

INTEGRATED SPECIALIZED EARLY-COURSE PSYCHOSIS TREATMENT SERVICES - UNIVERSITY PSYCHIATRIC HOSPITAL VRAPCE MODEL

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SUMMARY

First episode of psychosis presents a critical period in terms of numerous associated risks, but also possibilities for effective therapeutic interventions. There is a continued focus on early interventions in prodromal states and early course of frank psychosis, aimed at ensuring faster remission, reducing relapses, achieving better long-term functioning, and preventing adverse outcomes linked to untreated psychosis and chronic psychotic disorders. A number of different specialized treatment models and services exist trying to close knowledge gaps and provide clinical interventions to first-episode psychosis (FEP) patients, but there is still no generally accepted standard of care informing our every-day practice. FEP and early-course psychosis specialized treatment model developed in 2004 in University Psychiatric Hospital Vrapče rests on integration of care across different organization units and clinical presentation acuity levels and patient needs (intensive care, FEP inpatient unit, FEP outpatient services including day hospital). Such integration of FEP services allows for flexible entry point on multiple levels, earlier structuring of therapeutic alliance for those requiring inpatient care, reduction of risks associated with FEP, quicker formation of long-term treatment plans, reduction of delay in accessing specialized services, and a more coordinated diagnostic process and recruitment of FEP patient population. Detailed evaluations of outcomes and comparisons with different treatment models are necessary in order to assess strengths and weaknesses of each specific model and inform modifications to current practice models.

Key words: early psychosis – schizophrenia - early intervention - standard of care

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INTRODUCTION

Schizophrenia (SCZ) is a debilitating mental disorder with lifetime prevalence of around 1%, and represents almost a paradigmatic psychiatric and psychotic disorder that in a significant number of patients shows chronic course of exacerbations and remissions, and causes severe impairment affecting different aspects of work and social functioning (Harvey et al. 2012, Sadock et al. 2014, Fervaha et al. 2014). Given the course of the disorder and the effect exacerbations have on mental and social functioning of patients, clinical staging model has made its way into the field of treating psychoses (specifically SCZ) in an attempt to position patients on the continuum of the illness course, and improve predicting outcomes, remaining functional capacity, and tailoring appropriate and timely therapeutic interventions (McGorry & Yung 2003, McGorry et al. 2006). The idea of phase-specific treatment interventions (early-course interventions) in SCZ lies upon findings showing progressive functional decline, increased brain abnormalities in later stages of the disorder, and link between longer duration of untreated psychosis (DUP) and poorer functional outcome, as well as response to subsequent antipsychotic treatment (Harrigan et al. 2003, Perkins et al. 2005, Keshavan & Amirsadri 2007). Early interventions in frank psychosis should therefore theoretically ensure faster remission, fewer subsequent episodes, better long-term functioning, and prevent adverse outcomes linked to untreated psychosis and later stages of the

illness (Wyatt 1991). It has been suggested that there is a critical period of 5 years from onset of SCZ during which appropriate interventions can influence long-term outcomes (Birchwood et al. 1998). Based on this we have recently seen a surge in programs and treatment interventions aimed at prevention of psychosis, early interventions in first-episode psychosis (FEP), and interventions in early-stage psychosis. The idea of those programs is to either identify the population at risk early and offer them adequate treatment and monitoring in order to delay or avoid illness onset, or in the case of existing psychotic symptoms to facilitate early interaction with medical services and initiate early treatment to receive DUP and achieve quick remission (Schmidt et al. 2015). Two major, and most often separated, fields of interventions have thus developed, one aimed at identifying at-risk populations and prodromal states, and the other one focusing on identification of psychotic patients and early initiation of treatment in that population.

Although specialized FEP programs are based on findings of early application of antipsychotics leading to better outcomes, work in FEP programs goes beyond simple early application of antipsychotic medications in those diagnosed with psychotic disorder. First psychotic episodes present differential diagnostic challenge, and require detailed coordinated evaluation of possible underlying causes, as well as detailed evaluation of levels of functioning in different areas (Falkai 1996). In addition to that, SCZ develops usually in late adolescent period and in young adults, critical periods carrying with them

numerous difficulties in social aspects, in accessing health services, conceptualizing need for and remaining in long-term treatment plans and structure. In line with that, delay in treatment can arise not only from not recognizing symptoms and thus not seeking help, but also from delays stemming from inadequate interactions with health care system once the help is finally asked for (sometimes for symptoms not immediately seen as part of psychotic disorder). Prolongation of time needed to reach specialized care leads to longer DUP, possible further functional decline, and might discourage patients and their families from persisting in seeking help and adhering to future therapeutic plans. One study found that vast majority of FEP patients had multiple contacts with health care professionals before they reached adequate services (Cougnard et al. 2004). Although most of the delay might be attributed to contact with family physicians not sensibilized enough to FEP, it is highly likely that the delay can also be seen due to general psychiatry emergency services, that patients are referred to, having insufficient staff, time, training, or resources to adequately diagnose and deal with FEP patients. Different factors leading to prolonged delay in accessing adequate care in FEP are being studied and conclusions reached from different studies are being incorporated in specialized FEP programs (Malla et al. 2010).

Different approaches to identifying and treating FEP and early-course psychosis patients have been implemented, with some programs focusing on community-wide activities and others looking towards family physicians or general psychiatry services. Numerous multidisciplinary clinical/research groups and programs were established (such as Yale University's Specialized Treatment Early in Psychosis – STEP, The Douglas Institute's Prevention and Early Intervention Program for Psychosis /PEPP-Montréal) to drive research in the field and offer specialized clinical services (Srihari et al. 2014, Srihari et al. 2015). Most specialized programs focus on outpatients, whether referred from inpatient units or recruited directly from the community. In addition to antipsychotic treatment, non-pharmacological interventions are taking an increasingly important part in FEP programs. This is not only because of problematic adherence to antipsychotic treatment which is to be expected in FEP, or the wish to avoid adverse events linked to antipsychotics, but also because of the additional therapeutic value granted by psychosocial interventions. There has been evidence of positive effects of cognitive-behavioral therapy (CBT), family education and support, and educational and vocational training, in reducing psychotic symptoms and aiding functional recovery in FEP patients (Leavey et al. 2004, Jackson et al. 2005, Lecomte et al. 2008, Nuechterlein et al. 2008, Killackey et al. 2008). All those interventions are finding their place in structured specialized FEP programs.

Evidence suggests that early interventions in the FEP population do indeed lead to reduction in DUP,

especially when administered in the context of specialized programs and groups as opposed to interventions in non-specialized services (Melle et al. 2004, Schimmelmann et al. 2008). Research shows that early application of atypical antipsychotics in FEP prevents brain changes associated with chronic SCZ, while early-course specialized programs reduce hospital (re)admissions, prevent relapses, improve functional outcome, and may even prove to be financially beneficial for health care systems (Marshall et al. 2005, Nakamura et al. 2007, Killackey & Yung 2007, Bertelsen et al. 2008). There is a trend suggesting positive effects continue over time and persist even after the patient leaves early-intervention services (e.g. overall less days spent in the hospital even after 5 years), although some studies suggest not all effects persist at 5-year follow-up points (Agius et al. 2007, Bertelsen et al. 2008, Agius et al. 2010). Open questions still prevent us from defining and agreeing on best standard of care in FEP and early-course psychosis treatment.

INTEGRATED SPECIALIZED EARLY-COURSE PSYCHOSIS TREATMENT MODEL – DEVELOPMENT AND STRUCTURE

Following all of the existing evidence on the value of early interventions and specialized treatment for patients with FEP, specialized clinical services for FEP emerged in 2004 at the University Psychiatric Hospital Vrapce (Zagreb, Croatia), and have been undergoing constant evolution until today. Basic principles on which the program was based and still functions include:

- gradual stepwise addition of specific interventions and services;
- individual treatment plan;
- integration of inpatient and outpatient services for FEP;
- integration of pharmacological and psychosocial interventions.

Basis for the formation of FEP program was not, as is the case in most other centers, outpatient FEP services, but a FEP inpatient unit (First Psychosis Unit) with 32 beds. Inpatient unit was formed as result of the fact that a significant number of patients in their first psychotic episode might present with aggression or disorganized behavior severe enough to warrant inpatient treatment (Wasser et al. 2017). Avoiding treatment of those individuals in non-specialized units can help reduce the time delay to accessing specialized diagnostic and treatment interventions, which might help to reduce future risks (health and forensic), and help relieve suffering of those patients and their families. In addition, the unit was formed as part of the Department of Diagnostics and Intensive Care, allowing for treatment across the spectrum of different clinical presentations (e.g. disorganized and aggressive behavior requiring intensive psychiatric care and secure environment) to be handled

by the same multidisciplinary team. Positioning of the FEP inpatient unit within Department of Diagnostics and Intensive Care also allowed for fast evaluation and recruitment of FEP patients who were admitted for various other reasons to the intensive care unit, or for diagnostics procedures, and found to be psychotic during the initial diagnostic process. Such vertical integration of services allows for a patient to be treated by the same medical team and coordinated by the same attending psychiatrist from intensive care (if necessary), through inpatient FEP unit, all the way to outpatient FEP services. Vertical integration of such type allows for multiple entry points into the program without the potential treatment initiation lag that might ensue as the result of the need to coordinate between different services.

FEP program at the University Psychiatric Hospital Vrapce offers services to FEP patients, as well as on those early in the course of the psychotic disorder. Generally, as stated in literature, early course is considered to mean 5 years since the disease onset. A strict cut-off regarding illness duration is not enforced, however, and patients are individually assessed based on remaining functional capacity and perceived benefit from specialized treatment programs. Activities at the FEP unit and in the FEP program focus on tailoring individualized treatment plan for each patient, in line with the concept of heterogeneous disease etiology, underlying mechanisms, clinical presentations, functional impairments, social specifics and needs. Diagnostic plan is formed on an individual basis, based on a number of factors pertaining to specific clinical presentation, heredity, lifestyles, and associated health risks. Same is true for the treatment plan. Both diagnostic and treatment plans are planned and executed within a multidisciplinary team including psychiatrists, psychologists, neurologists, social worker, social pedagogues, occupational therapists, and nurses. According to specific individual needs (diagnostic or treatment),

other specialists/diagnostic interventions/treatment interventions can be included.

Guidelines for psychopharmacological treatment in FEP are generally followed, but also modified based on specific individual needs (e.g. possible earlier introduction of clozapine if so warranted by specific clinical presentation, periods of concomitant use of two antipsychotics with differing mechanisms of action) (Silić 2015). After patients have undergone initial diagnostic evaluation and stabilization in emergency psychiatry setting (if such intervention was necessary), they are involved in a number of psychosocial interventions at the First Psychosis Unit (Ostojić 2015, Savić 2015). Individual and group psychosocial interventions, as well as interventions available for family members, are listed in Table 1.

Psychosocial interventions administered at the unit, along with modifications in antipsychotics therapy regimen, form a stepping-stone towards structured outpatient interventions. All of the interventions available to inpatients are also available in the outpatient services with varying levels of intensity and frequency, based on specific patient needs. As a way of additional structuring of already available outpatient services, and as an additional link between inpatient FEP services and intermittent outpatient interventions, in 2015 FEP Day Hospital started functioning as an integral part of FEP services. Day Hospital within FEP services offers same psychosocial interventions available to inpatients, but structured and modified to allow for greater capacity of outpatients, but also increased specific needs (occupational functioning, academic performance, more pronounced social demands). Figure 1 shows the flow of interventions starting from intensive care, all the way to outpatient services including day hospital. Same health care professionals follow patients along this path of care and interventions, allowing for possible returns to previous levels of care if needed, and for access to services at any point along this integrated system of care.

Table 1. Psychosocial interventions available at the First Psychosis Unit

Individual	Group	Family
CBT	CBT	Support therapy Psychoeducation
Support therapy	Support group	
Psychoanalytical psychotherapy	Integrative psychotherapy	
Integrative psychotherapy	Psychoeducation	
Psychoeducation	Metacognitive training	
Metacognitive training	Quality of life training	
Quality of life training	Social skills training (SST)	
Compliance strengthening	Anger management therapy	
Fitness therapy	Planning/evaluating of daily activities	
	Occupational therapy	
	Fitness therapy	
	Art therapy	
	Therapeutic community	

Table 2. Discharge diagnosis

Diagnosis	All Patients	First Hospitalization Group
Schizophrenia	31.5%	20.1%
Acute psychosis /SCZ features	17.4%	26.4%
Acute psychosis /other	6.3%	8.7%
Psychosis /non specified	15.6%	19.0%
Schizoaffective disorder	6.8%	3.7%
Schizotypal disorder	2.5%	2.0%
Bipolar affective disorder	4.1%	3.6%
Delusional disorder	3.0%	2.5%
Depression	2.1%	2.7%
Personality disorder /borderline	2.9%	2.9%
Personality disorders /other	1.2%	1.4%

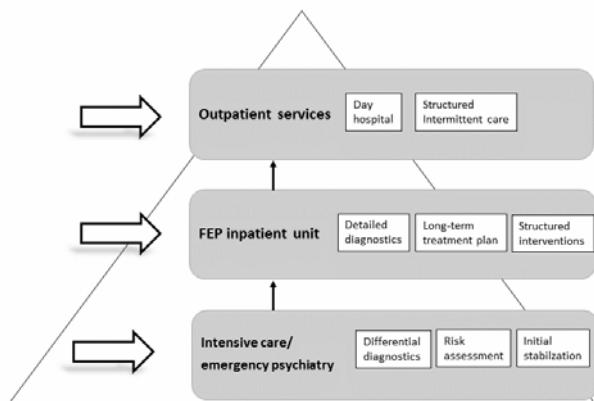


Figure 1. Illustrates integrated care for first-episode psychosis (FEP) patients, starting with intensive care unit and progressing towards outpatient services, allowing for entry points at all levels

FEP UNIT/SERVICES USERS SPECIFICS (2004-2017)

By the end of 2017, total of 3137 patients were treated in the First Psychosis Unit at the University Psychiatric Hospital Vrapce. That number shows the strain on the FEP program implemented there, but also the amount of experience the therapeutic team gathered over the years. Not all patients were FEP, as mentioned, so individuals considered to be early in the course of a psychotic disorder were also treated at the same unit. Of all the patients admitted to inpatient early-course psychosis services, 1772 were hospitalized for the first time. Figure 2 shows number of first admissions in the total number of patients treated over time.

56.1% of patients were male (55.2% in the population of first hospitalization patients), and the average age of patients treated in the First Psychosis Unit was 29.34 (SD 8.27). Average age for those hospitalized for the first time did not differ significantly from the overall average age (28.6, SD 8.50). Number of days spent in the FEP inpatient services showed significant variability. It averaged around 54.6 days (SD 31.17). In the population of patients hospitalized for the first time, average inpatient treatment period was 56.32 (SD

31.72). Given the fact that First Psychosis Unit included patients being admitted for evaluation through emergency psychiatry services, there were patients treated for as short as 1 day (2 patients). The longest treatment in the inpatient unit was 196 days. 162 out of 1772 patients in the population of first hospitalization FEP and early-course patients spent more than 100 days in the inpatient unit. Figure 3 shows trend of average hospitalization duration over time.

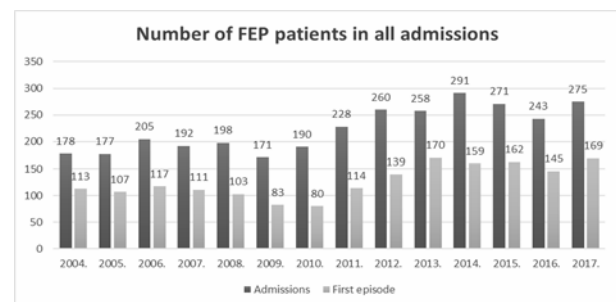


Figure 2. Shows number of patients hospitalized for the first time at the First Psychosis Unit and the total number of admissions (Patients previously hospitalized but early in the course of the disorder were admitted to the unit as well)

Since the FEP unit was formed as part of the Department of Diagnostics, and patients were recruited early in the illness course (acute state – first contact with mental health services) while no definitive diagnosis was established, a number of discharge diagnoses were noted at the end of the differential diagnostic evaluation and the treatment at the unit. Table 2 shows most common leading discharge diagnoses for patients treated at the unit.

12% of all patients treated in the inpatient FEP unit had the diagnosis of cannabinoid use disorder (12.8% of those hospitalized for the first time). Alcohol use disorder was noted in 10.6% of patients (9.9% of those hospitalized for the first time).

As far as continuing treatment after being discharged from FEP inpatient unit, 77.4% of patients after the first hospitalization continued outpatient follow-ups. A two-year follow-up showed that 70% of patients continued using outpatient services (Ostojić 2015).

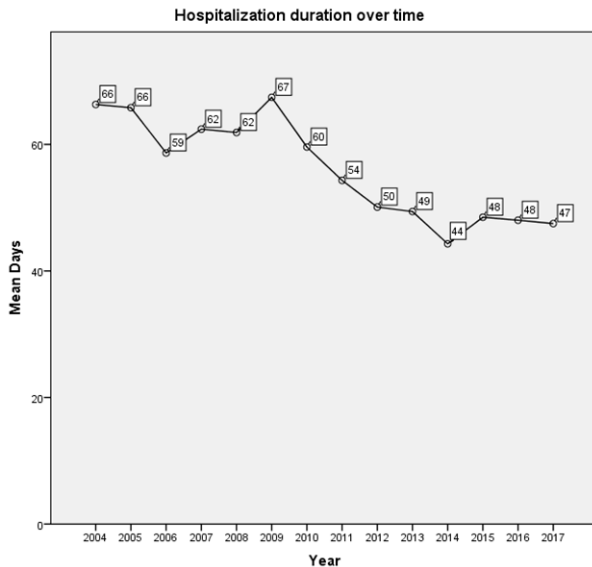


Figure 3. Shows trend of average hospitalization duration in the First Psychosis Unit over time

Since 2015 specialized FEP day hospital has become an integral part of the FEP services at the Psychiatric Hospital Vrapce, and until end of 2017 109 patients were treated in the FEP day hospital. Of those patients 6 used day hospital services twice, and 2 patients did that 3 times. Average duration of treatment in FEP day hospital was 48.8 days but significant variation was present (SD 27.63). The shortest reported treatment duration in 2015-2017 period was 2 days, and the longest 99 days. 40 patients (36.6%) had the duration of treatment in FEP day hospital of more than 60 days. Of all the patients treated in the FEP day hospital, 95.5% continued their treatment in outpatient FEP services.

Duration of untreated psychosis (DUP) & Rehospitalizations

Although detailed research on specific variables of patient population at the First Psychosis Unit (such as DUP and rehospitalization rates) for the entire period since 2004 was not done, there is some limited data on specific time periods and patient populations treated in those periods. Research on 180 early-course SCZ patients treated at the FEP unit (first hospitalization) from 2006 till 2009, and re-evaluated after 6 months, showed average inpatient treatment duration of 10 weeks (± 3.5 weeks), and average DUP of 7 months. Duration of inpatient treatment was determined by intensity of psychotic symptoms at the time of admission. Over 6 month follow-up after discharge only 1 patient was re-hospitalized (Ostojić 2015).

DISCUSSION

Even though SCZ and psychotic disorders do not necessarily represent most common psychiatric disorders, nature and burden of those disorders (loss of

social and occupational functionality, reduced life expectancy) warrant continued clinical and research interest in those disorders (Reininghaus et al. 2015). Clinical staging in medicine in general, and the concept of the importance of progression of psychotic disorders from prodromal to chronic stages, has shifted focus towards earlier phases of SCZ and SCZ spectrum disorders, with the implied intention of intervening early enough to avoid dysfunction associated with chronic psychosis. There is now a large body of research into first episode psychosis and early course psychotic disorders, ranging from basic neuroscience research to functional outcome and social functioning research. All of previously mentioned facts lead to formation of a number of research/clinical units/groups specialized in at-risk populations or individuals early in the course of the psychotic disorder. Importance of early interventions (pharmacological and psychosocial) and their possible impact on outcomes was proved, but there remain questions on how long lasting those effects are, how long should our interventions last, and what exactly would be the appropriate standard of care recommended for different stages of a psychotic disorder (SCZ in particular) (Tihonen et al. 2018). All available first- and early-psychosis services need to give answers to those numerous remaining questions, at the same time expanding our knowledge base through research and offering much needed clinical service, thus finding themselves faced with daunting obstacles. One of those obstacles is heterogeneity of SCZ and even more so of wider psychosis disorders spectrum (etiological as well as clinical), making it almost impossible to tailor uniform services/interventions that would fit everyone.

Most FEP/prodromes services will focus on outpatients, trying to recruit individuals in prodromal phases, early phases of frank psychosis characterized by milder symptoms, or after initial inpatient treatment, in case psychosis onset was characterized by severe disorganization or aggressive (towards self or others) behavior that necessitated inpatient treatment. Regardless of how good we get at identifying individuals with prodromes (daunting task in itself given the retrospective nature of the concept and the possible variations in presentation), a number of individuals will have a dramatic transition into psychosis with severe symptoms and risks whose management will not be possible without inpatient services (especially in cases of comorbid substance abuse) (Milton et al. 2001, Látalová 2014). Adequate early handling of those cases, appropriate and timely initiation of treatment, and forming early and stable therapeutic alliance, might all influence future treatment and not less importantly allow for “primary forensic prevention” (preventing incidents that might lead to contact of patients with criminal justice system) (Wasser et al. 2017).

Specialized FEP services at the University Psychiatric Hospital Vrapce started not primarily from outpatient facilities, but with First Psychosis Unit, inpatient

unit embedded within Department of Diagnostics and Intensive Care. As much as focusing FEP services around an inpatient unit might sound counterintuitive, such organization allowed for integration of services and interventions on various levels. In addition to integration of types of intervention (pharmacological & psychosocial), it was possible to integrate levels of service/care within the same mental health team, accounting for various clinical presentations and needs of FEP patient population:

- Intensive care/emergency psychiatry services;
- First psychosis inpatient unit;
- First-episode psychosis outpatient services.

Integration across different possible levels of care, clinical presentations, based on individualized risks and needs, grants a level of stability to a patient interacting with mental health services (possibly for the first time) and starting his long road towards recovery. Close interaction with emergency psychiatry services also allows for early detection of psychotic individuals and their prompt inclusion in specialized FEP programs and interaction with specialized mental health care teams. Availability of FEP beds, however, does carry with it an inherent risk of promoting longer hospital stays and increased cost to the system, possibly also linked to worse functional outcomes. That risk is mitigated by the fact that presented model of integrated care includes structured outpatient intervention/services that can accept a patient as soon as their condition and remaining functional capacity allows it. In line with that, it was shown that the duration of treatment at the FEP inpatient unit continues to drop over time, probably parallel to development and strengthening of outpatient services.

Patients treated within the presented integrated FEP model of care, include not only FEP patients but also those in early course of psychotic disorder with enough remaining capacity to participate in therapeutic interventions and benefit from them. That is the reason the most common discharge diagnosis happens to be schizophrenia, followed by acute psychotic episode. In the population of FEP patients being treated for the first time as might be expected, the most common discharge diagnosis is acute psychotic episode (SCZ-like and with SCZ features). Flexible criteria for inclusion in these clinical services allow for more focus to be placed on strengths and needs of an individual patient who might benefit from early-course psychosis intensive interventions, as opposed to focusing on a illness duration cut-off. As integrated FEP service model retains a strong diagnostic aspect to its services (differential diagnosis of first psychotic episodes), there is a long list of discharge diagnoses coming out of those services. It is expected that individuals diagnosed with, for example, borderline personality disorder or depression will not continue their interaction with specialized FEP services after discharge, but staying in outpatient follow-ups

seems to be overall high (77.4% of patients after first hospitalization in FEP unit, 95.5% of patients after FEP day hospital treatment). Those numbers might be even higher if we account for patients continuing their outpatient treatments in other hospitals, mental health centers. It would be important to see, however, how long those follow-ups persist over longer time periods and how that correlates with functional outcome.

Around 12% of patients had cannabinoid use disorder diagnosed, and around 10% alcohol use related disorder, but both numbers might be an underestimation of substance use problem in this population. Patients evaluated to be psychotic primarily due to for example alcohol use or cannabis use get transferred to specialized Substance-use units and programs, and are not included in the statistics of patients who finish their treatment in the specialized FEP unit. Also, around 12% of patients fulfilled criteria for cannabis use disorder, which does not take into account users who might just fall short of those criteria. Even these numbers do point to the need of specific interventions aimed at psychoactive substance use in FEP populations.

No matter the structure and models applied to specialized treatment programs, the only way to evaluate adequately their usefulness and their place in every-day clinical practice is to make detailed evaluation of outcomes and compare them to different treatment models for the same population. Specialized services focusing primarily on clinical aspects usually suffer from lack of detailed evaluations and appropriate comparisons. Same is true for the model of care for FEP and early-course psychosis patients at the University Psychiatric Hospital Vrapce, but that might change soon as a result of recent application of SCZ/FEP register (also an idea stemming from the same institution). SCZ/FEP register, even though not answering the need for randomized trials, will allow for easier comparisons between different institutions/units/groups and models of care, and inform us about possible strengths and weaknesses of current integrated model of care.

CONCLUSIONS

There is a continued focus on FEP and early-course psychosis stemming from research that shows benefit of interventions in early stages of psychotic disorders. There are FEP clinical/research services, primarily focusing on outpatient interventions, but still no standard of care recommendations have been implemented. Specialized integrated FEP treatment model at University Psychiatric Hospital Vrapce allows for flexible entry into services on multiple levels, based on clinical presentation and patient's needs (intensive care, inpatient FEP unit, outpatient FEP services), but there is need for a detailed evaluation of outcomes and comparison with different models of care in order to adequately assess utility of such a model.

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Contribution of individual authors:

Draženka Ostojić is the services leader, designed the review, collected and analyzed patient data, and wrote the first draft of the paper;

Ilaria Čulo collected and analyzed patient data, and gave critical comments to the first draft and revised it;

Ante Silić collected patient data, and gave critical comments to the first draft and revised it

Suzana Kos collected patient data, and gave critical comments to the first draft and revised it;

Aleksandar Savić helped design the review, collected and analyzed patient data and co-wrote first draft.

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