (Kishimoto et al. 2013). They show an advantage in efficacy, and fewer extrapyramidal symptoms, but more weight gain in the treatment of EPP (Emsley et al. 2008).

A growing body of knowledge confirms the role of psychotherapy and sociotherapy in FEP treatment; most of the early intervention services (EIS) offer cognitive-behavioral therapy (CBT), psychoeducation and family involvement, targeting reduction of risk symptoms and improvement of the level of functioning (Müller et al. 2014). EIS is superior to treatment as usual (TAU) across all outcomes, supporting the need for the use in patients with EPP (Correll et al. 2018). Patients in EIS (vs. TAU) are more likely to remain in contact with specialized mental health services, have a stronger working alliance and have greater client satisfaction (Albert et al. 2017). EIS offering supportive psychodynamic psychotherapy (compared with TAU group for FEP) improve the levels of social function and general psychopathology significantly (Rosenbaum et al. 2012, Harder et al. 2014).

Integrative medicine is a patient-centered model that considers evidence-based pharmaceutical treatments as well as sociocultural factors, nutritional status, mind-body medicine, and preventative medicine in both the eradication of illness and the promotion of long-term wellness; in Croatia, the first EIS based on group psychotherapy for patients in the early-phases psychosis (RIPEPP) was established in Psychiatric Hospital "Sveti Ivan" (Restek-Petrovic et al. 2012) to which the founding of the Centre for integrative psychiatry (CIP) in 2015 was continued. Through the CIP multimodal program, the patients with EPP receive ESI based on the biopsychosocial model, trough personalized pharmacotherapy and inclusion in the psychotherapy and sociotherapy program in a psychotherapeutic inpatient unit or day hospital unit (Mayer et al. 2017). Upon hospital discharge, innovative and integrated interventions based on group psychotherapy, CBT and family therapy are offered to patient and families (Matic et al. 2018).

The evaluation of the CIP multimodal Early Intervention Services for Early-Phase Psychosis program was conducted for FEP, the findings of which confirmed the effectiveness of the CIP multimodal EIS programs, indicating that multimodal EIS program has significant effects on the treatment of EPP; patients who receive EIS demonstrated lower hazard for relapses (Matic et al. 2018). The limitations to the previous study were that the participants were not randomized, the retrospective nature of the study, lack of differentiation of the particular psychotherapeutic strategy and approach, and the relatively low number of patients treated in day hospital (Matic et al. 2018).

The time for a follow-up is short to allow major modifications to the research methodology, and tackle all the limitations, so the present study will report on the same indicators of treatment efficacy as the first round of the study did, to increase the overall effectiveness of the previous research by increasing the sample and prolonging the observation period, and subsequent to the original research to ascertain if the intervention efficacy has hanged.

SUBJECT AND METHODS

Study design and setting

We performed a retrospective cohort study on the sample of 454 patients admitted to Psychiatric Hospital "Sveti Ivan", Zagreb Croatia, from January 2, 2015, to December 5, 2018. The end of follow up was March 5, 2019. The study was approved by the Ethics Committee of the Psychiatric Hospital "Sveti Ivan". Zero time for the assembly of cohorts was the end of treatment in the acute department after the initial adherence and control of acute psychotic symptoms was achieved.

Participants

The targeted population were patients diagnosed with early-phase psychosis (total duration of the diagnosed disorder ≤5 years) and admitted to the psychiatric hospital for acute treatment. We selected the consecutive sample of all eligible patients admitted during the enrollment period. Patients were eligible if they were aged 18–64 years and resident within the study areas at the time of their first presentation with a diagnosis of psychosis by ICD-10 criteria (F20–29); We did not perform the power analysis before the data collection but decided to collect the data on all patients.

Outcomes

Our primary outcome was the time to rehospitalization because of relapse during the first 12 months from the hospital discharge. Our secondary outcome was the time to rehospitalization because of relapse during the first 24 months from the hospital discharge.

Intervention

Our independent variable was the CIP multimodal EIS (psychotherapeutic inpatient unit and/or day hospital after the end of treatment in the acute unit) dichotomized into groups: EIS, no-EIS. Duration of EIS treatment correlate with duration of hospitalization on the psychotherapeutic inpatient unit and/or day hospital.

When included in a psychotherapeutic inpatient unit or day hospital, all patients participate in all the segments of the program. The therapeutic CIP multimodal EIS program of the psychotherapeutic inpatient unit and the day hospital is held through comprehensive early intervention program for patients with psychotic disorders as a psychotherapeutic and psychosocial treatment as well as rehabilitation, including psychodynamically oriented group psychotherapy, multifamily groups, CBT workshops, metacognitive training, psycho-education, occupational therapy and recreation, socio-therapy and recreational therapy, antistigma workshops, anti-stress workshops, therapeutic community meetings including both the staff and the patients, field trips, film workshops, nutrition workshops and workshops with a social worker (Mayer et al. 2017, Sago et al. 2018).

Possible confounders

Possible confounders whose effects we tried to control using a multivariable analysis were patients' gender, age, education, work status before the admission dichotomized into categories i) employed or student, ii) unemployed or retired, current smoking of tobacco, psychiatric hospitalization before the enrollment and previous

treatment with antipsychotics, substance abuse, suicidality, existence of psychiatric comorbidities, year of admission to the hospital, reason for the hospitalization, did the patient came to the hospital alone, with friends and family or she/he was brought by ambulance or police, patient awareness of the illness estimated by the psychiatrist, duration of treatment in the acute department and the overall duration of hospitalization. We collected the data and controlled the effects of antipsychotic therapy at hospital discharge operationalized as i) number of antipsychotics (monotherapy, two or three drugs combinations), ii) antipsychotic generation (1st, 2nd and clozapine), iii) way of usage and generation (1st generation oral, 1st generation LAI, 2nd generation oral, 2nd generation LAI), and we controlled the effects of other psychiatric therapies at discharge: benzodiazepines, mood stabilizers, antidepressants, anticholinergics, hypnotics and sedatives, as well as the total number of psychiatric drugs used. We collected all the data from the hospital electronic medical records.

Table 1. Participants sociodemographic and clinical characteristics (n=454)

	EIS (n=260)		no EIS (n=194)	
Sociodemographic characteristics				
Gender				
men	155	(59.6)	113	(58.2)
women	105	(40.4)	81	(41.8)
Age (years), median (IQR)	27	(23-33)	31	(25-40)
Age (years)				
<25	87	(33.5)	46	(23.7)
25-29	70	(26.9)	41	(21.1)
30-34	52	(20.0)	30	(15.5)
35-39	26	(10.0)	28	(14.4)
≥40	25	(9.6)	49	(25.3)
Education				
primary	15	(5.8)	22	(11.3)
secondary	189	(72.7)	133	(68.6)
university	56	(21.5)	39	(20.1)
Work status				
employed or student	129	(49.6)	96	(49.5)
unemployed or retired	131	(50.4)	98	(50.5)
Current smokers	118	(45.4)	93	(47.9)
Clinical characteristics				
Previous psychiatric hospitalizations	109	(41.9)	65	(33.5)
Previous treatment with antipsychotics	132	(50.8)	73	(37.6)
Substance abuse	92	(35.4)	71	(36.6)
Suicidality	23	(8.8)	11	(5.7)
Psychiatric comorbidities	85	(32.7)	66	(34.0)
Year of admission to the hospital				
2015	60	(23.1)	46	(23.7)
2016	69	(26.5)	38	(19.6)
2017	80	(30.8)	52	(26.8)
2018	51	(19.6)	58	(29.9)
Reason for the hospitalization				
first occurrence	163	(62.7)	135	(69.6)
relapse	88	(33.8)	52	(26.8)
other	9	(3.5)	7	(3.6)
How did the patient come to the hospital				
alone, with family or friends	134	(51.5)	78	(40.2)
brought by ambulance or police	126	(48.5)	116	(59.8)
Patients at least partially aware of the illness	129	(49.6)	75	(38.7)
Duration of treatment in acute department (days), median (IQR)	19	(11-30)	21	(12-35)
Duration of total hospitalization (days), median (IQR)	59	(42-77)	22	(12-37)

Abbreviations: IQR = interquartile range; Data are presented as number (percentage) of patients if not stated otherwise;

Statistical analysis

We performed the primary analysis using a Cox proportional hazard regression. Before the analysis, we tested the proportional hazard assumption by testing the independence of residuals and time, testing for non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time and by visual inspection of Kaplan-Meier curves and plot of Schoenfeld residuals on log time with the Lowess smoothing curve. First, we did a series of univariate Cox regressions of the independent variable and all preplanned possible confounding factors on the time to the rehospitalization because of relapse within 12 months from hospital discharge. In the second step, we did a multivariable Cox regression including all preplanned covariates. In the primary analysis, we did not apply a correction for multiple testing because all analysis and included variables were preplanned and because we interpreted only one adjusted hazard ratio (HR). We presented the results of both: bivariable, unadjusted and multivariable, adjusted analysis by hazard ratios, their 95% confidence intervals (CI) and levels of statistical significance. As a median time to rehospitalization because of relapse was not reached we presented the mean time in months with its $CI_{95\%}$. In the analysis of the secondary outcome, we corrected statistical significances for multiple testing using the sequential Holm-Bonferroni correction. We set the level of statistical significance at a two-tailed $p<0.05$, and all confidence intervals at the 95% level. None of the collected variables had missing data. We did the analysis using R Core Team (2018) R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org.

RESULTS

Participants characteristics

We enrolled 511 patients admitted to the hospital because of acute early psychosis (MKB-10 F23) between January 1, 2015, and December 31, 2018. One patient was excluded from the analysis because at the end of follow up she was still hospitalized. Additionally, we excluded 51 patients who were not discharged nor received EIS but were admitted to the chronic department. Finally, we excluded five patients whose antipsychotic therapy was not properly recorded in the medical electronic documentation system. Overall, we excluded 57/511 (11.1%) participants. The final sample size used in this analysis was n=454 patients.

Two study groups were comparable with regards to gender, work status, current smoking, substance abuse, suicidality, number of psychiatric comorbidities, duration of treatment in the acute department, treatment with mood stabilizers and hypnotics or sedatives and the overall number of psychiatric drugs (Table 1). Patients who received EIS were somewhat younger, better educated, with a larger number of previous psychiatric hospitalizations, previous treatment with antipsychotics. They were more often admitted because of the relapse but more often came to the hospital alone or with family or friends as opposed to being brought by ambulance or police. They were more often at least partially aware and critical of the disease and had a markedly longer duration of hospitalization (Table 1). Patients who received EIS were more often treated with a combination of antipsychotic drugs, and with clozapine, and somewhat more often with 2nd generation antipsychotics, antidepressants and anticholinergics (Table 2).

Table 2. Therapy at hospital discharge (n=454)

	EIS (n=260)		no EIS (n=194)	
Antipsychotics				
monotherapy	106	(40.8)	96	(49.5)
two drugs combination	117	(45.0)	77	(39.7)
three drugs combination	37	(14.2)	21	(10.8)
Generation				
1st	61	(23.5)	59	(30.4)
2nd	246	(94.6)	172	(88.7)
clozapine	73	(28.1)	39	(20.1)
Way of usage and generation				
1st generation oral	56	(21.5)	54	(27.8)
1st generation LAI	9	(3.5)	14	(7.2)
2nd generation oral	175	(67.3)	119	(61.3)
2nd generation LAI	109	(41.9)	69	(35.6)
clozapine	73	(28.1)	39	(20.1)
Benzodiazepines	136	(52.3)	124	(63.9)
Mood stabilizers	58	(22.3)	50	(25.8)
Antidepressants	70	(26.9)	21	(10.8)
Anticholinergics	79	(30.4)	47	(24.2)
Hypnotics and sedatives	31	(11.9)	19	(9.8)
Number of psychiatric drugs, median (IQR)	3	(2-4)	3	(2-4)

Abbreviations: LAI = long acting injectables; IQR = interquartile range; Data are presented as number (percentage) of patients if not stated otherwise;

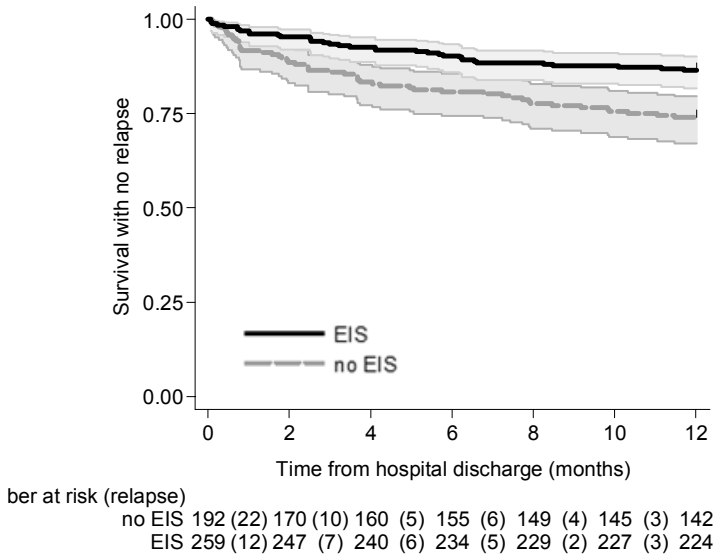

Figure 1. Cumulative probability of survival with no rehospitalization for relapse by early intervention services (EIS) after the hospital discharge; shaded area represents 95% confidence intervals (n=454)

Time to rehospitalization because of relapse within 12 months from the hospital discharge

Visual inspection of the plot of the Schoenfeld residuals on log time with the Lowess smoothing curve did not indicate a deviation from the proportional hazard assumption. Test of the deviation from the proportional hazard in EIS and non-EIS group was not significant (ρ=0.05; X^2=0.22; df=1; p=0.637).

After the adjustment for all preplanned possible confounding factors, effects modifiers and competing exposures using the Cox proportional hazard regression, patients who received EIS had significantly and clinically relevantly lower hazard for rehospitalization because of relapse during the first 12 months from the hospital discharge (HR=0.39; CI95% 0.21-0.61; p<0.001) (Table 3). The median time to rehospitalization because of relapse was not reached in any group. Mean (CI95%) time to rehospitalization because of relapse was 10.9 (10.6-11.3) months in the group who received EIS, and 9.6 (9.0-10.2) months in the group who did not (Table 3). The association of EIS with the hazard for rehospitalization because of relapse during the first 12 months from the discharge, was significant and clinically relevant in the bivariable, unadjusted analysis as well (Table 3, Figure 1).

Time to rehospitalization because of relapse within 24 months from the hospital discharge

After the adjustment for possible confounders, patients who received EIS had a significantly lower hazard for rehospitalization because of relapse during the first 24 months (HR=0.43; $CI_{95\%}$ 0.28-0.66; p<0.001; sequential Holm-Bonferroni corrected p_{corr}=0.003). Mean ($CI_{95\%}$) time to rehospitalization because of relapse during the first 24 months was 20.7 (19.8-21.5) months in the group who received EIS, and 18.0 (16.7-19.2) months in the group who did not. Bivariable, unadjusted hazard ratio for rehospitalization because of relapse during the first 24 months from discharge was significant too (HR=0.56; $CI_{95\%}$ 0.39-0.80; p=0.003; sequential Holm-Bonferroni corrected p_{corr}=0.004).

DISCUSSION

Our naturalistic, registry-based, retrospective cohort study strongly indicated the efficacy of the CIP multimodal EIS on time to hospital readmission during the first 12 and first 24 months from hospital discharge. Not only did the patients who received EIS have 61% lower hazard for rehospitalization because of relapse in the 12 months, but they also had 44% lower hazard for rehospitalization in the 24 months, supporting the study hypothesis that programs constituting EIS contribute to the prolongation of time to the hospital readmission. These results are in line with the results of the previous evaluation of the CIP multimodal EIS, where similar results were found (Matic et al. 2018). Other studies also reported that relapse rates in the first 2 years are considerably lower in EPP who participated in EIS than those reported when TAU is provided; however, relapse rates raised considerably in the second year (Robinson et al. 1999, Craig et al. 2004, Petersen et al. 2005), more dramatically than in the case of the existing study.

Given the significant impact of adherence to medication on risk of relapse, especially in the first year of treatment (Alvarez-Jimenez et al. 2012, Coldham et al. 2002), the CIP multimodal EIS program may have some clear cut advantages on the adherence of patients to therapy as compared to other EIS programs reported in literature, especially programs that are comparable to this study's intervention by the high level of support and

Table 3. Time to rehospitalization for relapse within 12 months from the hospital discharge by the Early intervention services (n=454)

	n	Mean* time (months)	($CI_{95\%}$)	Bivariable, unadjusted			Multivariable, adjusted		
				HR	($CI_{95\%}$)	p	HR	($CI_{95\%}$)	p
Program									
no EIS	184	9.6	(9.0-10.2)	1			1		
EIS	270	10.9	(10.6-11.3)	0.48	(0.31-0.73)	0.001	0.36	(0.21-0.61)	<0.001
Covariates adjusted for									
Gender									
male	268	10.3	(9.9-10.8)	1			1		
female	186	10.5	(10.0-11.0)	0.81	(0.52-1.25)	0.341	0.99	(0.61-1.60)	0.965
Age (years)	454			0.99	(0.96-1.01)	0.212	0.97	(0.95-1.00)	0.032
Education									
primary	37	9.4	(8.1-10.8)	1			1		
secondary	322	10.4	(10.0-10.8)	0.50	(0.28-0.91)	0.024	0.67	(0.36-1.26)	0.212
university	95	10.8	(10.2-11.5)	0.41	(0.19-0.86)	0.018	0.63	(0.28-1.38)	0.245
Working status									
employed or student	154	10.4	(9.9-10.8)	1			1		
unemployed or retired	229	10.4	(10.0-10.9)	1.02	(0.67-1.55)	0.915	0.86	(0.54-1.34)	0.496
Reason for the hospitalization									
first occurrence	163	10.4	(10.0-10.8)	1			1		
relapse	88	10.3	(9.7-10.9)	1.01	(0.61-1.67)	0.961	1.56	(0.70-3.50)	0.280
other	9	11.3	(9.9-12.7)	0.27	(0.04-2.09)	0.209	0.31	(0.04-2.53)	0.275
How did the patient come to the hospital									
alone, with family or friends	212	10.7	(10.2-11.1)	1			1		
brought by ambulance or police	242	10.2	(9.7-10.7)	1.34	(0.84-2.15)	0.226	1.15	(0.70-1.88)	0.583
Patients at least partially aware of the illness									
no	250	10.1	(9.6-10.6)	1			1		
yes	204	10.8	(10.4-11.2)	0.65	(0.40-1.04)	0.073	0.79	(0.49-1.30)	0.356
Duration of acute treatment	454			0.99	(0.98-1.00)	0.145	0.98	(0.97-1.00)	0.007
Duration of hospitalization	454			1.00	(0.99-1.00)	0.402	1.01	(1.00-1.01)	0.002
Previous psychiatric hospitalizations									
no	280	10.3	(9.9-10.8)	1			1		
yes	174	10.5	(10.0-11.0)	0.91	(0.59-1.41)	0.675	0.57	(0.29-1.14)	0.115

Abbreviations: CI = confidence interval; HR = hazard ratio for relapse; p = two-tails statistical significance of HR calculated using Cox proportional hazard regression
* Median time to relapse was not reached in any group

Table 3. Continous

	n	Mean* time (months)	($CI_{95\%}$)	Bivariable, unadjusted			Multivariable, adjusted		
				HR	($CI_{95\%}$)	p	HR	($CI_{95\%}$)	p
Previous treatment with antipsychotics									
no	249	10.3	(9.9-10.8)	1			1		
yes	205	10.5	(10.0-11.0)	0.87	(0.57-1.33)	0.525	1.09	(0.56-2.13)	0.806
Substance abuse									
no	291	10.4	(10.0-10.8)	1			1		
yes	163	10.4	(9.9-11.0)	1.07	(0.70-1.65)	0.757	0.96	(0.59-1.55)	0.862
Having a physical comorbidity									
no	401	10.4	(10.1-10.8)	1			1		
yes	53	10.3	(9.3-11.3)	0.98	(0.51-1.88)	0.941	1.25	(0.61-2.55)	0.542
Antipsychotics									
monotherapy	202	10.3	(9.8-10.8)	1			1		
two drugs combination	194	10.7	(10.2-11.1)	0.75	(0.45-1.25)	0.274	0.40	(0.19-0.83)	0.014
three drugs combination	58	9.9	(8.9-11.0)	1.21	(0.61-2.42)	0.585	0.41	(0.14-1.21)	0.106
Generation									
1^{st}	61	9.4	(8.6-10.2)	2.63	(1.62-4.29)	<0.001	4.36	(1.99-9.54)	<0.001
2^{nd}	246	10.5	(10.1-10.8)	0.44	(0.21-0.93)	0.031	1.44	(0.59-3.53)	0.428
clozapine	73	10.7	(10.2-12.3)	0.81	(0.46-1.42)	0.456	1.70	(0.81-3.58)	0.163
Benzodiazepines	136	10.0	(9.5-10.5)	1.67	(1.02-2.73)	0.040	1.41	(0.88-2.25)	0.158
Mood stabilizers	58	10.2	(9.5-10.9)	1.26	(0.74-2.14)	0.393	1.17	(0.71-1.93)	0.546
Antidepressants	70	10.8	(10.1-11.4)	0.64	(0.34-1.21)	0.172	0.89	(0.47-1.69)	0.720
Anticholinergics	79	10.4	(9.8-11.1)	0.97	(0.58-1.64)	0.911	1.12	(0.68-1.85)	0.663
Hypnotics and sedatives	31	9.2	(7.9-10.4)	2.17	(1.14-4.14)	0.019	1.62	(0.88-2.97)	0.118

Abbreviations: CI = confidence interval; HR = hazard ratio for relapse; p = two-tails statistical significance of HR calculated using Cox proportional hazard regression
* Median time to relapse was not reached in any group

availability to patients through assertive case management and emphasis on family intervention provided (Malla et al. 2008). Additionally, timely use of the LAI antipsychotics (Kishimoto et al. 2013), which is known to prevent cognitive decline of patients and improve the general psychopathology (Rosenbaum et al. 2012, Harder et al. 2014), most likely contributes to the efficacy of the overall EIS in delaying the time to rehospitalization. Furthermore, all part of EIS programs (psychoeducation workshops for patients and their family members, psychodynamic group psychotherapy for patients, psychodynamic group psychotherapy for family members of patients, day hospital, multi-family groups, cognitive behavioral workshops, metacognitive training, occupational therapy, socio-therapy and recreational therapy, nutrition workshops, workshops with a social worker as well as other socialization techniques in a supportive environment) (Restek-Petrovic et al. 2012, Sago et al. 2018), possibly jointly contribute to a better adherence to medication than EIS programs reported on in the literature previously.

The efficacy of the CIP multimodal EIS approach may be constituted by the improvement in emotional regulation and reduction in the intensity of symptoms through understanding intrapsychic experiences and emotional acceptance, enabling the processes which allow individuals to form a more integrated sense of self and others (Lysaker et al. 2018), development of a shared understanding of the illness in the family through enhancing skills in problem solving and communication, and having a safe place to discuss issues and learn about their patterns of relating to one another, recognition of patients' own strengths and weaknesses, emotion recognition and understanding how to deal with negative emotions, how to plan goal achievement, how to cope with stress, solve the problem, focus on emotions (Sago et al. 2018), strengthening the patients to be aware of and reflecting upon their own thoughts, feelings, and intentions, and those of other people, and ultimately formulating the connection between these events into a larger complex representations of themselves and others (Inchausti et al. 2016).

The success in the reduced hazard for relapse (especially in the second year after discharge) should be carefully assessed in the future examining the profile of the patients enrolled in the EIS, which was not the focus of the present study. It is possible that patients who are likely to be nonadherent to therapy, and thus under elevated hazard for relapse, were excluded from the EIS through a systemic bias; consequently it is possible that patients with the lower 'psychotherapeutic capacity' were included in the EIS less frequently than those with more adequate capacities, influencing their adherence to medicines and through that the final outcome, the relapse. Evidence show that patients who receive mental health services engage less in treatment, or disengage more from it, for different factors; specific groups of patients, such as patients with personality disorder, patients with low insight, patients with a history of prior admissions, patients from areas of higher deprivation or patients that have problems with substance misuse, may be particularly vulnerable (Puntis et al. 2018, Lal & Malla 2015). In order for EIS beneficiaries to benefit from services optimally, understanding the elements that define service engagement and disengagement in EIS is critical (Tibbo 2015). In order to confirm the extraordinary success of the intervention described in this study, a more detailed analysis of factors confounding the inclusion of patients with EPP in the EIS is suggested. Clinical implications of such analysis would be that patients under elevated risk of being treated "as usual" optimally benefit from EIS services.

Limitations of the study

The main limitation of our study is that patients were not randomly assigned to EIS. For this reason, we cannot reliably claim causal effects of EIS on the prolongation from the hospital discharge to relapse, although we tried to control a large number of possible confounding factors. The second limitation was the relative imprecision of the operationalization of our exposure. We have not taken into account the type of psychotherapy, the number of psychotherapeutic sessions, activities, frequency, and duration of visits to the daily hospital. However, this probably lowers the precision but not the direction of our findings and conclusion. Third, we performed the study in the large psychiatric hospital in the Croatian capital, and our findings should only cautiously be generalized to the total population of Croatian patients with early psychosis treated in small psychiatric wards, in general hospitals and more rural areas of the country. We don't have any evidence-based reason to believe that our findings would be substantially different in different clinical and sociodemographic settings, but this limitation should be taken into account. Fourth, we collected the data from the Hospital electronic medical records, and the severity and structure of psychotic symptoms are not registered routinely. Therefore, we lack the data on this important confounder. We tried to minimize its effect by excluding 51 patients who were not discharged nor received EIS but were admitted to the chronic department, and by adjusting the analysis for a number of antipsychotics used, duration of acute treatment, duration of hospitalization and patients' awareness of the illness. While this measures probably controlled the effect of the worst clinical pictures, we still did not control for the differences in psychotic symptoms structure and severity, although they may be causes of both, EIS and the time to the rehospitalization because of relapse. Future studies should collect the data on this important confounder. Sixth, we were

not able to collect the data on duration of untreated psychosis while its effect may be similar to the effects of the severity of psychotic symptoms. Seventh, as this was a real-life retrospective study, we had the follow-up data only on the patients who continue to be treated in our institution and we recorded the outcome only in patients who were rehospitalized in our hospital. For this reason, our outcome had good specificity but may have lower sensitivity. Eight, although we adjusted the analysis for the antipsychotic treatment, we did not control the possible effects of different dosing. The strength of our study was its real-life setting, the fact that we controlled a relatively large number of possible confounders, relatively long follow-up and the properly powered analysis.

CONCLUSION

Our study indicated efficacy of the CIP multimodal EIS in patients with EPP the time to the hospital readmission because of relapse during the 12 and 24 months from the hospital discharge. These results strongly support the need for implementation of multimodal EIS in all patients with EPP.

Acknowledgements:

The study was funded by Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia.

Conflict of interest: None to declare.

Contribution of individual authors:

All authors contributed to the conception of this manuscript, the literature search, the interpretation of the obtained results, participated in drafting and revising the article critically.

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