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Adaptation and Assessment  
of Efficacy of Early Intervention Programme  
for Patients with Schizophrenia Spectrum  
First-Episode Psychosis in Latgale Region

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## Abbreviations used in the Thesis

EIP	Early Intervention Programme
APA	American Psychiatric Association
DALYs	Disability Adjusted Life Years
CDSS	Calgary Depression Scale for Schizophrenia
ICC	Intraclass Correlation Coefficient
F20	ICD-10 classification code: Schizophrenia
F23	ICD-10 classification code: Acute and Transient Psychotic Disorders
GAF	Global Assessment of Functioning
LAT-EIP	Latvian Early Intervention Programme
LPA	Latvian Psychiatric Association
SEMS	State Emergency Medical Service
NOS-DUP	Nottingham Onset Schedule-Duration of Untreated Psychosis
DUP	Duration of Untreated Psychosis
DUD	Duration of Untreated Disease
OR	Odds Ratio
FPE	First-Episode Psychosis
WHO	World Health Organization
RSWG	Remission in Schizophrenia Working Group
SAI-E	Schedule of Assessment of Insight-Expanded Version
SAPS	Scale for the Assessment of Positive Symptoms
SANS	Scale for the Assessment of Negative Symptoms
ST	Standard Treatment
SPKC	Latvian Centre for Disease Prevention and Control
ICD-10	World Health Organization's International Statistical Classification of Diseases and Related Health Problems, 10th Revision

## Introduction

The World Health Organization (WHO) identifies mental health as one of its priorities due to the widespread incidence of mental health disorders, i.e., 38.2 % of the European population is diagnosed with a mental disorder (Wittchen, Jacobi, Rehm, Gustavsson, et al., 2011), and in terms of DALYs (Disability Adjusted Life Years), 10.4 % of the time spent with a disease globally, is associated with mental and neurological diseases, and addiction disorders. 56.7 % of the mental disorders representing the above mentioned disease groups are the cause to disability adjusted life years (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2016). One of the priorities stated in the World Health Organization's Mental Health Action Plan for 2013 – 2020, which is outlined as a binding document in the Mental Health Action Plan for 2013 – 2020 of the Ministry of Health of the Republic of Latvia, aims at achieving successful reintegration of patients with mental disorders into society and improvement of their wellbeing (World Health Organization, 2013). Nowadays, when dealing with mental disorders in research and in clinical practice, a particular attention is paid not only to treatment of symptoms but also to preservation and restitution of patient functioning. For one of the most significant disorder groups, namely schizophrenia spectrum psychotic disorders, more effective treatment strategies are still being explored. According to the largest data collection of the epidemiological studies on mental disorders in Europe, the average 12-month period prevalence rate of schizophrenia spectrum disorders was 1.2 %, affecting five million European inhabitants (Wittchen et al., 2011). The above-mentioned study outlined that schizophrenia is one of the seven leading causes of disability adjusted life years (DALYs) in the group of mental disorders in adults in Europe. In Singapore, schizophrenia ranks third in causes of disability among persons aged 15 to 44 years (Kinson, Hon, Lee, Abdin, & Verma, 2018), however in Latvia, in 2016, 23.5 % of the first-time disability determinations established for

mental disorders were related to schizophrenia spectrum disorders (State Medical Commission for the Assessment of Health Condition and Working Ability, 2016). Psychotic disorders represent the greatest non-fatal health impairment comparing to the total of all the other diagnosed diseases (Marchesi et al., 2015).

There has been increasing acknowledgment of the important role health plays in forming human capital thus becoming a key factor influencing economic growth (Simonsen, Faerden, Ueland, Vaskinn, Bjella, Andreassen, Romm, et al., 2018). Schizophrenia affects a proportionally large population group. The average age-of-onset of the disease is 18 to 25 years, and the disease accounts for major personal, social and health care related costs (Perälä et al., 2007); (Wittchen et al., 2011). Early adulthood is the age when symptoms of schizophrenia spectrum disorders appear (Anderson et al., 2019), coinciding with the period of life when professional development, socialization and romantic relationship is of utmost importance. Schizophrenia Outpatient Health Outcome Study (SOHO) revealed that, from patients who started treatment for schizophrenia spectrum psychotic disorders, only 24.2 % had a professional functioning role (working or studying), only 29.3 % were in a relationship, and 47.9 % were living on their own (Hong, Windmeijer, Novick, Haro, & Brown, 2009). Psychotic disorder burden manifests through, for example, constant inability to obtain education, to be employed, to ensure necessary living conditions, and to establish a relationship (Morgan et al., 2012). The above mentioned functioning disorders affecting social, professional and personal life following schizophrenia spectrum first-episode psychosis (FEP) are defined as secondary complications (Wong et al., 2012).

Untreated psychotic disorders and repeated exacerbations cause suffering to persons and their families and account for major health care expenses (Bhattacharyya et al., 2021); (Hakulinen et al., 2019). For some European countries, overall direct expenses associated with schizophrenia account for up to 2 % of their national healthcare budget, which corresponds to the expenses

associated with healthcare of patients with cancer and cardiovascular disorders (Knapp, Mangalore, & Simon, 2004).

Over the past two decades, there has been a significant increase in interest in treatment of early stage psychotic disorders (Bošnjak, Kekin, Hew, & Kuzman, 2016). Moreover, the quest for treatment strategies which could supplement pharmacological treatment methods and improve patient functioning are of a particular interest when treating negative psychotic symptoms of schizophrenia spectrum (Drake, 2000). In order to achieve a better long-term disease related outcome when treating psychotic disorders, the first two years are decisive (Harrison et al., 2001). The sooner the treatment initiation takes place, the higher the chance of obtaining symptomatic and functional remission (Crumlish et al., 2009); (Perkins, Gu, Boteva, & Lieberman, 2005). Currently in Latvia, the most common treatment for psychotic disorders is the standard approach, which in practice is characterized by advising patients who are discharged from an acute psychiatric unit where the first-episode psychosis was treated, to use a psychiatric outpatient consultation service on their own initiative and of their own free will. Research literature shows that patients with FEP who used outpatient consultation services provided in the framework of public care sector's standard treatment model sought on their own initiative were often irregular, of a short duration and with limited resources for providing non-pharmacological care (Wong et al., 2012).

Internationally, the enthusiasm regarding the early intervention concept increased in the late 1980s, and in 1992, the first Early Intervention Programme *Early Psychosis Prevention and Intervention Centre* (EPPIC) was established in Australia (Edwards, 2002). It is still regarded as the example of early intervention models for patients with psychotic disorders. Early intervention treatment for patients with schizophrenia spectrum includes biopsychosocial treatment during which all health care specialists work together and involve in the treatment process both patients and their family members. The early intervention model



suggests the need to assess the course of the disease during regular medical check-ups, to organize psycho-educational therapy sessions, to explain the importance of medication use, to implement optimized psychopharmacological treatment strategies, to consult psychologist, as well as to offer social and employment support. All the intervention elements are adopted according to patient symptoms, clinical peculiarities of the disease, characteristics of patient's personality and living conditions, as well as patient's objectives and wishes (Kline & Keshavan, 2017); (White, Luther, Bonfils, & Salyers, 2015b). The early intervention model is an example of patient-centred healthcare (Kline & Keshavan, 2017), which represents a treatment approach currently used in medicine worldwide, and also in Latvia, it is one of the key elements of the Public Health Policy (Ministry of Health of the Republic of Latvia, 2014) The Public Health Guidelines for 2014–2020 established by the Ministry of Health of the Republic of Latvia and approved by the Order No. 589 adopted on October 14, 2014, of the Cabinet of Ministers, are consistent with the Declaration of Mental Health (January 2005, Helsinki, WHO European Ministerial Conference on Mental Health), which outlines the following priorities set by the WHO and its Member States, i.e., to support persons with mental health problems and their family members, to implement comprehensive, complex and efficient mental healthcare within the system comprising promotion, prevention, treatment, and rehabilitation (Cabinet of Ministers of the Republic of Latvia, 2014). By its nature, an early intervention programme is an outpatient mental healthcare service which in the long term, provides for reduced patient load in inpatient facilities, for expanded outpatient treatment service, and for implementation of Health Policy objectives, i.e., inter-sectoral collaboration where health, social and wellbeing sectors aim at implementing a joint health care (Ministry of Health of the Republic of Latvia, 2014). The report published by the European Psychiatric Association regarding early intervention programmes suggested that 18 European countries (from a total of 29 countries who participated in the

survey) have adapted early intervention programmes. Interestingly, the author of the study discovered that early intervention programmes were not related to economic development of the countries, however there is a positive link with early intervention programme establishment and with the number of specialists working in mental healthcare (Maric et al., 2018). Several early intervention models have already been established worldwide and used with a scientifically proven effectiveness in patients with schizophrenia spectrum disorders, e.g., *Outreach and Support in South London (OASIS)*, *The Lambeth Early Onset community team (LEO)*, and *Advocacy group in Early Intervention in Psychosis (IRIS)* in the UK (Fusar-Poli, Byrne, Badger, Valmaggia, & McGuire, 2013), *OPUS Early Intervention Programme* in Denmark (Nordentoft et al., 2015), *EPPIC* in Australia (Hetrick et al., 2018), *Early Treatment and Identification of Psychosis (TIPS)* in Norway (Sönmez et al., 2016), and *National Institute of Mental Health Recovery After an Initial Schizophrenia Episode Early Treatment Programme (RAISE-ETP)* (Kline & Keshavan, 2017).

Large longitudinal studies have shown that patients who were included in early intervention models in healthcare showed significant disease management improvements, i.e., fewer hospital readmissions, lower degree of institutionalization, better treatment and medication compliance, and improved clinical indicators, i.e., not only significant reduction in positive symptoms but also significant improvements in negative symptoms, better quality of life which can be explained by better functional and social remission rates (patients are more often capable to lead an active social life again, resume studies and return back to work, live independently and establish a family). An additional benefit was shown to be patient satisfaction with the treatment process (Bertelsen et al., 2009); (Hegelstad et al., 2012); (P. Fusar-Poli et al., 2013); (McGorry, Killackey, & Yung, 2008); (Morrison et al., 2011). Marshall et al. a meta-analysis of randomized controlled studies from 2011 revealed that an early intervention in

case of psychotic disorders reduced inpatient bed occupancy rate and increased the possibility for the person with psychotic disorders to live independently (Marshall & Rathbone, 2011). The number of bed days spent in an inpatient facility for patients with schizophrenia in Latvia is disproportionately high. The statistical report *Psihiskā veselība Latvijā* [Mental Health in Latvia] (Disease Prevention and Control Centre, 2019) revealed that in 2016, patients with schizophrenia spectrum had 404 723 bed occupancy days in an inpatient facility which is the highest rate comparing to all the psychiatric diagnosis groups accounting for 40.3 % of the number of bed days in the psychiatric diagnosis group. According to the statistical report regarding healthcare in the Baltic States published in 2017, patients diagnosed with a psychiatric disorder in 2016 had the highest number of occupied bed days and accounted for 25 % of the total bed days (Latvian Centre for Disease Prevention and Control, 2017). The report states that patients diagnosed with a psychiatric disorder in Estonia and Lithuania utilized 14 % of the bed days. The trend where patients with schizophrenia spectrum disorders relatively often receive inpatient care and are hospitalized for an extended period of time is closely related to the standard treatment approach (outpatient services received on patient's own initiative and with a minimal or non-existent access to psychosocial interventions). In 2018, Correll and the co-authors published the largest systematic review to date which included meta-analysis and meta-regression statistical estimations, proved that early intervention was superior to standard treatment aiming at reducing recurrent hospitalization episodes, at restoring patient functional activity at work or school, and at reducing the severity of the positive or negative schizophrenia symptoms (Correll et al., 2018). Hence, the most frequently asked question in the scientific literature is no longer *Should early intervention be used?*, the question is now *What is the best way to implement early intervention in clinical practice when treating patients with first-episode psychosis?* and it remains to be answered

(Hodgekins et al., 2015); (Reading & Birchwood, 2005); (Ruggeri & Tansella, 2011).

During the study conducted in the framework of the Doctoral Thesis, the first early intervention programme for patients with schizophrenia spectrum disorders in Latvia and Latgale region, will be developed. Moreover, adaption and implementation of the programme in psychiatric practice by tailoring patient's individual needs and by assessing its clinical efficacy is intended.

### **Aim of the Thesis**

The aim of the Thesis is to adapt the early intervention programme for patients with schizophrenia spectrum first-episode psychosis in clinical practice, to assess the programme's efficacy through clinical and functional indicators and compare it to the standard treatment over a 12-month period following schizophrenia spectrum first-episode psychosis.

### **Objectives of the Thesis**

1. Adapt an early intervention programme described in evidence-based medicine in accordance with the resources allocated to mental healthcare in Latvia and with the regional peculiarities.
2. Explore the socio-demographic indicators (age, sex, mental disorders in family, lifetime suicide attempts, education, employment, living conditions) and clinical symptomatology indicators (positive and negative symptoms of schizophrenia, depression symptoms in patients with schizophrenia, insight of one's own disease), duration of an untreated disease and an untreated psychosis in patients with schizophrenia spectrum first-episode psychosis.
3. Clarify the usability of the early intervention programme in clinical practice, explore indirect compliance indicators (inclusion in an early

intervention programme, patient participation and study's opt-out proportion, use of medication during treatment, execution of treatment recommendations over a 12-month period following schizophrenia spectrum first-episode psychosis).

4. Assess the efficacy of the early intervention programme through clinical and functional indicators after a 12-months follow-up period comparing to standard treatment.
5. Assess patients included in the intervention programme regarding the frequency of recurrent hospitalizations and the number of disability determinations over a 12-month period following schizophrenia spectrum first-episode psychosis.
6. Provide recommendations based on the conclusions of the Thesis regarding the implementation of the early intervention programme when treating patients with schizophrenia spectrum first-episode psychosis.

## **Hypotheses of the Thesis**

- Patients with schizophrenia spectrum first-episode psychosis who are treated in accordance with an early intervention programme have lower clinical symptom severity scores, higher social functioning scores, fewer recurrent hospitalizations and fewer cases of disability determinations over the course of one year following schizophrenia spectrum first-episode psychosis.
- Adaption and implementation of an early intervention programme in the Latvian psychiatric healthcare system aiming at treating patients with schizophrenia spectrum disorder is achievable.

**Research question:** Does the use of the early intervention programme comparing to the standard treatment improve clinical and functional scores in patients with schizophrenia spectrum first-episode psychosis in Latgale Region?

## **Novelty of the Thesis**

This is the first early intervention programme developed for this particular patient population suffering from schizophrenia spectrum first-episode psychosis. Being conscious of the resource constraints, it was of utmost importance to develop this early intervention programme in real-life settings, i.e., in a state operated psychiatric facility, without increasing the cost of patient treatment and by restructuring the existing resources according to the treatment principles and elements recommended by the international treatment guidelines for schizophrenia spectrum disorders. The practical part of this Thesis contains a unique early intervention programme adapted specifically to Latvia and run by a team consisting of a care coordinator, a psychiatrist, a psychologist, a nurse, and an employment specialist. The implementation of this Early Intervention Programme as a novel treatment method in Latvia would improve access to multidisciplinary outpatient mental healthcare services designed for patients with schizophrenia spectrum first-episode psychosis.

## **Ethical considerations**

All patients before enrolling in the study were informed orally, they were given unlimited time for patient questions and written information regarding the study; all patients confirmed their voluntary participation in the study with a signature. The participating patients could opt-out from the study at any time without any impact on their further treatment. The authors of the study made sure that all the professionals involved in the study were specialist in their own discipline and that the care in accordance with the guidelines applicable both in

Latvia and in the European Union was provided. All the study phases were performed in accordance with the ethical principles, and an authorization (No. 114/21.12.2017) to conduct the study was obtained from the Research Ethics Committee of Rīga Stradiņš University.

# 1 Materials and Methods

The design of the study conducted in the framework of this Thesis is a quasi-experimental prospective cohort study with a control group. The patients who received successively proposition to participate in the study had been admitted to the Acute Psychosis Inpatient units of Daugavpils Psychoneurological Hospital (DPNH) with schizophrenia spectrum first-episode psychosis (FEP) in the period between January 1, 2016, and December 31, 2018. The patient flow of this study is shown in the Figure 1.1.

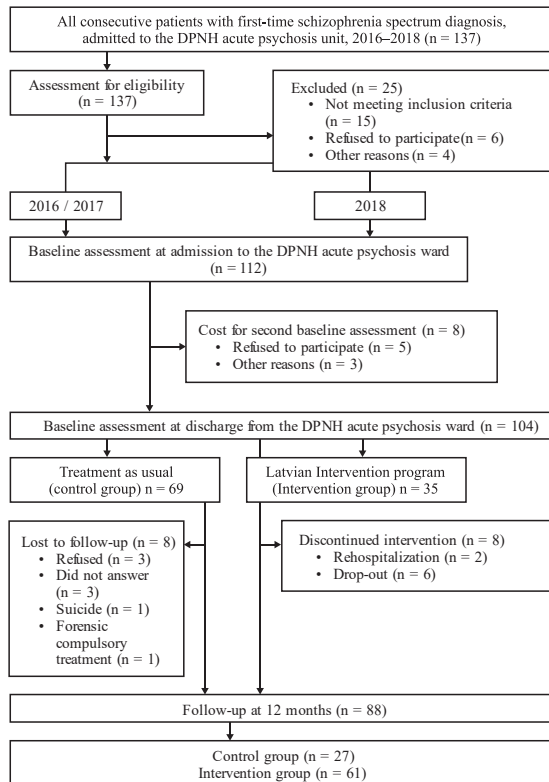


Figure 1.1 **Patient flow of the study conducted in the framework of the Doctoral Thesis**

DPNH – Daugavpils Psychoneurological Hospital



All patients included in the study who were admitted to DPNH's Acute Psychosis Inpatient Units were receiving their treatment in accordance with the common clinical principles defined in the applicable guidelines in Latvia (LPA, 2014). After being discharged from the Hospital, the patients included in the control group were receiving standard treatment. This means that after psychiatric hospital discharge, the following treatment is based on voluntary principles which meant that the patient could choose his outpatient psychiatrist and received mainly pharmacological treatment. The patients included in the intervention group were treated in accordance with the Early Intervention Programme (LAT-EIP) over a 6-month period following their hospital discharge (please, refer to the Attachment 3 with the description of the treatment plan for the LAT-EIP).

Equal inclusion / exclusion criteria were defined for both patient groups, equal assessments were performed, and equal requirements were established for participant opt-out from the study. For both control and intervention groups the follow-up period was set to 12 months starting from the day patient was discharged from hospital where he was treated for FEP.

## **1.1 Conditions for conducting study in the framework of the Thesis**

There are four hospitals with psychiatric units operating 24/7: Riga Psychiatric and Narcology Centre, Daugavpils Psychoneurological Hospital, Jelgava City Hospital *Ģintermuiža*, and Strenči Psychoneurological Hospital. In addition, a small department in Piejura Hospital in Liepaja can admit patients with acute psychiatric disorders. In practice, all patients with a psychiatric emergency, including episodes of psychosis, are transferred by the State Emergency Medical Service (SEMS) and treated in one of the above-mentioned hospitals. Patients with chronic disorders are admitted and receive their treatment

at Daugavpils Psychoneurological Hospital's Unit in Aknīste. Daugavpils Psychoneurological Hospital (DPNH) is the second biggest psychiatric hospital in Latvia with an emergency unit operating 24/7 and providing emergency care, inpatient and outpatient psychiatric care services to the entire Latgale region with the population size amounting to: 276 501 inhabitants in 2016, 270 173 inhabitants in 2017, and 264 756 in 2018 (Official Statistics Portal, 2021). During the study, the data in DPNH admission Data Base regarding the patients hospitalized with duty psychiatrist set diagnoses F20 or F23 according to the ICD-10 (WHO, 1993) were monitored every 24 hours. Patients admitted to DPNH's Emergency department with FEP are then hospitalized and transferred to Acute Psychosis Unit for men or to Acute Psychosis Unit for women.

## **1.2 Patient study inclusion and exclusion criteria**

Study inclusion criteria: 1. Patient is at least 18 years old; 2. Patient is capable of giving informed consent regarding the participation in the study; 3. F23 or F20 diagnoses (ICD-10); 4. First-episode psychosis in patient's lifetime. 5. Patient wants and can receive treatment after FEP. The inclusion criteria were developed in the most non-discriminatory manner possible in order to maintain a real-life study selection. For this reason, users of addictive substances were not excluded, and each patient was assessed individually. Exclusion criteria: 1. Psychosis episode of organic aetiology, e.g., brain injury, secondary psychosis episode; 2. Exogenously induced psychosis episode (e.g., narcotic substances); 3. Comorbid mental retardation (IQ < 70) based on previous health history; 4. Antipsychotic medication use for longer than the last 4 weeks.

### **1.3 Structure of clinical interview**

Within the framework of the study, the number of the clinical assessments in both groups was as follows: the first two to five days after being admitted to the inpatient facility, approximately five days before discharging from the inpatient facility, and 12 months after schizophrenia spectrum FEP (the reference point is considered to be the beginning of treatment in an inpatient facility or the first admission day), and the fourth interview took place in case if patient had agreed upon it before refusing to continue to participate in the study. Each clinical assessment consisted of partially structured face-to-face or remote interviews developed over the course of the Thesis which were based on similar publications regarding studies on psychotic disorders conducted by world-renowned EIP centres (Austin et al., 2013); (Buchy, Bodnar, Malla, Jooper, & Lepage, 2010); (Petrakis et al., 2012). With patient consent supplementary or more detailed information was given by patient families, retrieved from DPNH's medical archives and from received medical documentation including medical notes of patient's treating psychiatrist.

The clinical interview consists of three successive sections: sociodemographic part, help seeking behaviour and psychopathological symptom assessment. Thesis' clinical interview lasted 45 to 60 minutes.

#### **Sociodemographic data**

Upon enrolling in the study, the following sociodemographic data were obtained through targeted questions answered by patients, i.e., sex, age, years spent in an educational facility studying, living conditions (answers were categorized using 3 options: living independently, living together with relatives, living together with family), employment status (answers were categorized using 3 options: employed / studying / unemployed), psychical disorders in family anamnesis (categorized: yes / no), suicide attempts over the course of lifetime

(categorized: yes / no), group of disability related to psychotic disorders (categorized: yes / no).

## **Psychiatric help-seeking behaviour**

Help-seeking behaviour was determined by using targeted questions during the clinical interview. The questions asked during the interview were as follows: 1. Who initiated help-seeking? Answers are categorized using 4 options: patient him / her-self / family members / other / health care specialists; 2. Before hospitalization, which health care special did you contact regarding psychotic disorder complaints (answers were categorized using 4 options: general practitioner / psychiatrist / other / nobody).

The information regarding the way patient was admitted to psychiatric hospital's emergency unit was obtained from the documentation categorized using 5 options: unaccompanied / accompanied by relatives / using State Emergency Medical Service / using State Emergency Medical Service and police escort.

## **Tools used in psychopathological symptom assessment**

List of the scales used and their description:

1. Clinically positive and negative symptoms of schizophrenia were assessed using two scales: SAPS (Scale for the Assessment of Positive Symptoms) (Andreasen, 1984) and SANS (Scale for the Assessment of Negative Symptoms) (Andreasen, 1983); both are extensively used worldwide in studies of schizophrenia spectrum disorders (Klimidis et al., 1993). The SAPS is widely used in assessing positive symptoms and includes five main positive psychotic (schizophrenia spectrum) symptom groups which are as follows: hallucinations, nightmares, affective disorders, behavioural disorders, and thought disorders.

The SANS is widely used for assessing negative symptoms and includes five main negative psychotic (schizophrenia spectrum) symptom groups which are as follows: affective flattening, alogia, apathy, anhedonia-asociality, and attention deficit disorders. The SANS and the SAPS are recognized as being particularly suitable for assessing psychopathological symptoms in patients with schizophrenia spectrum first-episode psychosis (Fulford et al., 2014); (Tibber et al., 2018), and additional studies highlight accuracy determining negative symptoms in patients with schizophrenia spectrum psychotic disorders (Kircpatrick et al., 2006). The symptoms included in the SAPS and the SANS are rated on a scale of 0 (none) to 5 (severe). Higher scores for both scales indicate more severe psychotic disorder. The SAPS and the SANS scales use assessment score across all domains for better comparison between these variables at admission and discharge (Andreasen, Arndt, Miller, Flaum, & Nopoulos, 1995).

2. Global Assessment of Functioning (GAF) scale was used to assess professional and social functioning (Endicott et al., 1976). This scales has an inter-observer coherence for assessing patients with psychotic disorders (Startup et al., 2002). The GAF is a widely used scale for assessing functioning over the past month. The GAF provides a general description of functioning (level of severity) both socially and professionally. The GAF 100-point scale divided into 10 ranges with a 10-point interval each was used in this Thesis. The lowest score from 1 to 10 points (the first range) is applied when patient manifests constant / persistent inability to maintain a minimal standard of personal hygiene, and there is a risk that this person harms himself or someone else. The highest score from 91 to 100 (the 10<sup>th</sup> range) is applied when there are no symptoms, and person is high functioning.

In research, the most often used criteria for defining schizophrenia spectrum first-episode psychosis remission evaluates the functional capacity by using the GAF scale (Andreasen et al., 2005); (Austin et al., 2013); (Norman et al., 2018).

3. The Calgary Depression Scale for Schizophrenia (CDSS) was used for assessing symptoms of depression in patients with schizophrenia spectrum disorder (Addington, Addington, & Maticka-Tyndale, 1993). The scale consists of nine questions related to symptoms of depression, and physicians assess answers using the following point system: 0 – no symptom; 3 – severe symptom. The scale has good reliability and validity with a 77 % specificity and a 92 % sensitivity in patients with depressive episode with schizophrenia diagnosis starting from the total estimate of 6 (Addington et. al., 1993).
4. Compliance and insight assessment will be evaluated using the Schedule of Assessment of Insight- Expanded Version (SAI-E), which is designed specifically for patients with psychotic and mood disorders (David, Buchanan, Reed, & Almeida, 1992). The advantage of this scale is that compliance is assessed in relationship to particularities of reasoning and specific symptoms peculiar to patients with psychotic disorders (Sanz et al., 1998). During the interview, physician asks patients eleven topics regarding their understanding of their condition and the link between symptoms and pathological process. Answers are assessed according to the point system on a scale of 0 (absence of understanding) to 4 (patient gives an appropriate explanation for his condition). The second part of the scale is designed for the interviewer's clinical assessment regarding patient compliance (medication use and healthcare specialist help-seeking). Higher score indicates better patient understanding.

5. The duration of untreated disease and untreated psychosis is assessed by using the Nottingham Onset Schedule-duration of untreated psychosis version (NOS-DUP) (Singh et.al., 2005). The NOS-DUP is a short, interviewer guided interview designed to measure different periods in the development of psychosis. The NOS-DUP interview is designed for clinicians to be used as an initial assessment. Onset of disease is defined as the time between the first changes in mental state or behaviour observed until the development of symptoms of psychosis (transition to clinical psychosis). The NOS-DUP highlights several ways to define the duration of untreated psychosis. The definitions used in this study are as follows: 1. Duration of untreated psychosis (DUP): time from the first observed psychosis symptoms until the beginning of treatment with antipsychotic medication, and 2. Duration of untreated disease (DUD): time from the prodrome until the beginning of treatment with antipsychotic medication. In order to conduct NOS-DUP interview, the following successive and standardized activities were carried out: After the use of other methods, i.e., medical anamnesis establishment and mental state clarification, the NOS-DUP was employed as early as possible following the onset of disease, and the interview contained open questions and standardized disease descriptions (Singh et al., 2005). Similarly to other studies, the hospitalization date was considered to be the time of initiation of an adequate treatment (Schultze-Lutter et al., 2015).

## **Determination of correlation of internal coherence coefficient for study assessments**

In this Thesis, during clinical assessments, maximum efforts were made to avoid subjective deviations, which could be linked to the fact that the author of the Thesis is a psychiatrist participating in the LAT-EIP programme and is treating patients with FEP. In the framework of the study, the clinical assessments were conducted by the author of the Thesis and by an accompanying independent evaluator; more complex cases were assessed in collaboration with a psychiatrist having at least 5 years of clinical experience in psychiatry. An analysis was conducted to estimate the internal correlation coefficient of assessments issued by evaluators (the analysis is shown in the Table 1.1). Internal coherence coefficient (ICC) was used to assess the mutual consensus of signs, and they were classified as follows:  $< 0.5$  = weak;  $0.5-0.75$  = medium;  $0.75-0.9$  = good;  $> 0.90$  = excellent (Table 1.1).

Table 1.1

### **Interclass correlation coefficient amongst interviewers**

<b>Scale</b>	<b>ICC (95 % TI)</b>
Scale for the Assessment of Positive Symptoms	0.82 (0.44 – 0.95)
Scale for the Assessment of Negative Symptoms	0.83 (0.46 – 0.95)
The Calgary Depression Scale for Schizophrenia	0.87 (0.57 – 0.96)
The Schedule for the Assessment of Insight-Expanded version	0.87 (0.58 – 0.96)
The Global Assessment of Functioning	0.86 (0.54 – 0.96)

## **Assessment of remission and functional rates**

Patients included in the study of this Thesis were assessed after a 12-month follow up period to clarify whether remission was achieved or not. The achieved remission was characterized as positive and negative symptom severity of schizophrenia with a value of less than three points (according



to the SAPS and the SANS scales) over the course of a six-month uninterrupted period, and according to the GAF scale with a value of more than 61 points, and patient is employed, works or studies.

### **Additional medical patient data collection after discharge from inpatient facility and over 12-month follow-up period**

Information regarding the number of outpatient service visits, the use of recommended pharmacological treatment and medication, recurrent hospitalization frequency and bed days spent in an inpatient facility, and the data regarding patient's disability status were obtained from the DPNH medical documentation (inpatient and outpatient register cards) or with a patient's consent obtained during the clinical interview, the data were collected from outpatient medical documentation (for control group patients) established by treating psychiatrist.

#### **1.4 Patient safety concerns and opt-out from study**

LAT-EIP philosophy is based on a patient driven and patient tailored early intervention programme, therefore patient has the right to opt-out from specific intervention elements and to continue his treatment with the preferred intervention elements. Discontinuation of patient participation in the study was defined as a situation where patient was not reachable on phone (patient stopped answering repeated calls and did not answer to text messages) and did not show up for appointments three times in a row. Early intervention programme does not expect to have adverse events. Safety assessment was directed towards adverse events of psychopharmacological treatment and the well-known adverse events of psychotic disorders. Psychiatrist assessed possible adverse events during regular medical check-ups, and acted immediately according to the treatment guidelines, if such events were observed.

## 1.5 List of data statistical methods and justification of choice

Data were analysed using IBM SPSS v.25. and R v.4.0.1 programmes. Kolmogorov-Smirnov test was used for the verification of normal distribution of quantitative data. Demographic data and admission data were collected and assessed with the aim to evaluate intervention and control group comparability.

Categorical data were described as number (n) and percentage (%) ratio. Pearson's chi-squared test or Fisher's exact test were used for independent categorical variable comparison in accordance with the conditions of their use, and when assessing Pearson's  $\chi^2$  or Fisher's exact test statistic effect size, the Cramer's V value estimation was obtained, however McNemar's test was used for dependent group comparison. Independent Samples t-test or Paired Samples t-test were used to analyse the distribution of quantitative characteristics; Cohen's *d* value was used to assess statistic effect; alternatively, Mann-Whitney or Wilcoxon statistical test, and (r) estimation was established in order to assess their statistic effect.

Multifactor regression methods were used to identify predictors of the outcomes of standard or intervention treatments. A single factor and a multifactor adjusted logistic regression were used to find and assess the association between characteristics. The results were expressed in Odd Ratios (OR) with 95 % confidence interval. In the study,  $\alpha = 0.05$  was chosen as significance level; subsequent p value 0.05 or less was considered as statistically significant.

## 2 Results

### 2.1 Control and study group characteristics

Socio-demographic characteristics of patients in the control ( $n = 61$ ) and in the intervention group ( $n = 27$ ) are shown in the Table 2.1. Analyzing patients according to their affiliation to the group (control or study group), it was established that control group patients ( $Md = 32$ ;  $Q1-Q3: 27.0-39.0$ ) were statistically significantly younger comparing to the patients ( $p = 0.04$ ) included in the intervention group ( $Md = 29$ ;  $Q1-Q3: 24.0-32.0$ ), please, refer to the Figure 2.1.

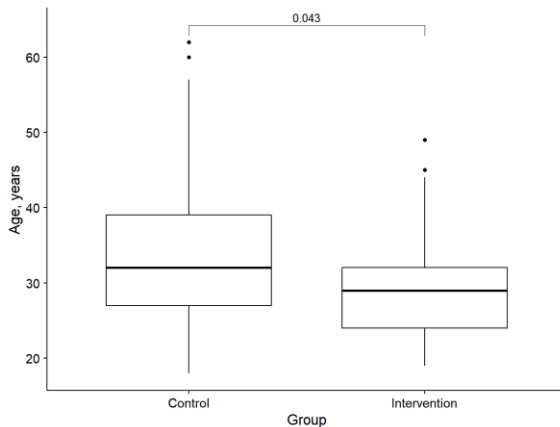


Figure 2.1 **Box diagram with patient age in years for intervention and control groups**

A statistically significant difference in the number of women and men in the control and in the intervention groups was observed ( $p = 0.007$ ). There was no significant statistical difference between the control group and the intervention group in regard to adverse hereditary disorders (family mental diseases reported by patient) and suicide attempts ( $p > 0.05$ ). Before treatment initiation and study enrolment, there was no difference between the patient

groups, however when assessing with the Fisher's test, the differences were found in living conditions. The effect size which was estimated using the Cramer's V value was 0.26 meaning that the statistic effect is insignificant (refer to the Table 2.1).

Table 2.1

**Patient socio-demographic characteristics for control and intervention groups upon study enrolment**

Parameter	Control group (n = 61)		Intervention group (n = 27)		P value
	n	%	n	%	
Male	32	52.5	23	85.2	0.007
Female	29	47.5	4	14.8	
No unfavourable family history of hereditary disease	44	72.1	22	81.5	0.505
Unfavourable family history of hereditary disease	17	27.9	5	18.5	
No history of past suicide attempts	55	90.2	22	81.5	0.301
Past suicide attempts	6	9.8	5	18.5	
Employed / studies	20	32.8	10	37.0	0.885
Unemployed / not studying	41	67.2	17	63.0	
Lives alone	6	9.8	5	18.5	0.042
Lives with relatives / parents	30	49.2	18	66.7	
Lives in own family	25	41.0	4	14.8	
Age in years, Md (Q1;Q3)	32.0 (27.0; 39.0)		29.0 (24.0; 32.0)		0.042
Education in years, Md (Q1;Q3)	13.0 (10.0; 14.0)		13 (12.0; 13.0)		0.392

**2.2 Help-seeking behaviour for psychotic symptoms in patients with schizophrenia spectrum first-episode psychosis**

Help-seeking behaviour in the control and intervention group did not differ: 50.8 % of patients in the control group and 66.7 % of patients in the intervention group before contacting mental healthcare specialist of an inpatient facility had not sought help for psychotic disorder symptoms (p = 0.628), the results are shown in the Table 2.2. The situation where patients voluntarily

admitted themselves to hospital was observed in 11.5 % of the cases in the control group and in 14.8 % of the cases in the intervention group ( $p = 0.413$ ). Considerable proportion of patients who were admitted to a psychiatric hospital with schizophrenia spectrum first-episode psychosis were accompanied by an escort: 24.6 % in the control group and 37.0 % in the intervention group ( $p = 0.626$ ).

Table 2.2

**Psychiatric help-seeking behaviour of study patients**

Parameter	Control group (n = 61)		Intervention group (n = 27)		p value
	n	%	n	%	
Previous help-seeking behaviour					0.628
• None	31	50.8	18	66.7	
• Psychiatrist visit	16	26.2	6	22.2	
• General practitioner visit	3	4.9	2	7.4	
• Other	3	4.9	0	0	
• Multiple specialist visits	8	13.1	1	3.7	
Initiator for seeking help					0.413
• Patient	7	11.5	4	14.8	
• Family members	47	77.0	23	85.2	
• Medical staff	6	9.8	0	0	
• Other	1	1.6	0	0	
Arrival at the psychiatric hospital					0.626
• Alone	5	8.2	2	7.4	
• Brought by family members	21	34.4	9	33.3	
• Ambulance	20	32.8	6	22.2	
• Ambulance with police escort	15	24.6	10	37.1	

**2.3 Duration of untreated disease and untreated psychosis, persistence of diagnosis**

The duration of untreated disease (DUD) ( $p = 0.387$ ) and the duration of untreated psychosis (DUP) ( $p = 0.325$ ) for both groups did not differ. After a clinical interview of inpatients included in the control group, the diagnosis F20 was made in 50.8 % of the cases, and in the intervention group in 37.0 % of the

cases ( $p = 0.335$ ); after a 12-month follow-up period, there was no difference in the distribution of the diagnosis and F20 was made in 67.2 % of the cases in the control group and 51.9 % of the cases in the intervention group ( $p = 0.257$ ).

## **2.4 Description of clinical symptoms in hospitalized patients receiving treatment for first-episode psychosis in both groups**

The median length of hospitalization duration for treating first-episode psychosis in the control group was 28.0 bed days (18.0 – 41.0), and in the intervention group the median length of the duration was 24.0 bed days (18.5 – 31.5),  $p = 0.245$ . The clinical psychopathology, i.e., positive psychotic symptoms, negative psychotic symptoms of schizophrenia, and depressive symptoms linked to schizophrenia psychotic symptoms in both groups did not differ for patients with first-episode psychosis at admission nor at discharge from the inpatient facility. By assessing the clinical outcomes of the treatment, e.g., changes in symptoms, effect size was estimated for symptom changes at the beginning of treatment and at discharge from the inpatient facility. In this Thesis, Cohen's  $d$  effect size interpretation is as follows: insignificant effect  $d = 0.1 - 0.3$ , medium size effect  $d = 0.3 - 0.5$ , significant effect  $d > 0.5$ . The only differences in both study groups were found in changes of patient insight at the time of patient discharge from the inpatient facility. When assessing total points, the level of the insight was higher in the intervention group,  $p = 0.03$ . The value in points is shown in the Table 2.3.

Table 2.3

**Changes in clinical psychopathological symptoms expressed in scale points and size of effect in study group patients receiving standard treatment in emergency care psychiatric unit**

Parameter	Control group (n = 61), M (SD)	Intervention group (n = 27), M (SD)	p value
SAPS at admission to the hospital with FEP	70.41 (22.6)	69.41 (19.5)	0.83
SAPS at discharge from the hospital after FEP	30.7 (18.37)	26.30 (14.86)	0.24
p value	< 0.001	< 0.001	–
<b>Cohen's d effect size</b>	<b>1.98</b>	<b>2.43</b>	–
SANS at admission to the hospital with FEP	60.62 (26.29)	54.48 (14.9)	0.17
SANS at discharge from hospital after FEP	36.92 (25.72)	36.67 (16.83)	0.96
p value	< 0.001	< 0.001	–
<b>Cohen's d effect size</b>	<b>0.9</b>	<b>1.22</b>	–
CDES at admission to the hospital with FEP	7.74 (5.76)	6.96 (6.85)	0.61
CDES at discharge after FEP	4.63 (4.21)	5.48 (4.49)	0.41
p value	0.53	< 0.01	–
<b>Cohen's d effect size</b>	<b>0.61</b>	<b>0.26</b>	–
SAI-E at admission to the hospital with FEP	15.07 (12.48)	18.56 (10.26)	0.17
SAI-E at discharge after FEP	29.03 (11.4)	34.11 (9.18)	<b>0.03</b>
p value	< 0.001	< 0.001	–
<b>Cohen's d effect size</b>	<b>1.20</b>	<b>1.62</b>	–

SAPS (Scale for the Assessment of Positive Symptoms)

SANS (Scale for the Assessment of Negative Symptoms)

CSSD (The Calgary Depression Scale for Schizophrenia)

SAI-E (The Schedule of Assessment of Insight Expanded version)

GAF (The Global Assessment of Functioning)

## 2.5 Analysis of indicators determining intervention efficacy

### 2.5.1 Functional score (global functioning, employment and living conditions) analysis

#### Global functioning

Global functioning was assessed at the time of hospitalization of patients with FEP and after a 12-month follow-up period. The GAF scale was divided into 10 ranges with a 10-point interval each. The functioning of patients in the study groups was assessed by starting with 21<sup>st</sup> point, because the values from 0 to 20 points (0 = indeterminable, 1–10 and 11–20) mean that patient does not have day-to-day functional activities and depend on others for help. At the time of admission, the global functioning score for patients in both groups did not differ at the level of ranges ( $p = 0.350$ ), and after a 12-month follow-up period, there was a difference in range distribution between the intervention and the control group ( $p = 0.001$ ) with a significant statistical effect value (Cramer's  $V = 0.18$ ). For range distribution in percent, please refer to the Table 2.4.

Table 2.4

#### Comparison of intervention and control groups using global functioning scale ranges; Cramer's V effect size was estimated for groups

GAF score (intervals)	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
	$p = 0.350$ Cramer's V (effect size) 0.12							
Intervention group, (n = 27) At admission to the hospital with FEP	0	0	3	10	10	3	1	0
Control group, (n = 61) at discharge from hospital after FEP	5	6	6	19	13	8	4	0



Table 2.4 continued

GAF score (intervals)	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
<b>p = 0.001</b> Cramer's V (effect size) 0.18								
Intervention group, (n = 27) After 12-month follow-up	0	0	0	11	2	8	5	1
Control group, (n = 61) After 12-month follow-up	0	1	17	24	8	5	6	0

FEF – First episode psychosis

GAF – The Global Assessment of Functioning

When comparing the intervention group and the control group, a significant difference was found in global functioning after a 12-month follow-up period, and the median value was 61–70 GAF points for the intervention group and 51–60 GAF for the control group,  $p < 0.001$ . And when assessing the GAF change dynamics for each group separately, the GAF for the control group remained unchanged ( $p = 0.79$ ), and the GAF showed a statistically significant increase for the intervention group after a period of one year ( $p = 0.004$ ), refer to the Table 2.5.

Table 2.5

**Changes of GAF before treatment initiation  
and after a 12-month follow-up period for both groups**

Parameter	Control group (n = 61), Md (Q1;Q3)	Intervention group (n = 27), Md (Q1;Q3)	p value
GAF before start of treatment	6.00 (5.00; 7.00)	7.00 (6.00; 7.00)	0.238
GAF after 12-month follow-up	6.00 (5.00; 7.00)	8.00 (6.00; 8.00)	<b>0.001</b>
p value	0.790	<b>0.004</b>	–

GAF – The Global Assessment of Functioning

## Employment scores

Employment scores for the control group and the intervention group are shown in the Table 2.6. At the time of hospitalization of patients with FEP, the employment scores of the groups did not differ, however after a 12-month follow-up period, those patients who were employed in the intervention group made up a significantly bigger proportion, i.e., 62.9 % comparing to 31.1 % in the control group  $p = 0.01$ .

Table 2.6

### Employment scores at time of treatment initiation and after 12-month follow-up period in control and intervention groups

Parameter	Control group (n = 61)		Intervention group (n = 27)		p value
	n	%	n	%	
<b>At start of treatment of first episode of psychosis</b>					
Employed / studies	20	32.8	10	37.1	0.885
Unemployed / not studying	41	67.2	17	62.9	
<b>After 12-month follow-up</b>					
Employed / studies	19	31.1	17	63.0	<b>0.01</b>
Unemployed / not studying	42	68.9	10	37.0	
p value McNemar's test	0.95		<b>0.03</b>		–

McNemar's statistical test analysis showed that employment of intervention group's patients changed in a statistically significant manner with an average statistic effect size starting from the departure values and after a 12-month follow-up period ( $p = 0.03$ ,  $\phi = 0.43$ ). The numerical analysis showed that 8 (29.63 %) patients with FEP included in the intervention group who were not employed at the time of admission, started to work following the EIP after a 12-month follow-up period, and there was only one patient in the intervention group who had been employed at the moment of enrolment in the study and stopped working after a 12-month period. However, in the control

group, no statistically significant patient employment changes were observed at the moment of treatment initiation and after a 12-month follow-up period ( $p = 0.90$ ); half of the patients, i.e., 30 (49, 18 %), in the control group were not employed at the time of treatment initiation and remained unemployed after a 12-month period.

### **Analysis of indicators determining intervention efficacy: patient living conditions**

The patient living condition analysis showed that the living condition characteristics for inpatients with FEP at the time of inclusion in the study between the control and the intervention group differed significantly ( $p = 0.042$ ), and the statistical difference increased after a 12-month follow-up period ( $p = 0.028$ ), please refer to the Table 2.7.

Table 2.7

#### **Living condition characteristics at time of treatment initiation and after 12-month follow-up period in control and intervention groups**

Parameter	Control group (n = 61)		Intervention group (n = 27)		P value
	n	%	n	%	
<b>At start of treatment of first episode of psychosis</b>					
Lives alone	6	9.8	5	18.5	<b>0.042</b>
Lives with relatives / parents	30	49.2	18	66.7	
Lives with own family	25	41.0	4	14.8	
<b>After 12-month follow-up</b>					
Lives alone	6	9.8	7	25.9	<b>0.028</b>
Lives with relatives / parents	34	55.6	17	63.0	
Lives with own family	21	34.3	3	11.1	

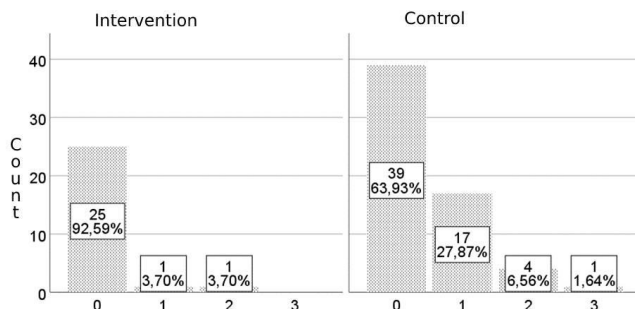
### **2.5.2 Assessment of positive and negative psychotic symptoms for schizophrenia after 12-month long follow-up period**

The psychopathological symptom assessment made using the SAPS and the SANS scales and by comparing the summed overall scores obtained over a 12-month follow-up period, showed that the psychopathological symptoms in the intervention group were with a less significant severity, i.e., with a smaller total amount of points. The differences were established using the scale for the assessment of positive psychotic symptoms of schizophrenia: intervention group vs. control group median values 2.00 (IQR = 0.00–7.00) vs. 5.00 (IQR = 2.00–11.00); the Mann-Whitney test  $p = 0.029$ , and the scale for assessing negative psychotic symptoms of schizophrenia: intervention group vs. control group median values 5.00 (IQR = 0.00–7.00) vs. 8.00 (IQR = 2.00–14.00); the Mann-Whitney test  $p = 0.028$ .

### **2.5.3 Recurrent hospitalizations over 12-month period after schizophrenia spectrum first-episode psychosis**

The analysis performed using the Fisher's exact test revealed a significant association for the number of recurrent hospitalizations over a 12-month period between the control and intervention groups ( $p = 0.01$ ): almost all patients (92.6 %) included in the intervention group did not have any recurrent hospitalization, however 36.0 % of the patients included in the control group had at least one recurrent hospitalization, please refer to the Figure 2.2. A detailed review of the recurrent hospitalization cases registered over a 12-month period after the first-episode psychosis allowed to draw a conclusion that two patients (7.4 %) included in the intervention group were repeatedly hospitalized, and 22 patients (36.0 %) included in the control group were repeatedly hospitalized from whom 27.9 % ( $n = 17$ ) had one recurrent readmission over a period of one year, 6.6 % ( $n = 4$ ) had only two readmissions, and 1.6 % ( $n = 1$ ) had only three

readmissions,  $p = 0.019$ . The odds ratio was calculated, and the results showed that the odds of being readmitted to hospital over the period of one year were 4.41 higher for the patients in the control group comparing to the intervention group (OR = 4.41; 95 % TI: 1.56–12.45;  $p < 0.05$ ).



**Figure 2.2 Cases of recurrent hospitalizations in each study group over period of 12-month follow-up after discharge from hospital with first-episode psychosis**

### **2.5.4 Disability determination established in accordance with psychotic disorders over 12-month period after FEP**

After a 12-month follow-up period disability determination was made for 7.4 % of the patients in the intervention group ( $n = 2$ ), and for 34.4 % or 21 patients in the control group ( $p = 0.017$ ).

### **2.5.5 Psychiatric outpatient consultation over 12-month follow-up period after FEP**

Upon the discharge from hospital where patients had been admitted for first-episode psychosis, all patients were given advise to continue treatment and to pursue assessing their condition using regular medical check-ups carried out by an outpatient psychiatrist. The number of consultations over a 12-month period after discharge from hospital in both groups did not differ, however it was

observed that 3.7 % or only one patient in the intervention group had consulted psychiatrist once comparing to 21.2 % (n = 13) of the patients in the control group who had not consulted or had consulted once to receive medication without consulting a doctor,  $p = 0.120$ . The distribution of psychiatric consultations for both groups is showed in the Table 2.8. Pearson's chi-squared test analysis between the number of psychiatric consultations in the intervention group and the control group showed that patients in the control group had 0–1 psychiatric consultation 6.25 (TI 95 % 1,11–10.0,  $p = 0.04$ ) times more often than patients in the intervention group.

Table 2.8

**Number of psychiatric outpatient consultations over 12-month follow-up period after FEP**

Number of outpatient visits	Intervention group (n = 27)		Control group (n = 61)		P value
	n	%	n	%	
0 or 1	1	3.7	13	21.3	0.120
2 to 5	12	44.4	16	26.2	
6 to 10	7	25.9	17	27.9	
More than 10	7	25.9	15	24.6	

**2.5.6 Physician's recommendations for medication use and status of medication use after 12-month period**

Upon discharge of inpatients following first-episode psychosis, all patients according to the guidelines were advised to use antipsychotic medication. The medication by their chemical names prescribed at the time of discharge to inpatients in both study groups did not have a statistically significant difference ( $p > 0.05$ ), and the medication by their chemical names 12 months after first-episode psychosis did not differ ( $p > 0.05$ ). At the discharge from hospital after FEP three most recommended medication in intervention group and control group were as follows: Olanzapine (29.6 % vs 29.5 %), Risperidone (22.2 % vs 23.0 %) and Aripiprazole (7.4 % vs 11.5 %), other (40.8 % vs

36.0 %). After 12 months follow-up the three most recommended medications in intervention group un and in the control group were: Olanzapine (37.0 % vs 21.3 %), Risperidone (14.4 % vs 24.6) and Aripiprazole (7.4 % vs 9.8 %), other (41.2 % vs 44,3 %).

A statistically significant difference was observed in the medications the use of which was interrupted by patients contrary to physician's recommendations: three patients or 11.1 % in the intervention group stopped using medication on their own initiative, and 32.80 % (n = 20) of the patients in the control group stopped using their medication. The analysis using Pearson's chi-squared statistical test for assessing medication use interruption between the patients in the intervention group and in the control group showed a significant correlation (p = 0.018) and the odds ratio (OR) calculations revealed that the patients in the control group did not use medications (contrary to recommendations) 6.35 times more often than the patients in the intervention group (OR = 6.35; 95 % TI: 1.60–46.50; p = 0.018).

### **2.5.7 Remission status 12 months after first-episode psychosis**

Remission status calculations after a 12-month period showed that the difference in remission scores was statistically significant for patients in the study groups. 74.0 % of the patients in the intervention group were in remission comparing to 44.4 % in the control group, p = 0.019. Odds ratio determination revealed that the patients in the intervention group were in remission 3.51 (95 % TI 1.33–10.20, p = 0.019) times more often comparing to the patients in the control group. In the framework of the Thesis, a binary logistic regression model was developed allowing to determine the probability of event occurrence depending on the included predictors and assess the factors of impact of the remission event. The developed model is statistically significant (p < 0.001); the Nagelkerke's R<sup>2</sup> value is 0.18, which means that 18 % of the remission changes

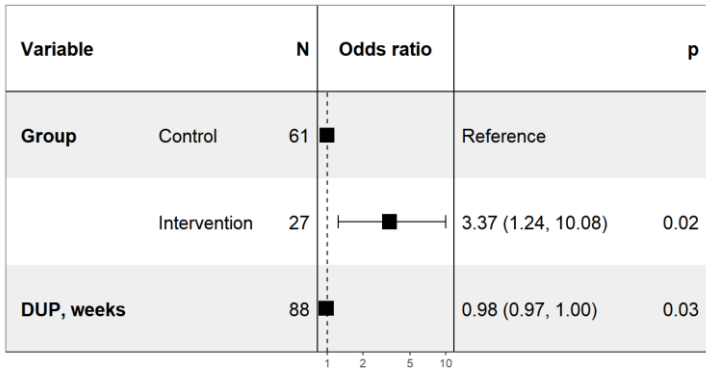
are explained by the predictors included in the model. Predictor impact strength is shown in the Table 2.10. The strongest predictor which explained the remission best was the intervention group (Wald's coefficient = from 5.27); the duration of untreated psychosis in weeks follows the latter according to the impact strength (Wald's coefficient = 4.82), refer to the Table 2.9 and the Figure 2.3.

Table 2.9

**Impact predictors of remission**

Parameter	Wald test	p value	OR (95 % CI)	OR <sub>weighted</sub> (95 % CI)
Intervention group	5.27	0.02	3.36 (1.19 – 9.48)	3.06 (1.04–9.80)
DUP in weeks	4.82	0.03	0.98 (0.97 – 0.99)	0.98 (0.97–0.99)

DUP – duration of untreated psychosis



**Figure 2.3 Logistic regression model for determination of remission predictors**

DUP – duration of untreated psychosis

The developed logistic regression model was adjusted with other factors of potential remission predictors (living conditions, number of years of education, employment) revealed that the changes in the odds ratio of the group



were insignificant: from 3.37 to 3.06; and the changes in the DUP were not detected; moreover, living conditions, length of education and employment did not have a statistical significance regarding the course of remission ( $p > 0.05$ ), please refer to the Figure 2.4.

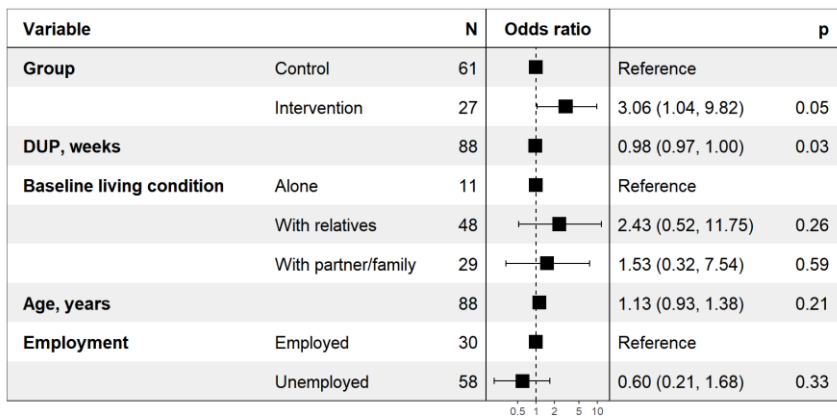


Figure 2.4 **Adjusted logistic regression model for remission predictors assessment**

DUP – duration of untreated psychosis

## 3 Discussion

### 3.1 Comparative socio-demographic description of control and intervention groups

From 88 patients included in the Thesis study, 62.5 % were male participants ( $n = 55$ ), the gender proportion differed in the control group where 58.2 % ( $n = 32$ ) of the patients were male participants, however in the intervention group 87.9 % ( $n = 29$ ) were male participants ( $n = 0.007$ ). Schizophrenia is more common among males, and the reported odds ratio of 2.37 ( $OR = 2.37$ ) signified that patient with schizophrenia spectrum psychosis would be a male (Golay et al., 2016). Similar results were published in the systematic literature review in 2012, and it showed that among 4721 included patients, the probability for a male patient to be diagnosed with schizophrenia spectrum was 2.5 times higher (95 % TI 1.8 – 3.3) (Cascio, Cella, Preti, Meneghelli, & Cocchi, 2012). The proportion of male and female participants in this Thesis study is comparable to studies conducted in other countries, e.g., the proportion of male participants reported in the Early Intervention Programme conducted in the USA was 74.7 % (Ven et al., 2020); in another Early Intervention Programme conducted in the USA reported that the proportion of male participants was 83 % (Ventura et al., 2011); in a large cohort FEP study in Norway, 75 % of the patients were male comparing to an Early Intervention Programme conducted in Canada where 75.9 % of the patients were male participants (Anderson et al., 2018); (Norman et al., 2018). The proportion of male participants in the Early Intervention Programme conducted in Italy was 80.5 % (Preti, Meneghelli, Pisano, & Cocchi, 2009), and a smaller proportion of male participants was reported in a FEP cohort study conducted in Spain, i.e., 58 % (Bergé et al., 2016). Gender proportion must be interpreted in context taking into consideration study's different methodological differences, i.e., if the study includes patients suffering from schizophrenia spectrum first-episode psychosis with a maximum

possible accuracy, as is often the case in specialized treatment programmes for psychotic disorders, the male participant proportion will be higher, comparing to a methodology, which provides broader criteria for inclusion and possibly without exclusion of accompanying affective disorders, the gender proportion equals. When studying psychosis episode (F23, ICD-10) only, without including first-episode psychosis related to schizophrenia spectrum (F20, ICD-10) in selections, the proportion of female participant increases (Castagnini & Berrios, 2009).

In the framework of this Thesis, the median age of the patients included in the control group was 32.0 years, and in the intervention group 29.0 years ( $p = 0.042$ ); similar median age was reported in the Early Intervention study project *GET UP PIANO* conducted in Italy, where patient age was 31.5 years in the standard treatment (control) group, and 29.3 in the intervention group,  $p = 0.017$  (Ruggeri et al., 2015). The patient age is comparable to other studies of patients with FEP where the average age was from 19.9 to 30.2 years (Cratsley, Regan, Mcallister, Simic, & Aitchison, 2008); (Malla et al., 2002); (Kvig et al., 2017). One of the largest studies carried out on patient population affected by schizophrenia is the SOHO (Schizophrenia Outpatient Health Outcome) study which showed that the average age for the schizophrenia onset in the prospective naturalistic outpatient selection was 28.5 years (Hong et al., 2009). The studies conducted in real-life settings where patients are included following their admission to health care facility with exacerbation of disease, the age of patients is higher comparing to specifically designed early psychosis recognition studies. There is a time-lag between the onset of symptoms and receiving help; other related terms used in psychiatry are Duration of Untreated Disease (DUD) and Duration of Untreated Psychosis (DUP) (Hastrup et al., 2018); (Murru et al., 2018). The studies conducted in Latvia regarding acute psychotic disorders where patients are included at the time of admission to Riga Psychiatric and Narcology Centre's emergency care unit, the average age of

patients with FEP was 35.7 (SD 12.3 TI 95 % +/- 3.6) for female participants and 30.0 years (SD 10.8 TI 95 % +/- 3.7) for male participants (Rusaka & Rancans, 2014a). A targeted assessment of EIP efficacy showed that the age of patients with FEP is as follows: 26.6 years for patients in the OPUS Programme conducted in Denmark (Petersen, Jeppesen, Thorup, Abel, Øhlenschläger, et al., 2005) and 30.3 years for patients in the AESOP EIP conducted in the UK (Revier et al., 2015). There are various explanations for the age of patients with FEP starting their treatment, and they are related to the personal factors (severity of symptoms of disease, individual course of disease, comorbid conditions, e.g., substance abuse) and social factors (support from family, stigmatization of social environment), and healthcare factors (e.g., access to mental healthcare) (Lihong et al., 2012). In both study groups, the duration of years spent at an education facility did not differ, i.e., 13 years on average, which is similar to the data reported in the literature from other countries (Chang et al., 2017). We are making a guess that at the beginning of prodromal psychosis symptoms in the late teenagerhood and early adulthood, which transition to psychosis, significantly affect patient capacity to pursue their education, therefore an unfinished higher education is a regular and modifiable sign.

Mental disorders among patient blood relatives of the first and the second degree were studied for both control and the intervention groups, and the results obtained in these both groups did not differ. In the control group 27.9 % of the patients had mental disorders running in families comparing to 18.5 % in the intervention group. The study involving psychosis patients conducted in the period between 2010 and 2011 in Latvia, showed that 15.6 % of the patients reported mental disorders running in family (Rusaka & Rancans, 2014b). It is stated in the scientific literature that 24.7 % of the patients with psychotic disorders have mental disorders reported in their family anamnesis (Ayesa-Arriola et al., 2019).

The most severe adverse disease outcome for patients with psychotic disorders is a committed suicide the risk of which significantly increases with each suicide attempt reported in the patient's anamnesis. Suicide death risk in patients with psychotic disorders is 20 times higher comparing to general population (SMR = 20.0, 95 % TI 11.7 – 34.5) (Revier et al., 2015). The EIP conducted in Singapore reported that after a 2 year long follow-up period, 1.2 % of the patients had died by suicide (Verma et al., 2012). The study conducted in the framework of this Thesis revealed no difference between the study groups regarding the suicide attempts reported by patients themselves. 9.8 % of the patients in the control group and 18.5 % in the intervention group answered the question *Have you had a suicide attempt during your life?* with an affirmative reply. Scientific literature reveals that 14.3 % of the patients included in the studies conducted in the USA involving patients with FEP, had given an affirmative reply to suicide attempts over the course of the lifetime (Ventura et al., 2011). The cohort study involving patients with FEP in Norway, showed that 26 % had reported suicide attempts over the course of their lifetime (Barrett et al., 2010), however in the EIP (Programme 2000) involving a cohort of patients with FEP in Italy, revealed that 8.6 % of the patients had reported suicide attempts over the course of their lifetime (Preti et al., 2009). A prospective study carried out in Sweden with a follow-up period of 8 years on average showed that 45 % of the patients with schizophrenia spectrum FEP had attempted suicide (Harvey et al., 2008). Suicide attempts can be directly related to psychotic symptoms (e.g., as commanding, insulting unbearable pseudohallucinations), or to an equally important major emotional suffering caused by a primary depressive episode after an experienced psychosis or by secondary symptoms of depression possibly due to antipsychotic medication use.

### **3.2 Help-seeking behaviour in patients with first-episode psychosis**

Due to this acute condition and psychosis manifestations, low insight regarding one's condition, lack of criticisms regarding the reality, as well as behavioural changes defined by psychotic experience, the first contact with health care facilities for these patients can be accompanied by aggression, e.g., patient is transported to psychiatrist using State Emergency Medical Service and with a help of police (Anderson, Fuhrer, & Malla, 2010). One of the most discussed questions in psychiatry is related to patient experience regarding their first contact with mental healthcare facilities. In order to protect persons with symptoms of psychosis, as well as those around them, provision of healthcare without patient consent in accordance with the law is needed (Medical Treatment Law of the Republic of Latvia, 2014). The study conducted in Australia showed that 40 % of the patients with FEP are brought to psychiatric emergency unit by police (Petrakis et al., 2012). The study carried out in the framework of this Thesis showed that 24.6 % of the patients included in the control group were brought by the State Emergency Medical Service and police comparing to 37.0 % of the patients in the intervention group; however, an opposite ratio was reported studying patients who admitted themselves to hospital, i.e., 8.2 % in the control group and 7.4 % in the intervention group. The literature in regard to this matter reveals that usually manifestation of symptoms lead to psychiatric healthcare-seeking, and for 37.8 % of the patients these symptoms are nightmarish statements, for 27.6 % hallucinations, for 8.9 % suicidal tendencies, and for 5.4 % these are symptoms of depression (Coldham, Addington, & Addington, 2002). This study conducted in the framework the Thesis revealed that 50.8 % of the patients with psychotic symptoms in the control group and 66.7 % in the intervention group had not sought help, therefore the psychiatric emergency care unit was the first contact they had with a healthcare specialist. 26.2 % of the

patients had consulted a psychiatrist in the control group comparing to 22.2 % in the intervention group; only a small proportion of the patients had consulted their general practitioner (GP) regarding the psychotic disorders, i.e., 4.9 % in the control group and 7.4 % in the intervention group. The literature shows that in 52 % of cases, the first contact with a healthcare specialist is provided by psychiatric emergency care units, and in 18 % of the cases the service provider is their GP (Addington et al., 2002). In the United Kingdom, majority of psychiatric disorders are treated at the primary care level, and for 35.2 % of the patients with FEP, the first contact with a healthcare provider was their GP comparing to 21.3 % for whom the first contact was hospital emergency care unit (Bhui, Ullrich, & Coid, 2014).

A significant result obtained while studying patient behaviour when seeking help is a help-seeking initiator: for 77.0 % of the patients in the control group and for 85.2 % in the control group the initiators were family members, and only 11.5 % of the patients in the control group sought help for psychotic symptoms and did that of their own free will comparing to 14.8 % in the intervention group. It is indicated in the literature that for those patients whose psychosis episode manifests with acute positive symptoms, help-seeking takes place earlier comparing to those whose psychosis episode develops slowly and with hidden symptoms (Chen et al., 2005). In addition, it was reported that more often help-seeking in the prodromal phase with an onset of first psychotic symptoms was initiated by patients themselves, was initiated by other persons, generally family members (Schultze-Lutter et al., 2015). This indirectly shows signs or symptoms of the mental state of the patients included in the study in the framework of this Thesis, which are peculiar to an acute psychosis episode manifesting through a loss or a partial loss of contact with reality and impairment of their insight regarding their condition. When assessing help-seeking behaviour, it is critical to consider the key role family members play when dealing with persons experiencing FEP and the provision of healthcare to the

latter; this justifies the need to include in the EIP supportive psycho-educational and psycho-emotional interventions for family members.

### **3.3 Adaptation of EIP (LAT-EIP) to patients with schizophrenia spectrum first-episode psychosis in Latvia**

In the framework of the study of the Thesis, the LAT-EIP team enrolled their first patient on February 1, 2018, and in the period until December 31, 2018, 35 patients were offered opportunity to participate from whom 27 patients completed the programme, 2 were repeatedly admitted to hospital, and 6 stopped attending their consultations set up in the framework of this programme in the period of their first three visits on average. The reasons for interruption of the programme were various: the main reported reason was that the Daugavpils Psychoneurological Hospital was located too far from their place of residence (up to 90km). The motivation to participate in the treatment of these patients with psychotic disorders can be affected by the following aspects: severity of symptoms, adverse effects of medication, patient convictions and attitude towards medications, patient insight regarding their condition, as well as support received during treatment (social support and relationships) (Nyanyiwa et al., 2021). In the framework of this study, maximum effort was made by the EIP team to build a positive attitude regarding the treatment, to increase patient understanding, to minimize negative convictions regarding psychotic disorders, and to initiate the most appropriate treatment with antipsychotic medication the adverse effects of which were systematically monitored. It should also be noted that there were factors which could not be influenced in this study, i.e., patient socioeconomic factors and that after the first episode psychosis, medical imaging allowing to predict a more severe course of disease or view other structural changes in the brain which potentially could affect patient insight regarding their condition was not carried (Bedford et al., 2012).



17.1 % of the patients chose to opt-out or to terminate their participation in the programme; this result is comparable to the reported in the studies published in scientific literature showing that on average 7.1 % to 31.1 % of patients opt-out of early intervention programmes (Lau et al., 2019); (Norman et al., 2018); (Verma et al., 2012). A study on early intervention applicability conducted in Italy indicated that if 20 % of patients opt-out and more than 50 % of programme interventions has been visited, then programme is applicable (Ruggeri et al., 2015). Based on the listing of Daugavpils Psychoneurological Hospital Outpatient Unit (psychiatrist consultations, psychologist consultations) as well as the listing established during this Thesis study indicating psycho-educational and psycho-supportive sessions and employment specialist involvement in these sessions, the LAT-EIP team carried out the planned interventions for the patients enrolled in the study at an average rate of 81.8 %. By reorganizing the resources of Daugavpils Psychoneurological Hospital Outpatient Unit according to the LAT-EIP structure and by engaging specialists interested in working with psychotic disorders it is possible to apply early intervention model as a treatment method in practice for treating patients with schizophrenia spectrum disorders also in conditions with restricted financial resources.

### **3.4 Efficacy assessment of Early Intervention Programme in Latvia (LAT-EIP) developed for patients with schizophrenia spectrum first-episode psychosis**

#### **3.4.1 Efficacy of LAT-EIP indicated by psychopathological symptom scores**

Improvement of patient clinical symptoms is one of the main objectives when treating a disease; it is generally the main objective when treating using medications. It should be noted that in both study groups, the first-episode psychosis was successfully treated in the inpatient facility leading to an

improvement in positive psychotic symptoms of schizophrenia with a significantly higher efficacy (control group  $d = 1.98$ , intervention group  $d = 2.43$ ), as well as a decrease in negative symptoms of schizophrenia (control group  $d = 0.9$ , intervention group  $d = 1.22$ ). The results obtained in this Thesis study correspond to results published in literature stating that treating only with antipsychotic medication without psychosocial interventions relatively poorly improves negative symptoms of schizophrenia (Norman et al., 2018); (Thorup et al., 2005). When assessing the symptoms of depression in patients with schizophrenia, the obtained points at the moment of discharge from an inpatient facility of the patients in the control group were 4.63 (SD 4.21) and in the intervention group 5.48 (SD 4.49), meaning that at the beginning of the intervention programme, the score is lower comparing to 6.6 (SD 4.8) points on average reported in literature (Lyngstad et al., 2018). It is important to note that the Thesis study cohort, similarly to the study mentioned above, did not reach the level of confirmed depression (7 points), therefore immediate patient involvement in the treatment in an outpatient facility after a discharge from hospital, could prevent postpsychotic depression which can develop over the course of the first year after FEP (Häfner et al., 2005). After a 12-month follow-up period, the control and the intervention groups differed in terms of symptom expression: less pronounced positive psychosis symptoms of schizophrenia ( $p = 0.029$ ) and less pronounced negative psychosis symptoms of schizophrenia ( $p = 0.028$ ) were observed in the intervention group. The results correspond to the ones reported in literature revealing that multiprofessional team work (including psychosocial interventions) in the framework of the EIP has a significantly higher efficacy in improving psychopathological symptoms of schizophrenia, and is the most efficient way to improve the scores of negative symptoms of schizophrenia (Correll et al., 2018). In addition, it has already been described in scientific literature that early intervention reduces positive and negative symptoms of schizophrenia in a more efficient way comparing to

standard treatment, and the use of medications is not the only explanation (Thorup et al., 2005).

When assessing the clinical scores obtained at the time of patient with FEP admission to inpatient facility in the control and the intervention group, the only differences observed were related to patient insight regarding their medical condition at the time of discharge from inpatient facility: for the patients in the intervention group the level of insight was higher comparing to the control group, i.e., 34.0 points (31.0–39.5) and 30.0 points (31.0–39.5) respectively. The increase in patient insight in the intervention group can be explained by the educational work which was carried out with patients before their discharge in the framework of the inclusion of patients in the LAT-EIP. We can consider that early intervention encompassing educational work has been shown to be valuable already before treatment initiation in an outpatient facility in the framework of the programme. Patient psycho-education is a widely acknowledged method for ensuring a better disease outcome in patients with psychotic disorders (Xia, Merinder, & Belgamwar, 2011). It is important to ensure the initiated psycho-educational continuity in an inpatient facility and later on in the framework of the EIP in an outpatient facility, because, in accordance with literature, a greater importance should be attached to raising insight regarding patient's medical condition over the course of the first six months of disease, and not the level of insight as a cross-sectional score at the time of FEP (Saravanan et al., 2010).

### **3.4.2 Efficacy of LAT-EIP in improving living conditions, promoting employment and reducing disability**

For young persons at the onset of schizophrenia manifestations, it is important to pursue their day-to-day activities and fulfil their professional intentions to gradually become independent. It is stated in literature that there is a significant difference between the large number of patients with schizophrenia

who have achieved symptomatic remission and are capable of carrying out day-to-day activities, as well as the small number of patients who have achieved both clinical and social recovery (Santesteban-Echarri et al., 2017).

When assessing the results obtained using the Global Assessment of Functioning (GAF) scale, the score of 61 points and more were more often observed in patients in the intervention group comparing to the control group, and a statistically significant difference was observed using Cramer's effect value 0.18,  $p < 0.001$ . The most frequently determined scale values at the time of treatment initiation for patients with FEP in the intervention and the control groups were from 51 to 60 points. The most frequently used value of 51 to 60 points for the patients in the control group remained after a one-year follow-up period comparing to the intervention group where the patient functioning score was 61 points and more. For comparison, in literature, the determined value by the Danish OPUS Early Intervention Programme using the GAF scale at the time of treatment initiation was 41.6 points (Petersen et al., 2005). The study carried out in Norway with a participations of patients with first-episode psychosis at the time of inclusion in the Early Intervention Programme, reported the value of 44.6 (SD 13.6) points using the GAF scale, and over a 12-months follow-up period, the GAF score had improved to reach 53.0 (SD 17.2) points (Lyngstad et al., 2018). The Swedish Early Intervention Programme *Parachute* demonstrated the GAF score of 65.0 points one year after treatment initiation (Strålin, Skott, & Cullberg, 2019). The study which compares early EIP with standard treatment (ST) in patients with psychotic disorders, the functioning level determined using the GAF scale at the time of treatment initiation in the EIP group was 44.46 (SD 13.81) and after a 9-month follow-up period, the score was 63.15 (SD 16.94) comparing to the ST group where at the time of treatment initiation the score was 45.69 (SD 12.96) and after a follow up period of 9 months, the score was 60.11 (SD 16.63). It is important to note that, similarly to the study carried out in the framework of this Thesis, there is no difference

between the study groups at the start of treatment, however after a 9-month long treatment period, the score of both groups differed ( $p = 0.006$ ) with the effect size of 0.35 (95 % TI 0.06-0.64) (Ruggeri et al., 2015).

Several studies carried out with the participation of patients with schizophrenia disorders revealed that already before treatment initiation a professional regression (job loss or interruption of studies) was observed, e.g., in Canada, 65.3 % of patients before treatment in the EIP were unemployed (Norman et al., 2011), in the UK, 77.6 % of patients were unemployed (Revier et al., 2015). Taking into consideration the needs of patients with psychotic disorders to promote their return to school or work, it is possible to provide support in changing their professional activity, therefore the EIP team included also an employment specialist, and an intensive psychosocial intervention work was carried out. There was a significant increase in employment rates for the patients participating in the LAT-EIP, i.e., 63 % of the patients in the intervention group were employed after a 12-month follow-up period. Interestingly, the LAT-EIP helped not only to keep patients in employment, but also to begin to work taking into consideration that 29.6 % of the study patients who were unemployed at the time of treatment initiation started to work over the course of the intervention programme. Such results were not observed in the control group where patients were receiving standard treatment. In Australia, 62.4 % of the patients who were treated in the EIP, after a 18-month follow-up period were employed (Conus, Cotton, Schimmelmann, McGorry, & Lambert, 2017). Promotion of patient independence is one of the fundamental EIP's psychiatric rehabilitation objectives aiming at reducing potential social and professional regression and preventing patient with schizophrenia living in State financed care centres. In the framework of the LAT-EIP, the desired result was achieved in the field of employment.

It is fundamental that patients maintain a day-to-day functioning on a level which does not require application for assessment of disability status due to symptoms of mental disorder. A large study which was carried out in 37 countries and included outpatients with schizophrenia (a total of 17 000 patients) who were receiving standard treatment over the course of three years after schizophrenia spectrum first-episode psychosis showed that 56 % had received functional disability determination (Ayesa-Arriola et al., 2013), and in the study conducted in Norway, 65 % of the patients with schizophrenia over the course of seven years after the diagnosis was made had received disability determination (Melle, Friis, Hauff, & Vaglum, 2000). The study conducted in the framework of this Thesis showed a statistically significant difference regarding the disability proportion in the groups. In the intervention group, two patients had received disability determination due to schizophrenia diagnosis comparing to 21 patients (34.4 %) in the control group. The study of patient with psychotic disorders self-assessment which was carried out over a follow-up period of one year showed that 63 % of the patients had reported that they were unable to integrate into society and carry out daily functioning; for this patient group, physicians considered that establishing disability diagnosis for 37 % of these patients due to functional disability was needed (Simonsen et al., 2018). The study of Simonsen and the co-authors conducted in 2018 where patient answers were analysed revealed that most often patients reported functional disability regarding the following skills: *having a good relationship with people, participating in social activities*, followed by *mutual understanding and communication skills*, and *activities of daily living*. The results confirming efficacy of the LAT-EIP of this Thesis, i.e., more than three times fewer disability status establishments in the intervention group, could be related to the work conducted by the multiprofessional team in the framework of the early intervention programme which was particularly aimed at strengthening social skills by using psychosocial interventions.

### **3.4.3 LAT-EIP efficacy indicated by indirect compliance scores, reduction of number of recurrent hospitalizations and remission achieved**

For patients with schizophrenia spectrum disorder, compliance is crucial in order to ensure continuity of the treatment aiming at reducing symptoms of psychosis which patients receive in an inpatient facility and a successful transition to a follow-up in an outpatient facility (Fenton, Blyler, & Heinsen, 1997). Physician can ensure patient compliance during consultations; therefore, it is essential to make sure patients attend these consultations and to establish a successful collaboration between specialist and patient. In this Thesis, the author analysed indirect compliance scores, i.e., consultations with specialist and medication use based on physician's clinical assessment and information provided by patients. Comparing psychiatric consultations in Italy between the standard treatment group and the intervention group, it was showed that after a 9-month follow-up period 91.3 % of patients of the EIP group continued to see physician comparing to 90.8 % in the standard treatment group,  $p = 0.866$  (Ruggeri et al., 2015). Similar results obtained in the study conducted in the framework of this Thesis proved that the total number of patient consultations in the intervention group and the control group did not differ suggesting that patients are open to seeing physicians. In the intervention group, 96.2 % of the patients had consulted physicians at least once comparing to the 78.7 % in the control group. 25.9 % of the patients in the control group and 27.9 % in the intervention group were open to consult physician 6 to 10 times a year. Calculations of Odds Ratio showed that patients in the control group consulted outpatient psychiatrist 6.25 times more often (TI 95 % 1.11–10.0,  $p = 0.04$ ) or not at all comparing to the intervention group. Such findings suggest that early intervention programme ensures treatment continuity from the moment of treatment initiation in an inpatient facility to the moment of receiving treatment in an outpatient facility comparing to standard treatment. Nevertheless, analyzing

the second indirect indicator, i.e., medication use according to physicians recommendations, the author discovered that 32.8 % of the patients in the control group had stopped using medications contrary to physician recommendations. 7.4 % of the patients in the intervention group had stopped using medications contrary to physician recommendations leading to consider the importance of providing additional services to ensure compliance; the team of the Early Intervention Programme consisted not only of psychiatrists, but also of a nurse and a care coordinator. Multiprofessional teamwork which helps to reduce risk factors leading to interruption of treatment is more efficient than a collaboration with a psychiatrist alone. The results of this Thesis study showed that the odds ratio for interruption of medication use contrary to physicians recommendations in the standard treatment group is 6.35 times higher comparing to the intervention group. It is known that antipsychotic medication with a robust evidence base is efficient in treating symptoms, however it is essential to continue the treatment as a maintenance therapy up to 36 months (Hasan et al., 2012).

In this Thesis study, the proportions of medications prescribed did not differ by their pharmacological names between the Early Intervention Programme and the control groups suggesting that treatment with medication prescribed for patients with FEP in the framework of this Thesis study was conducted accordingly to common clinical standards (LPA, 2014). The characteristics of the medications prescribed is comparable to data published in scientific literature in other countries (Aadamsoo, Saluveer, Kuunarpuu, Vasar, & Maron, 2011); (Norman et al., 2011); (Strålin et al., 2019); the most commonly prescribed medications are Risperidone (in the Thesis study, 22.2 % in the intervention group and 23.0 % in the control group; 34 % in the EIP in Sweden; 22 % in the EIP in London; in China, in patients with FEP 17.6 %; in Estonia, in patients with FEP 27 %); Olanzapine (in this Thesis study, 29.6 % in the intervention group and 29.5 % in the control group; 17 % in the EIP Sweden; 65 % in the EIP in London; in China, in patients with FEP 12.6 %; in Estonia,



in patients with FEP 43 %); Aripiprazole (in this Thesis study, 7.4 % in the intervention group and 11.5 % in the control group; in China, in patients with FEP 11.3 %), Quetiapine (in the Thesis study, 6.6 % in the control group, none in the intervention group; in China, in patients with FEP 12.8 %; in Estonia, in patients with FEP 10 %). Pharmacological treatment traditions might differ from one country to another; however, the fundamental principles remain similar and are based on the leading clinical guidelines.

In the last few decades, psychiatric healthcare has been reoriented from inpatient to outpatient psychiatric healthcare. Treating patients in an inpatient facility is irreplaceable in case of acute events, e.g., when treating psychosis episode. Nevertheless, when assessing the bed day occupancy for patients with mental disorders, it was observed that the incidence of first-episode psychosis patients and treatment provision in an inpatient facility is comparable to the data reported in literature in other countries, however in Latvia, the number of recurrent hospitalizations is significantly higher and therefore also the number of occupied bed days in an inpatient facility for patients with mental disorders. Some of the explanations could be reduced possibilities for patients to receive outpatient services (reduced accessibility to psychiatrists, restricted variety of outpatient services), as well as patient detachment from social role, i.e., unemployment and lack of independence which worsens treatment prognosis. It is possible to prevent admissions for treatment to inpatient facilities. It is possible through prevention of exacerbations of the disease and quality improvement of outpatient services. Admission to an inpatient facility as a most accessible way of receiving healthcare for patients suffering from schizophrenia spectrum disorders can enlarge detachment from their permanent residence and their usual environment thus making treatment more expensive for the healthcare system. Nevertheless, admission to inpatient facility, according to research studies performed in patients with schizophrenia spectrum, is recognized as one of the most obvious methods when assessing patients aiming at understanding if it is

a recurrent psychosis episode (relapse of disease); despite the differences in healthcare systems, psychosis episode remains an unambiguous clinical indication for admitting a patient to hospital (Burns, 2007). Data regarding patient with schizophrenia treatment from 10 European countries have been collected in this study conducted in real-life settings, and the results revealed that 80 % of all costs related to patient with psychotic disorder treatment over a course of one year, is carried out in an inpatient facility, however after a 3-year follow-up period of patients with schizophrenia diagnosis, 61 % of the difference of expenses generated by patients with a relapse of the disease and by those without one, were associated with the treatment provided in the inpatient facility (Hong et al., 2009). It is stated in research literature that early intervention comparing to standard treatment reduces the number of recurrent hospitalizations in patients with schizophrenia spectrum disorder (Correll et al., 2018). In accordance with the previously mentioned, the proportion of patients recurrently hospitalized between the control and the intervention group differed significantly in the study of this Thesis, i.e., 36.0 % and 7.4 % respectively. A more detailed analysis revealed that the odds of recurrent hospitalization for patients in the control group were 4.41 higher comparing to the intervention group. A study conducted in Latvia in collaboration with Riga Psychiatric and Narcology Centre which inpatients with FEP who received standard treatment over a course of approximately 2.5 years, 40.2 % of the patients were recurrently hospitalized (Rusaka & Rancans, 2014a). A study conducted in Finland where patients with first-time schizophrenia diagnosis were consecutively selected in the period between 2000 and 2007, showed that 57.8 % of the patients in the first two years after the first hospitalization who received standard treatment, were recurrently admitted to hospital (Tiihonen et al., 2011). Another study regarding the influence of early intervention on recurrent hospitalizations according to the statistical data obtained from the Danish Hospital Register, showed a 22 % reduction in hospitalizations among patients who received early intervention in

the first two years after schizophrenia spectrum first-episode comparing to standard treatment (Petersen et al., 2005).. Cox regression analysis showed the tendency ( $p > 0.05$ ) for patients receiving standard treatment to have 2.26 more recurrent hospitalizations comparing to the intervention group. It is a valuable indication that intervention programme could prevent adverse schizophrenia events, e.g., second psychosis episode, even though the course of the disease itself with recurrent psychoses cannot completely be prevented.

In the continuation of the discussion regarding patients with the course of schizophrenia spectrum, it should be pointed out that this is one of the most challenging questions in psychiatry. The authors of a study conducted in Italy on long-term remission with a participation of patients with symptoms of schizophrenia, stated in the discussion part that “schizophrenia is not a stable disorder, and remission, as well as recovery, is for many patients is a time limited occurrence, we cannot exclude that possible relapse may occur” (Marchesi et al., 2015). Therefore, creation of new treatment programmes has an increasing importance thus extending as much as possible the asymptomatic period or the period of remission of the disease in patients with schizophrenia spectrum psychotic disorders. Following the remission criteria used worldwide, i.e., the criteria established by Andreasen and co-authors (Andreasen et al., 2005), in the framework of this study, the author dichotomized remission in two categories: *Remission* and *No remission*. Literature reveals other approaches in describing remission of psychotic disorders, e.g., by using a more detailed division (symptomatic remission, functional remission, full remission or recovery), which is mostly related to different methodologies and strive for high statistical power (Austin et al., 2013). The results of this study allow to draw correct conclusions both by comparing the results obtained with studies that show dichotomous results and with studies in which a more detailed division was chosen. Independently of the chosen remission division, it is important to assess the effect of the treatment methods using patient disease outcome in a precise period of

time, which in literature is often a year or two years long follow-up period after first-episode psychosis (Nishida et al., 2018). It is needed to stress again that remission is a variable indicator in time, e.g., OPUS Early Intervention Centre study showed that 64 % of patients with first-episode psychosis reach a symptomatic remission at a certain time over a 10-year period (Austin et al., 2013). The results of this study conducted in the framework of this Thesis show that 74.1 % of the patients in the intervention group after a 12-month long follow-up period had achieved remission; these results are similar to the ones obtained in the Italian EIP *Programme 2000* which revealed that 67.2 % of the patients after a 12-month follow-up period achieved remission (Pret et al., 2009), and to the Swedish EIP *Parachute* where 68 % of the patients achieved a full remission after a period of one year (Strålin et al., 2019). When conducting a study with a participation of patients with first schizophrenia diagnosis in a 12-month follow-up period in an outpatient facility, Ventura and co-authors already in 2011 raised a question regarding the fact that despite the same remission criteria, remission results varied significantly in the scientific literature, i.e., from 24 % up to 78 % (Ventura et al., 2011) Explanations for such a wide range are various: Individual clinical characteristics, accessibility to healthcare and provision of services, treatment method, patient treatment compliance, social settings and support, as well as study objectives and methodology affect remission of patients. The odds ratio of the remission after a 12-month period of patients included in the study conducted in the framework of this Thesis and who received early intervention was 3.51 (TI 95 % 1.33 – 10.2) higher comparing to the control group in which patients received standard treatment. The results of this Thesis are comparable to those published in the Japanese EIP efficacy assessment study revealing that the odds ratio for achieving remission in patients included in the EIP, was 6.3 times higher comparing to patients receiving standard treatment (Nishida et al, 2018). It is important to note that the efficacy rates obtained in this Thesis comparing to remission achievement remained persistent also after

influencing factor comparison using logistic regression model indicating that treatment received within the EIP, and the standard treatment is the strongest factor determining whether patients with FEP would achieve remission or not over the course of a 12-month period after schizophrenia spectrum first-episode psychosis.

### **3.5 Advantages and disadvantages of the study**

The most significant advantage of the study conducted in the framework of the Thesis is its realization which was conducted in real-life clinical settings allowing to assess the efficacy of the Early Intervention Programme comparing to standard treatment and its appropriateness for the actual healthcare system regarding its implementation. Patients which were selected for this study encompassed the entire Latgale Region, both urban and rural areas. The study was conducted in the second largest psychiatric hospital in Latvia, Daugavpils Psychoneurological Hospital, which provides all available psychiatric services in the country. In terms of administration, task organization and patient load, Daugavpils Psychoneurological Hospital is comparable to other psychiatric hospitals in Latvia, therefore implementation of the adapted early intervention model in other psychiatric hospitals in Latvia is possible.

It should be noted that the study has its disadvantages. Despite the maximum effort that was deployed in order to include all patients consecutively during the study period, the psychotic disorder incidence determined in the study was comparable to scientific literature, and it should be noted that the size of the study selection could have influence on the use of statistical methods due to insufficient statistical power. The choice of study design, i.e., quasi-experimental study, study groups were not randomized, could be considered as a limitation. The control group was formed before the intervention group. It should be explained that during the study period, there were no significant changes in the

psychiatric healthcare system, there were no new guidelines, national clinical pathways and algorithms in treating schizophrenia were not approved yet, therefore patients in both groups could potentially receive comparable treatment in emergency psychiatric units and then patients in the control group continued to receive standard treatment in an outpatient psychiatric facility. It should be stressed that in this study, specific early intervention components were not analysed; the results of early intervention were assessed in terms of teamwork. In methodology, clinical symptoms were assessed using scales which were not validated in Latvia; physicians had gained knowledge about these scales (used for interviewing patients) during psychiatry residency training process or when receiving training using author provided training guidelines regarding the use of these scales. Although the author of this study acknowledges non-validation of these scales in the Latvian population as a disadvantage, it was considered that this did not influence the results, because none of these scales were given to patients for filling-out and all tools were used by physicians who are professionally skilled to use them, and they served as a part of the clinical interview only. Moreover, heterogeneity phenomena described in scientific literature in patients with psychotic disorders were considered as a disadvantage, i.e., patients are different in their socio-demographic characteristics, in their clinical manifestations and the way they recover (Hodgekins et al., 2015). Efforts were made to reduce these limitations when including strictly clinically assessed patients with schizophrenia spectrum acute first-time episode. Nevertheless, when realistically assessing the uninfluenceable part of the natural course of schizophrenia, it is important to understand that this limitation concerns all studies ever conducted with a participation of patients with schizophrenia spectrum in a real-life treatment setting. Moreover, another possible limitation: cognitive tests, which could show additional factors for achieving remission, were not used in this study. Supplementing the methodology with cognitive tests and widening instruments in order to assess patient social and professional

functioning is recommended for further studies regarding efficacy of treatment approaches in patients with psychotic disorders. Finally, the last limitation is the relatively short follow-up period, because according to literature, EIP is criticized for the instability regarding its efficacy in a long term (Albert et al., 2017), therefore the author suggests that in clinical practice, duration of intervention programme should be extended, and, in the future, it would be necessary to prolong the follow-up period of study.

## Conclusions

The results obtained in the Thesis approve the suggested hypotheses partially:

1. Patients with schizophrenia spectrum first-episode psychosis who received treatment in the framework of early intervention programme, after a 12-month period had less pronounced positive and negative symptoms, better professional functioning scores, fewer recurrent hospitalizations and fewer disability status establishments comparing to patients who received standard treatment; changes in living conditions or in social life regarding the treatment method were not observed.
2. Implementation of early intervention programme in the Latvian psychiatric healthcare system for treating patients with schizophrenia spectrum disorder is achievable.

The analysis of the results of the Thesis reveals several conclusions:

1. It is possible to develop and implement in practice an early intervention programme using existing resources and services in psychiatry.
2. Patients with schizophrenia spectrum first-episode psychosis are young people mainly male, with a poor employment rate already before the initiation of treatment, and median duration of untreated disease in this study cohort was two and a half years, the median untreated psychosis duration was two months.
3. Early intervention programme is possible to implement in the treatment process and the rates of patient participation and completion of this programme are high: 81.8 % of the included patients completed the LAT-EIP according to individual plan. Among patients receiving standard treatment, the termination of medication use contrary to



psychiatrist recommendations was observed 6.35 more often (95 % TI: 1.60 – 46.50;  $p < 0.01$ ) comparing to patients in the intervention group.

4. Patients who were receiving treatment in the framework of the early intervention programme had better functioning and employment scores comparing to patients receiving standard treatment. Patient living conditions differed already at the beginning of the study, and it is impossible to make statistically correct conclusions regarding the influence of the intervention programme on the change of living conditions over a 12-month follow-up period after first-episode psychosis.
5. The early intervention programme as a treatment method for patients with schizophrenia spectrum disorders aiming at achieving remission after a 12-month period is more efficient than standard treatment.
6. Patients who received treatment in the framework of the early intervention programme, were less often hospitalized and had fewer disability establishments due to psychotic disorders.

The results of the Thesis are comparable to research literature from other countries, and the conclusions drawn inspire justifiable optimism regarding treatment enhancement for patients with schizophrenia spectrum disorders in Latvia. However, results, taking into consideration the limitations described above, should be interpreted with precaution.

## **Importance of Thesis and practical recommendations**

This Thesis can be considered as the first step towards a further development and continual improvement of the early intervention programme in Daugavpils Psychoneurological Hospital and in outpatient psychiatrist practice also in other psychiatric hospitals in Latvia.

As the result of this Doctoral Thesis, the Latvian first early intervention programme in psychiatry for adults within the framework of a single diagnosis, which was adapted and implemented in the practice, was developed. The early intervention programme ensures a treatment carried out by multiprofessional team designed for patients with psychotic disorders addressing individual clinical and social needs. Until now, no other treatment programme in psychiatry specific to one diagnosis in Latvia has been implemented. Participation in the intervention programme gives opportunity for patients to receive psychiatric outpatient service, which is acknowledged of being the golden standard described in literature regarding psychotic disorders treatment, and thanks to this study, is now available also in Latvia. The early intervention programme corresponds to the theoretical principles of mental healthcare outpatient services defined in the Latvian Mental Health Care Improvement Plan 2019–2020 (Ministry of Health of the Republic of Latvia, 2018). The early intervention programme (LAT-EIP) model developed within the framework of the Doctoral Thesis is included in clinical algorithm and the patient pathway *Akūtu psihotisko traucējumu un pirmās šizofrēnijas epizodes atpazīšana, vadīšana un ārstēšana* [Recognition, management and treatment of acute psychotic disorders and first-episodes of schizophrenia] of the Latvian Centre for Disease Prevention and Control, which was published in November 2019 (Clinical algorithm, 2019). Algorithms set treatment standards in Latvia and early intervention is recommended as a treatment method for secondary psychiatric healthcare level for patients with

first-episode psychosis and schizophrenia. The developed early intervention programme was presented in several conferences organized by the Latvian Psychiatric Association and during psychiatrist training regarding early intervention programme and available treatment methods designed for patients with schizophrenia spectrum disorders. In the framework of this Doctoral Thesis, a workshop regarding the early intervention programme was organized in Strenči Psychoneurological Hospital (VSIA / State limited liability company), and a collaboration regarding the implementation of early intervention programme has been started in the Hospital *Ģintermuiža* (VSIA).

The results of the Doctoral Thesis, the knowledge collected from scientific literature and practical experiences gained allows to establish the following recommendations:

1. The early intervention programme is an efficient treatment method and its implementation in practice is achievable and provides patient treatment consistency within the mental healthcare system between inpatient and outpatient services. In order to ensure continuity in the treatment process, patient inclusion in the EIP must start at the time of treatment in an inpatient facility already and transition successively to treatment phase in an outpatient facility. The author suggests that from a patient perspective, this could reduce fragmentation of phases of healthcare services and promote stable therapeutic relationship with one team of specialists thus providing a better compliance in a long term.
2. Multiprofessional team should consist of specialists who are able to ensure social and professional needs of young people with schizophrenia spectrum. A crucial element is a participation of psychological intervention and employment specialist. It is recommended to strengthen, to diversify the work of the

multiprofessional team and to promote its availability for patients with schizophrenia spectrum disorders in mental outpatient healthcare.

3. Involving patient families is of a significant importance, i.e., consultations with their presence, as well as their participation in family member structured psycho-educational workshops. It is recommended to continue to pay attention to participation of patient families and relatives in the treatment process thus reducing burnout of patient relatives and providing psycho-emotional support.
4. Specialists working with early intervention programme should provide education addressing psychotic disorders which is divided in two main directions: 1. For specialists working with recognition of early signs of psychotic disorders and treatment methods; 2. Targeted education for youth (secondary school, institution of higher education, various interest educations and social networks / media) and for groups who are working with youth in order to reduce the duration of untreated psychotic disorders and the existing stigma regarding psychotic disorders, including schizophrenia, as well as promoting early intervention using mental healthcare specialist services.
5. It is recommended to perform an economic analysis using direct and indirect expenses related to schizophrenia spectrum disorder in Latvia in order to form an additional justification intended for healthcare policy makers with the aim to update implementation of early intervention in mental healthcare outpatient practice in Latvia.

## Publications

*On 17.07.2020 Author of the Thesis changed her last name from Bērze to Sīle*

### Scientific publications in international database editions

1. Sīle, L., Bezina, K., Kvartalovs, D., Ertis, R., Kikuste, S., Sapele, I., & Rancans, E. (2020). Naturalistic follow-up study of rehospitalization rates and assigned disability status of patients with first-episode schizophrenia spectrum psychosis in South East Latvia: preliminary results. *Nordic journal of psychiatry*, 75(2), 87–96. <https://doi.org/10.1080/08039488.2020.1799429>
2. Berze, L., Civcisa, S., Krone, I., Kvartalovs, D., Kikuste, S., Sapele, I., Lazovika, J., & Rancans, E. (2019). Implementing the Latvian Early Intervention Programme (LAT-EIP) for Patients with Schizophrenia Spectrum First-Episode Psychosis: Study Protocol. *Frontiers in psychiatry*, 10, 829. <https://doi.org/10.3389/fpsy.2019.00829>
3. Berze L., Bezina K., Pavlovs K., Kikuste S., Sapele I., Rancans E., “Clinical and sociodemographic characteristics in first-episode psychosis patients in a rural region of Latvia”. (2019). *Proceedings of the Latvian Academy of Science, Section B, Vol 73, No. 4 (721), 332–340.* <https://doi.org/10.2478/prolas-2019-0052>

### Thesis on international scientific conferences

1. Sīle L., Počopko A., Kikuste S., Rancans E. (2021). Small step for a big change: effectiveness of Latvian intervention programme. *European Neuropsychopharmacology*, Volume 53, Supplement 1, 2021, Page S132, ISSN 0924-977X, <https://doi.org/10.1016/j.euroneuro.2021.10.175>.
2. Berze, L., Civcisa, S., Kikuste, S., Sapele, I., & Rancans, E. (2020). Clinical pattern correlation with out-patient appointment adherence in first-episode psychosis treatment. *European Neuropsychopharmacology*, Volume 40, S292–S293. <https://doi.org/https://doi.org/10.1016/j.euroneuro.2020.09.379>
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4. Berze L., Slikova K., Pavlovs K., Kikuste S., Sapele I., Bodins V., Zile J., Samule I., Rancans E. (2018). Duration of untreated illness and its impact on social and personal functioning amongst schizophrenia spectrum patients in rural region of Latvia. *European Psychiatry*, 48S, S427–S428.

## **Presentations at international scientific conferences**

1. Sīle L., Rancans E., (2021). Early Intervention in Psychosis: An Innovation Trigger in a Challenging Environment (ID 517). 29th European Congress of Psychiatry. Virtual Congress.
2. Sīle L., Čivčiša S., Ķikuste S., Šapele I., Rancāns E., (2021). The effectiveness of Latvian Early intervention programme for first time schizophrenia spectrum psychosis patients. RSU konference “Knowledge for use in Practice”. Riga, Latvia
3. Berze L., Rancans E., (2019). Barriers to implementing an early intervention programme in limited resources settings and possible solutions. 27th European Congress of Psychiatry. Warsaw, Poland.
4. Bērze L., Čivčiša S., Krone I., Ķikuste S., Šapele I., Lazovika J., Rancāns E., (2019). Intervention in early psychosis: from scientific evidence to clinical practice in Latvia. RSU conference “Knowledge for use in Practice”. Riga, Latvia.
5. Berze L., Rancans E., (2018). Early intervention programme for first time psychosis patients in rural region of Latvia – first steps toward contemporary treatment. 32nd Nordic Congress of psychiatry. Reykjavik, Iceland.

## **Presentations at local conferences**

1. Bērze L., (2019). “The need of implementation of Early intervention for first psychosis patients”. Conference of Latvian Medical Association. Riga, Latvia.

## **Poster presentations at international scientific conferences**

1. Berze L., Cīvcīša S., Bezina K., Kikuste S., Sapele I., Rancans E. (2020). Vocational status among patients with first episode schizophrenia spectrum psychosis: standard treatment vs early intervention. 28th European Congress of psychiatry. Virtual congress.
2. Berze L., Cīvcīša S., Bezina K., Kikuste S., Sapele I., Rancans E. (2020). Latvian Early Intervention Programme (LAT-EIP) – first results of treatment efficacy in psychopathological symptoms among patients with first episode psychosis, e-poster presentation. 28th European Congress of psychiatry. Virtual congress.
3. Berze L., Krone I., Cīvcīša S., Kikuste S., Sapele I., Rancans E. (2020). In a search of an effective approach to shift the treatment for psychosis patients from hospital-based to outpatient-based in limited resource environment, Regional congress of World Psychiatric Association. Virtual congress.
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5. Berze L., Cīvcisa S., Krone I., Kikuste S., Sapele I., Rancans E. (2019). Starting early intervention programme for first episode psychosis patients in rural region of Latvia. 27th European Congress of Psychiatry. Warsaw, Poland.
6. Berze L., Rancans E. (2018). How and when schizophrenia spectrum patients get psychiatric help in rural region of Latvia, 32nd Nordic Congress of Psychiatry. Reykjavik, Iceland.

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