

## EARLY INTERVENTION SERVICES FOR EARLY-PHASE PSYCHOSIS - CENTRE FOR INTEGRATIVE PSYCHIATRY IN PSYCHIATRIC HOSPITAL "SVETI IVAN", CROATIA

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### SUMMARY

**Background:** There is a growing body of evidence suggesting that early and effective management in the critical early years of schizophrenia can improve long-term outcomes. The objective of this study was to evaluate time to relapse of the patients with early-phase psychosis treated in the Centre for integrative psychiatry (CIP).

**Subject and methods:** We performed a retrospective cohort study on the sample of 373 early-phase psychosis patients admitted to Psychiatric Hospital "Sveti Ivan", Zagreb Croatia: from January 1, 2015 to December 31, 2017. The primary outcome was time to relapse.

**Results:** Patients who were admitted to group psychotherapeutic program after the end of acute treatment had 70% lower hazard for relapse (HR=0.30; 95% CI 0.16-0.58). Patients who were included first in the psychotherapeutic program and then treated and controlled in the daily hospital had 74% lower hazard for relapse (HR=0.26; 95% CI 0.10-0.67).

**Conclusions:** In early-phase psychosis, integrative early intervention service has relevant beneficial effects compare to treatment as usual. These results justified the implementation of multimodal early intervention services in treatment of patients with early-phase psychosis.

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

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### INTRODUCTION

The course of schizophrenia is most often chronic, associated with significant personal suffering, disability, family burden, and suboptimal treatment outcome (Salomon et al. 2012, Vos et al. 2012, Kahn et al. 2015). However, there is a growing body of evidence suggesting that early and effective management in the critical early years of illness can improve long-term outcomes (McGorry et al. 2007, McGorry 2015). Most importantly, both are associated with benefits in the long-term outcomes of remission, relapse, and cognition (Karson et al. 2016). Untreated psychosis is almost certainly linked to poor outcomes both in the short- and longer-term due to neurobiological function abnormalities in the structure, cognitive impairments and neurobiological function, connectivity and neurochemistry of the brain (van Haren et al. 2007, Fusar-Poli et al. 2012, Rund et al. 2016, Murray et al. 2017). The efficacy of antipsychotic treatment in early-phase psychosis, in particular when initiated and maintained early in the course of the disease is well established. Moreover, inadequate intervention in early psychosis may lead to a poorer response to antipsychotics and potential treatment resistance, prolonged times to remission, as well as reduced recovery (Sheitman & Lieberman 1998, Emsley et al. 2013,

Lappin et al. 2018). It is well known that early psychosis patients have a high frequency of relapse during the 5 years after the FEP (Robinson et al. 1999) and that non-adherence to medication is the main predictive factor (Di Capite et al. 2016, Pelayo-Terán et al. 2017). Although recent studies showed that the risk of re-hospitalization is 32% lower in the FEP on long-acting injectable antipsychotic medications compared with treatment with equivalent oral formulations, there has been insufficient emphasis on using this treatment option in early psychosis patients (Tiihonen et al. 2017a).

To achieve a key treatment targets, sustained symptomatic and functional remission and relapse prevention in early psychosis, it is crucial to implement early integrative long-term intervention focus on the functional outcome of the disorder, with both continued antipsychotic treatment and psychosocial rehabilitation as essential treatment components (Correll et al. 2018).

The first early intervention service based on psychodynamic group psychotherapy for patients in the early-phases psychosis (RIPEPP) in Croatia was established in Psychiatric Hospital „Sveti Ivan” (Restek-Petrović et al. 2017). The founding of the Centre for integrative psychiatry (CIP) in 2015 was an important milestone in the gradual upscale of the early intervention services provided. The primary aim of the Centre for Integrative

Psychiatry is to fulfill the need of early-phase psychosis patients in order to improve functional outcomes and reducing long term disability during a critical illness period. The secondary aim is to raise the awareness of patients, family members and members of the community about the importance of recognizing, timely diagnosis and action on risk factors (i.e. changing unhealthy lifestyles), early intervention to prevent the development of various mental and physical illnesses and strive for holistic and individual approach to each patient, through various methods of treating the underlying disease and comorbidities, both in the institution and through mobile teams in the field and community-based institutions.

Through CIP program all the patients with early-phase psychosis initially receive early intervention services based on biopsychosocial model. Personalized pharmacotherapy, primarily with second and third generation antipsychotics, based on the principle "start low and go slow", resulting in the establishment of initial stabilization of the mental state with subsequent inclusion in the psychotherapy and sociotherapy program in a psychotherapeutic inpatient unit or daily hospital unit. In an evaluation of treatment of patients in early-phase psychosis treated at the hospital psychotherapeutic inpatient unit, significant improvement in the quality of life, positive trends in self-esteem and attitudes towards medications of patients were observed (Mayer et al. 2017). As the furthered step, upon hospital discharge, patients and families are included in several innovative and integrated multimodal interventions based on psychodynamic group psychotherapy, cognitive-behavioral therapy, and family therapy. The most important CIP outpatients programs are psychoeducation, anti-stigma, peer club, school of non-smoking and wellness programs.

However, further understanding of the outcomes for the early psychosis patients seeking treatment in the CIP is needed. This has the potential to assure the effectiveness of services in achieving improved recovery and to help adapt evidence-based pharmacologic approaches to reach patients and their families as they confront the onset of a psychotic illness. The objective of this study was to evaluate time to relapse of the early-phase psychosis treated in the CIP early intervention programs in the period between 2015 and 2017.

## SUBJECT AND METHODS

### Study design

We performed a retrospective cohort register study on the sample of 373 psychiatric patients admitted to Psychiatric Hospital "Sveti Ivan", Zagreb Croatia from January 1, 2015 to December 31, 2017. Data were compiled from paper charts and electronic records.

The data collected included patient demographic information (gender, age) and primary baseline diagnosis (Structured Clinical Interview for DSM-IV (SCID)

determined); patterns of health service and resource use including psychiatric admissions history and hospital days; social and functional information (relationship status, occupational activity, living arrangements and education); and psychotropic medication including number and type of psychotropic medication, monitoring of psychotropic medications, and monitoring of adverse effects of psychotropic medication using physical health parameters and investigations including documentation of blood pressure, weight, and body mass index (BMI). The study was approved by the institutional ethical committee.

### Participants

Our targeted populations were patients with a defined diagnosis of first-episode psychosis or a diagnosis of early-phase schizophrenia spectrum disorders (schizophrenia, psychotic disorder not otherwise specified, schizoaffective disorder, schizophreniform disorder, or delusional disorder) as per the 10th revision of International Classification of Diseases (ICD-10-DCR). The inclusion criteria were the confirmed targeted diagnoses. We excluded all patients with other diagnosis. The sample size was not decided a priori. The entire available population of all patients admitted to the hospital during the study period was evaluated. Power analysis was not performed.

### Variables

The outcome was time to the first re-hospitalization because of relapse. The independent variable was treatment program after the end of the acute phase. Hospital discharge with no program was used as the reference. Patients were discharged from the hospital when they reached standard criteria for achieving a stable therapeutic dosage and remission of symptoms. To this referent group, we compared three groups of patients in two programs: the psychotherapeutic program only, the daily hospital only, a combination of the psychotherapeutic program and the daily hospital. Pre-planned confounders whose effects we controlled by multivariable analysis were: gender, age, education, working status, duration of acute treatment, previous psychiatric hospitalizations, prior treatment with antipsychotics, substance abuse, having physical comorbidity and age at the first hospitalization for psychotic symptoms.

### Statistical analysis

The primary analysis was performed using a Cox proportional hazard model. Proportional hazard assumption was tested by the visual inspection of Kaplan-Meier curves. First, we did a series of univariate Cox regressions of the independent variable and all preplanned possible confounding factors on the time from hospital discharge to the re-hospitalization because of relapse.

In the second step, we did a multivariable Cox regression including all preplanned variables. 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 three adjusted hazard ratios (HR). With HR given as the standardized measure of the effect size, we presented their 95% confidence interval and levels of statistical significance. Statistical significance of the difference in the duration of hospitalization was calculated with Kruskal Wallis test. As the standardized measure of effect size with Kruskal Wallis test, we presented  $\eta^2$ , calculated as  $(\chi^2/(n-1))$  where  $\chi^2$  was Kruskal Wallis H coefficient, and n was a sample size. Post-hoc analyses of the differences in duration of hospitalization between particular programs were calculated with Mann-Whitney U test. These statistical significances were corrected for multiple testing by a sequential Holm-Bonferroni (H-B) correction. With Mann-Whitney U test, we presented r as the standardized measure of effect size. It was calculated as  $Z/(\sqrt{n})$  where Z was standardized Mann-Whitney U statistic, and n was a number of participants. Level of statistical significance was set at a two-tailed  $p < 0.05$ , and all confidence intervals were given at the 95% level. The analysis was carried out using the NCSS 12 Statistical Software (2018) (NCSS, LLC. Kaysville, Utah, USA).

## RESULTS

### Participants characteristics

We included a total population of 373 patients with early-phase psychosis (MKB-10 F23) admitted and treated in Psychiatric Hospital "Sveti Ivan" between January 1, 2015, and December 31, 2017. Men patients were more prevalent than women, and their median age was somewhat lower (Table 1). Slightly less than one-half of patients had been hospitalized before the current hospitalization, and the median (IQR) age of the first hospitalization was 28 (22-35). After the end of the acute phase, 129 (35%) of patients were discharged with no further programs (Table 2). Majority of the rest of patients, 166 (45%), were admitted to the psychotherapeutic program with no daily hospital or other programs, 17 (5%) were further treated in the daily hospital only, and 35 (9%) continue with the daily hospital after they finished the psychotherapeutic program. We excluded from the analysis 26 (7%) of patients who were admitted to the chronic department after the end of acute treatment. Median (IQR) overall duration of hospitalization was 45 (23-70) days. The median duration of hospitalization was significantly different in groups of patients that were discharged after the end of acute treatment and in different programs (Kruskal Wallis test,  $\chi^2=125.8$ ;  $df=3$ ;  $p=0.001$ ;  $\eta^2=0.36$ ). Median (IQR) duration of the hospitalization in patients who were discharged with no further programs after the end of acute

**Table 1.** Participants sociodemographic and clinical characteristics (n=373)

	n	%
Gender		
men	208	60.6
women	135	39.4
Age (years), median (IQR)	29	(24-36)
Age by gender (years), median IQR)		
men	27	(23-34)
women	31	(26-40)
Education		
primary	37	9.9
secondary	263	70.5
university	73	19.6
Work status		
employed	118	31.6
unemployed	202	54.2
retired	53	14.2
Current smokers	164	55.0
Clinical characteristics		
Previous psychiatric hospitalizations		
none	212	56.8
one	110	29.5
two or more	51	13.7
Age at first psychiatric hospitalization, median (IQR)	27	(22-35)
Previous treatment with antipsychotics	196	52.5
Substance abuse	133	36.4
Suicidality	28	7.5
Having a somatic illness	51	13.7
Number of psychiatric comorbidities		
no comorbidities	264	70.8
one	73	19.6
two	34	9.1
three	2	0.5

Data are presented as number (percentage) of patients if not stated otherwise; Abbreviations: IQR = interquartile range; Data were missing for current smoking in 75 (20.1%), and for the substance abuse in 8 (2.1%) participants

phase was 22 (12-38) days. This was significantly shorter than in group who were admitted to psychotherapeutic programs whose median (IQR) overall duration of hospitalization was 59 (44-77) (Mann-Whitney test,  $U=3058$ ;  $Z=-10.49$ ;  $p < 0.001$ ; H-B corrected  $p=0.005$ ;  $r=0.61$ ). Duration of hospitalization in patients treated in daily hospital only was, median (IQR) 32 (12-51) days, what was not significantly longer than in the immediately discharged group (Mann-Whitney test,  $U=861$ ;  $Z=-1.43$ ;  $p=0.151$ ; H-B corrected  $p=0.151$ ;  $r=0.12$ ), but what was significantly shorter than in patients admitted to psychotherapeutic programs (Mann-Whitney test,  $U=757$ ;  $Z=-3.12$ ;  $p=0.002$ ; H-B corrected  $p=0.006$ ;  $r=0.23$ ). The longest duration of the hospitalization was observed in the group of patients first admitted to the psychotherapeutic programs after the end of acute treatment, and then further treated in daily hospital, median

**Table 2.** Current hospitalization characteristics (n=373)

	n	%
Year of admission to the hospital		
2015	117	31.4
2016	113	30.3
2017	143	38.3
Reason for the hospitalization		
first occurrence	218	58.4
relapse	138	37.0
other	17	4.6
How did the patient come to the hospital		
alone, with family or friends	168	45.0
brought by ambulance or police	205	55.9
Emergency hospital admission	29	7.8
Coercive hospitalization	22	5.9
Intoxication within 24h before the admission	24	6.4
Patients at least partially aware of the illness	151	40.5
Duration of treatment in acute department (days), median (IQR)	21	(12-34)
Program after the end of acute treatment		
discharge only, no programs	129	34.6
psychotherapeutic program only	166	44.5
daily hospital only	17	4.6
psychotherapeutic program and daily hospital	35	9.4
chronic department or other	26	7.0
Duration of hospitalization, median (IQR)	45	(23-70)
Daily hospital within 3 months from discharge	49	13.1

Data are presented as number (percentage) of patients if not stated otherwise; Abbreviations: IQR = interquartile range; Data were missing for age at first psychiatric hospitalization in 8 (2.1%) participants

(IQR) 66 (49-90) days. This was significantly longer than in daily-hospital-only group (Mann-Whitney test,  $U=130$ ;  $Z=-3.28$ ;  $p=0.001$ ; H-B corrected  $p=0.004$ ;  $r=0.24$ ), but not in the psychotherapeutic-programs-only group (Mann-Whitney test,  $U=2373$ ;  $Z=-1.66$ ;  $p=0.098$ ; H-B corrected  $p=0.196$ ;  $r=0.12$ ). Upon hospital discharge majority of patients were treated with atypical antipsychotics: 66.5% (246/373) with 2<sup>nd</sup> generation oral antipsychotics, 38.1% (141/373) with 2<sup>nd</sup> generation long-acting injectable antipsychotics, 26.2% (97/373) with 1<sup>st</sup> generation antipsychotics, and 5.1% (19/373) with 1<sup>st</sup> generation long-acting injectable antipsychotics. Antidepressant medication was prescribed to 18.8% (70/373) and mood stabilizers to 20.6% (77/373) of patients (Table 3).

### Time to relapse

During the follow-up, 105 (28.5%) of patients experienced a relapse of the disease. Median survival with no relapse was not reached. Mean (95% CI) survival with no relapse was 29 (27-30) months. After the adjustment

**Table 3.** Therapy at hospital discharge (n=373)

	n	%
Antipsychotics		
monotherapy	163	44.1
two drugs combination	159	43.0
three drugs combination	48	13.0
Generation		
1 <sup>st</sup>	108	29.2
2 <sup>nd</sup>	340	91.9
clozapine	88	23.8
Way of usage and generation		
1 <sup>st</sup> generation oral	97	26.2
1 <sup>st</sup> generation LAI	19	5.1
2 <sup>nd</sup> generation oral	246	66.5
2 <sup>nd</sup> generation LAI	141	38.1
clozapine	88	23.8
Benzodiazepines	215	57.6
Mood stabilizers	77	20.6
Antidepressants	70	18.8
Anticholinergics	100	26.8
Hypnotics and sedatives	50	13.4
Number of psychiatric drugs, median (IQR)	3	(2-4)
Number of psychiatric drugs		
1	38	10.2
2	88	23.7
3	115	30.9
4	85	22.8
≥5	46	12.4

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

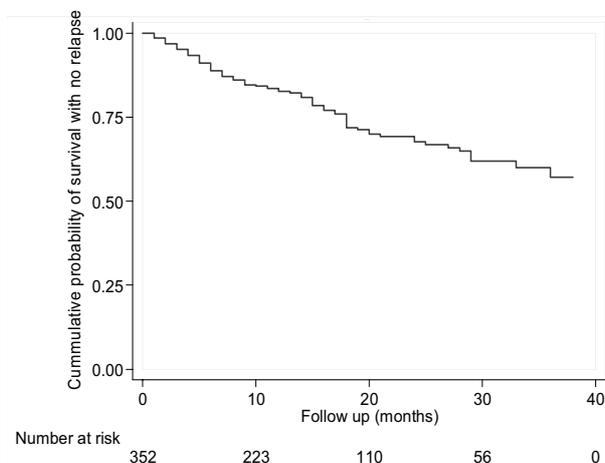
for gender, age, education, working status, duration of the acute treatment, previous psychiatric hospitalizations, previous treatment with antipsychotics, substance abuse, having a physical comorbidity and age at first hospitalization for psychotic symptoms, hospital program after the end of acute treatment was significantly and clinically relevantly associated with the time to relapse. Compared to the patients who were just discharged from the hospital with no further programs, patients who were included into the psychotherapeutic programs had 70% lower hazard for relapse (HR=0.30 (95% CI 0.16-0.58;  $p<0.001$ )) (Table 4, Figure 2). Patients who were included first in the psychotherapeutic program and then treated and controlled in the daily hospital had 74% lower hazard for relapse (HR=0.26 (95% CI 0.10-0.67;  $p=0.005$ )). In this naturalistic, registry-based, retrospective cohort study, obviously patients were not randomized to these two programs, but due to the large number of possible confounding factors that we controlled by multivariable Cox proportional hazard regression, it is strongly indicated that psychotherapeutic programs and daily hospital have relevant beneficial effects to the treatment of early psychosis.

Further studies should investigate in more details the possible synergic effects of combining two programs.

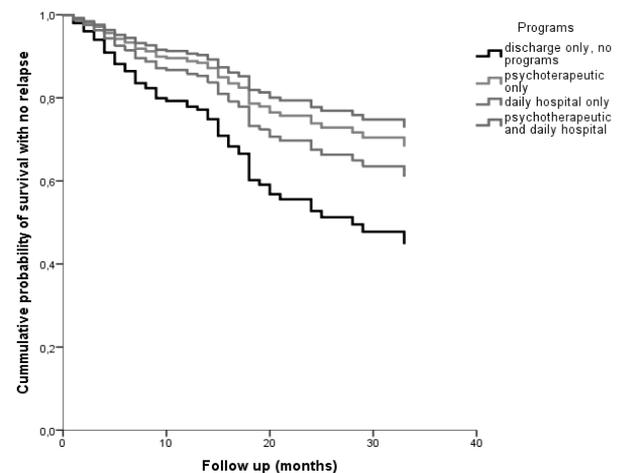
**Table 4.** Time to relapse by the hospital program (n=347)

	n	Mean time (months)	95% CI	Univariable			Multivariable, adjusted		
				HR	95% CI	p	HR	95% CI	p
<b>Program</b>									
discharge only, no programs	129	25	22-28	1			1		
psychotherapeutic program only	166	30	28-33	0.51	0.33-0.81	0.004	0.30	0.16-0.58	<0.001
daily hospital only	17	25	19-30	0.66	0.24-1.83	0.422	0.52	0.17-1.61	0.259
psychotherapeutic program and daily hospital	35	32	27-36	0.39	0.17-0.91	0.030	0.26	0.10-0.67	0.005
<b>Gender</b>									
male	213	29	27-31	1			1		
female	134	28	25-30	1.19	0.77-1.82	0.439	0.99	0.59-1.67	0.969
<b>Age (years)</b>									
	347			1.00	0.97-1.02	0.731	1.01	0.94-1.09	0.745
<b>Education</b>									
primary	33	23	18-28	1			1		
secondary	244	29	27-31	0.55	0.29-1.05	0.069	0.51	0.24-1.10	0.088
university	70	27	24-31	0.70	0.34-1.45	0.338	0.63	0.26-1.52	0.305
<b>Working status</b>									
employed or student	164	29	27-32	1			1		
unemployed	183	28	25-30	1.20	0.78-1.85	0.399	1.23	0.74-2.04	0.423
<b>Duration of acute treatment</b>									
	347			1.01	1.00-1.01	0.288	1.00	0.99-1.01	0.987
<b>Duration of hospitalization</b>									
	347			1.00	1.00-1.01	0.191	1.01	1.00-1.02	0.001
<b>Previous psychiatric hospitalizations</b>									
no	199	28	26-30	1			1		
yes	148	28	26-31	0.96	0.62-1.47	0.835	0.82	0.35-1.95	0.657
<b>Previous treatment with antipsychotics</b>									
no	166	28	26-31	1			1		
yes	181	28	26-31	0.94	0.62-1.44	0.779	0.94	0.43-2.03	0.867
<b>Substance abuse</b>									
no	211	27	25-30	1			1		
yes	128	30	27-33	0.72	0.45-1.16	0.178	0.66	0.38-1.16	0.148
<b>Having a physical comorbidity</b>									
no	303	28	27-30	1			1		
yes	44	28	24-33	1.02	0.55-1.88	0.949	1.28	0.59-2.77	0.530
<b>Age at first hospitalization for psychotic symptoms</b>									
	347			0.99	0.96-1.02	0.399	0.96	0.89-1.03	0.246

Abbreviations: CI = confidence interval; HR = hazard ratio for relapse; p = two-tails statistical significance of HR calculated using Cox proportional hazard regression; \* Patients admitted to chronic or other department (26 (7%)) after the end of acute treatment were excluded from this analysis



**Figure 1.** Kaplan-Meier cumulative probability of survival with no relapse



**Figure 2.** Adjusted cumulative probability of survival with no relapse by hospital program after the end of acute treatment

## DISCUSSION

This naturalistic, registry-based, retrospective cohort study strongly indicated that integrative multimodal early intervention service based on group psychotherapy programs and daily hospital program have relevant beneficial effects in relapse prevention compared to treatment as usual. This study addresses a pressing question (early integrative long-term intervention in early psychosis) in an important population (FEP or early-phase psychosis patients), going beyond available guidelines and data.

Notably, when looking at the time to the first re-hospitalization because of relapse, the clinical outcome diverged in the cohorts included in this study depending on the treatment program after the end of the acute phase. Psychotherapeutic and daily hospital programs showed a significant effect, compared with patients who were discharged from the hospital with no further programs, in achieving longer time to relapse and lower hazard for relapse, as a proxy for the success in treatment. Evidence stipulate favorable effect of using antipsychotics in treating early-phase psychosis, however, medication alone fail to maintain this improved status (Emsley et al. 2007), while research is needed to establish the potential for psychological treatments, alone and in combination with antipsychotics (Stafford et al. 2015, Sin et al. 2017). The findings of this study implies that patients with early-phase psychosis may have improved outcomes if they are not only treated with antipsychotic medications but also included in a combination of psychotherapeutic program and daily hospital, like the one provided in the CIP, and are in line with the results of recent meta-analysis of Correll et al. (Correll et al. 2018).

Majority of patients in our study were in their twenties and thirties, which is the usual age of onset of early-phase psychosis (Kessler et al. 2007). Approximately one-third of our patients were employed at the time of the diagnosis. Further, most of our patients were generally healthy prior to the first episode psychosis – most of them had no previous hospitalizations, and had neither psychiatric comorbidities nor somatic illness at the time of the admission to the hospital. Young people with the first episode of psychosis have a desire to work and to maintain contact with their social network (Rinaldi et al. 2010). With that in mind, one of the benefits to patients involvement in the integrative multimodal early intervention service based on group psychotherapy programs and daily hospital program prior to their discharge is to address the aspects of the illness that undermine their confidence and motivation, and encourage patients to achieve fullest potential through accessing the labor market, in the modality their specific situation allows them, with the support of their families. Further research should investigate specifically how CIP integrative approach to early-phase psychosis

patients affects their functional recovery, specifically in comparison to discharge without early intervention service programs.

Duration of hospitalization was longer in the group of patients who were admitted to psychotherapeutic programs directly or after acute phase treatment. In Correll's et al. meta-analysis (2018), the number of bed-days was shorter in the early intervention group than in treatment as usual group (mean (SD) 21, 20 vs. 30.41). Longer duration of hospitalization at the psychotherapy department in our patients may be due to the specificity of the psychotherapy process and healthcare system in Croatia. The early intervention service in the CIP program is implemented during hospitalization and is not necessarily separated as a standalone program and hence the number of days cannot be directly compared with the duration of hospitalization when the early intervention program is implemented mostly or only in the community. Since the community mental health service in Croatia is in its infancy, the treatment of patients with early-phase psychosis and early intervention is related to hospital care (Mayer et al. 2017). In patients treated in daily hospital, the duration of hospitalization is significantly shorter than in patients treated with psychotherapeutic programs during hospitalization. However, patients previously treated in both the acute department and the psychotherapeutic department, and then further treated in daily hospital, have the longest duration of hospitalization which is probably associated with the severity of the symptoms, but this should be the subject of further research.

A key issue in the management of FEP is relapse prevention in the early years after diagnosis when relapse rates are known to peak. Discontinuation of the initial antipsychotic therapy is a major concern in the course of treating FEP and early-phase psychosis, the cause of which may be primarily the negation of the disease itself and the likelihood of taking the drug. Many treatment guidelines recommend that after stabilization, antipsychotic treatment should be continued for 1–5 years and longer exposure should be avoided if possible. Tiihonen et al. (2017a) showed if antipsychotic treatment is started, no safe time point for discontinuation can be defined, at least during the first 8 years after the first episode. In our study, we showed that upon hospital discharge, the majority of patients were treated with 2<sup>nd</sup> generation oral antipsychotics (66.5%), and with 2<sup>nd</sup> generation long-acting injectable antipsychotics (38.1%). Despite the fact that LAIs antipsychotics are superior to oral antipsychotics in relapse prevention, and that there is growing body of evidence that LAI antipsychotics need to be a first line treatment in early-phase schizophrenia treatment, still the majority of patients are treated with oral antipsychotics (Stahl 2014, Tiihonen et al. 2017b). Although, benefits of the 2<sup>nd</sup> generation of LAI antipsychotic are recognized and are included in many

guidelines for management of early-phase of schizophrenia, facilitating relapse prevention and their use should not be confined to only those for whom non-adherence is a concern (Kane et al. 1998, Emsley et al. 2013, Llorca et al. 2013, Malla et al. 2013, Haddad et al. 2014, Karson et al. 2016, Remington et al. 2017).

### Limitations of the study

First limitation of our study is immanent to its observational nature: after the end of acute treatment, patients were not randomized but purposefully selected for psychotherapeutic program and daily hospital. Therefore, a number of unobserved confounders exist, and our results should be verified by the randomized controlled trial. Second limitation was the retrospective nature of the study and the fact that we collected data only from the hospital medical records. For this reason, we had no direct contact with patients and were unable to do more precise testing of their baseline characteristics, specific treatments and outcomes. For example, we recoded substance abuse only as the binary variable as it is recorded in our hospital medical records and ignored the possibly influential differences in the duration, type of the substance, and intensity of substance abuse. Third limitation was that we treated different programs on the administrative level. For example, we have not differentiated particular psychotherapeutic strategies and approaches, but treat them as one, unique program different from the acute one. Fourth, the number of patients treated in daily hospital was relatively low, and the number treated only in daily hospital after the end of acute treatment was very low. Reliability of our findings with regards to daily hospital is low, and there is high risk of an excessive beta error.

### CONCLUSION

Our study indicated that multimodal early intervention service based on psychotherapeutic programs or/and daily hospital have relevant beneficial effects to the treatment of early-phase psychosis. Those patients, who continued treatment with psychotherapeutic programs and/ or daily hospital, showed significantly lower hazard for relapses. The finding of this research confirmed the effectiveness of the multimodal early intervention service provide through the CIP programs and support the need of the widespread implementation of early intervention services.

### 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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**Conflict of interest:** None to declare.

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