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Evolution of schizophrenia patients treated with second generation long-acting injectable antipsychotics

SUMMARY

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BRAȘOV, 2023

To Mr. (Mrs.)

……

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of the Doctoral Thesis Analysis Committee

Named by order of the Rector of Transilvania University of Brașov
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Date, time and place of the public defense of the doctoral thesis: time……, room……

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At the same time, we invite you to take part in the public meeting for the defense of the doctoral thesis.
Thank you.

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List of abbreviations

5HT- 5-hydroxy-tryptamine
AMBRA1- Activating molecule in Beclin 1-regulated autophagy protein 1
AOR- adjusted odds ratio
AP- antipsychotics
mRNA - messenger ribonucleic acid
BDNF- Brain-derived neurotrophic factor; brain-derived neurotrophic factor
BZD - benzodiazepines
CCK- cholecystokinin
CHRM4- Cholinergic Muscarinic Receptor 4; muscarinic cholinergic receptor 4
COVID-19-Coronavirus disease 2019
COX-2- cyclo-oxygenase 2
CRF - corticotropin-releasing factor
CYP450- cytochrome P450
DA- dopamine
DALY - disability-adjusted life years
DGKZ- Diacylglycerol kinase zeta
DISC-1- disrupted in schizophrenia-1
DUP - duration of untreated psychosis
SD- standard deviation
DSM-5- Diagnostic and Statistical Manual of Psychiatric Disorders 5
EPS- extrapyramidal adverse effects
EMA- Ecological Momentary Assessment
FDA- United States Food and Drug Administration
FGA- first generation antipsychotic
FGA-LAI- first generation antipsychotic long-acting injectable
fMRI- functional magnetic resonance
GABA - gamma-aminobutyric acid
GAD67- glutamic acid decarboxylase, isoform 67
DF- statistical degree of freedom
GM-CSF- granulocyte-macrophage colony-stimulating factor
GPS- Global Positioning System
GSK-3- beta- glicogen sintază kinază 3 beta
CI- confidence interval
IDO- indoleamine 2,3-dioxygenase
IL- interleukins
LAI- long-acting injectables
CSF - cerebrospinal fluid
LSD - lysergic acid diethylamine
MDK- midkine
NICE - National Institute for Health and Care Excellence
NIMH- National Institute of Mental Health
NMDA- N-methyl-D-aspartate

NPY- neuropeptide Y
NRG1- neuregulin 1
NT- neurotensin
OAPs - oral antipsychotics
WHO - World Health Organization
OR- odds ratio
PANSS- Positive and Negative Syndrome Scale
PDSS - post-injection delirium-sedation syndrome
FES- first episode of schizophrenia
PET - positron emission tomography
PP1M- extended- release injectable paliperidone administered every month
PP3M- extended-release injectable paliperidone administered every 3 months
PP6M- extended-release injectable paliperidone administered every 6 months
PRELAPSE - Prevention of Relapse in Schizophrenia
QTc- corrected QT interval
ROLIN- Rating Opportunity for Long-Acting Injectable Antipsychotic Initiation Index
RR- relative risk
RSWG- Remission in Schizophrenia Working Group
RT-PCR - Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
SGA- second generation antipsychotic; second generation antipsychotic
SGA-LAI- second generation antipsychotic long-acting injectable antipsychotic
CNS - central nervous system
SPET - single photon emission tomography
SPSS - Statistical Package for the Social Sciences
ECT - electroconvulsive therapy
TRH - thyrotropin-releasing hormone
VIP- vasoactive intestinal peptide

ABSTRACT

Introduction: Evolution of schizophrenia is influenced by an early therapeutic intervention, and by the treatment type. Long-acting injectable antipsychotics, known as LAIs (term also used in this doctoral thesis), although apparently superior to oral antipsychotics, remain globally under-utilized.

Objectives: The thesis aimed to provide necessary information regarding LAIs. Objectives of the four studies were: to highlight long- and very long-term remission with LAI; evolution after switching from LAIs to oral antipsychotics; concomitant treatment of patients stabilized with LAI versus oral antipsychotics, and respectively highlighting the impact of the COVID-19 pandemic on LAI treatments.

Materials and methods: The research includes four non-interventional studies, approved by the Ethics Committee of the Clinical Hospital of Psychiatry and Neurology Brașov (Approval no. 3/26.09.2018). Study 1, Highlighting the long-term efficacy of LAIs, was observational retrospective, and followed 102 patients for 60 months. Study 2, Highlighting the effect of switch from LAIs to oral antipsychotics, was observational prospective, and followed 27 patients, stabilized on olanzapine LAI, for 12 months. Study 3, Concomitant treatment of patients stabilized on LAIs, was a cross-sectional study with 315 patients. Study 4, Highlighting the impact of the COVID-19 pandemic on LAI treatments, was a mirror study tracking the number of LAI initiations 12 months before the declaration of COVID-19 pandemic (March 12, 2020) and 12 months after that. t-test, F-test and Chi-square test were used. Results were analyzed using SPSS version 20.00, and p values below 0.05 were considered statistically significant.

Results: In study 1, relapses and hospitalizations were significantly lower in the SGA-LAI group compared to the OAP group (p=0.0152 and p=0.0016, respectively). Study 2 showed that discontinuation of LAI treatment (due to restrictions imposed by the COVID-19 pandemic) led to relapse in 71.4% of patients who switched to oral olanzapine (80% requiring hospitalization), and in only 16.6% of patients who remained on olanzapine LAI (p=0.0181), most likely due to recurrence of non-adherence. Study 3 showed that concomitant treatments with benzodiazepines and mood stabilizers are not significantly different in patients stabilized on LAI versus those on oral antipsychotics (p=0.98, respectively p=0.19). Less than half of the total group of patients were stabilized with monotherapy (43.17%). Study 4 showed a significant decrease in LAI initiations during COVID-19 pandemic (p=0.0353).

Conclusions: LAIs support long-term and very long-term remission in patients with schizophrenia. In case of discontinuation of LAI treatments, the risk of relapse is very high (most likely due to recurrence of non-adherence). Concomitant treatments with benzodiazepines and mood stabilizers did not differ significantly for LAI versus oral antipsychotics. The COVID-19 pandemic has had a major negative impact on LAI treatment initiations.

INTRODUCTION. MOTIVATION OF THE TOPIC CHOICE

Schizophrenia is a chronic and disabling condition, with an evolution characterized most of the time by relapses and remissions. Schizophrenia is among the most disabling and economically catastrophic conditions; it has been listed by the World Health Organization (WHO) in the top 10 conditions that contribute to the global burden of disease (Murray & Lopez, 1996). The main cause of disease progression is considered to be lack of adherence to treatment.

Multiple studies show that the evolution of patients, seen in terms of remissions/relapses, is influenced by the speed of the therapeutic intervention, but also by the type of treatment, with the balance leaning slightly towards the long-acting injectable antipsychotics, known internationally under the established name "long-acting injectable " and the acronym LAI (which will also be used in this thesis), and their introduction as early as possible, even after the first episode of schizophrenia (Lindenmayer et al., 2009; Tiihonen, 2012; Viala et al., 2012)

In the early 2000s, National Institute for Health and Care Excellence (NICE) guidance recommended LAI treatments for non-adherent patients or patients with multiple relapses (Https://Www.Nice.Org.Uk/Guidance/Cg178/Chapter/Recommendations #treatment-Options-to-Prevent-Psychosis, n.d.). New therapeutic guidelines consider LAI a treatment of choice as soon as possible after the onset of schizophrenia, in order to avoid relapses and brain damage (Hasan et al., 2013; Stahl, 2014).

Studies on LAI treatments still provide conflicting results. In previous years, meta-analyses showed that in controlled clinical trials LAI antipsychotics have similar efficacy to oral antipsychotics, and in naturalistic cohort and mirror studies they are clearly superior (Saiz, 2015). More recently, however, in May 2021, Kishimoto et al published a systematic review and comparative meta-analysis of randomized, cohort, and mirror trials of LAI versus oral antipsychotics in the maintenance treatment of schizophrenia. The authors consistently identified a significant benefit of LAI compared to oral antipsychotics in preventing hospitalizations and relapses in both controlled and naturalistic clinical trials (Kishimoto et al., 2021). However, LAI treatments are still widely underutilized (Nasrallah, 2018; Taipale et al., 2018; D. M. Taylor et al., 2018).

The topic was chosen in order to cover informational gaps regarding this future therapeutic option: to date, there are no studies on long-term and very long-term remission support with LAIs, and there are no studies of therapeutic switch from LAI antipsychotics to oral antipsychotics. Also, there is no data on the concomitant treatment of stabilized patients with LAI versus oral antipsychotics, nor are there studies of the impact of the COVID-19 pandemic on LAI treatments.

CHAPTER 3 – SECOND GENERATION LONG ACTING INJECTABLE ANTIPSYCHOTICS

3.3 EFFICIENCY AND TOLERABILITY OF LAI

3.3.2 LAI versus oral antipsychotics

The meta-analysis of the first controlled clinical trials comparing FGA-LAI with oral medication, including more than 800 patients, found no difference in relapse rates, tolerability, and anticholinergic use, while clinical improvement was more significant in cases treated with LAI (Adams et al., 2001). A subsequent review concluded that the rate of relapse was significantly increased in patients treated with oral antipsychotics compared to those treated with LAIs (Schooler, 2003). Patients initiated on LAIs or switched from oral medication to LAI reported significant improvements, not only in schizophrenia symptoms control, but also in quality of life, satisfaction, and functioning (Kaplan et al., 2013). Leucht et al., in a systematic meta-analysis of long-term controlled clinical trials in schizophrenic outpatients, showed a lower risk of relapse (10% and 30% relative and absolute risk, respectively) and dropout due to inefficiency in the case of LAI compared to oral medication (C. Leucht et al., 2011). Kishimoto highlighted different study results depending on design (similar efficacy of LAI to oral antipsychotics in controlled clinical trials, and superiority in observational studies) (Kishimoto et al., 2014). Although the results of mirror studies have shown the superiority of LAI compared to oral antipsychotics in preventing hospitalization, the authors recommend caution in their interpretation, considering the possible biases (waiting bias, natural course of the disease, time effect) (Kishimoto et al., 2013).

3.3.3 LAI versus LAI

It has been shown that there is a significant improvement in psychotic symptoms and movement disorder-related symptoms after switching to risperidone LAI (Lasser et al., 2004; D. Taylor, 2009) and a significant reduction in the rate of hospitalizations compared to conventional LAIs (Grimaldi-bensouda et al., 2012). Patients treated with risperidone LAI had higher levels of satisfaction, health and sleep status, and better quality of life than those treated with haloperidol decanoate (Mihajlović et al., 2011). Switching from haloperidol decanoate to risperidone LAI can improve cognitive functions, including memory, executive functions, motor processing, and attention (Suzuki & Gen, 2012).

Olanzapine LAI and risperidone LAI have almost identical treatment completion rates at 12 months; however, conclusions are limited by differences between studies (Ascher-Svanum et al., 2012). The QUALIFY study (aripiprazole LAI versus paliperidone LAI) showed the superiority of aripiprazole LAI over paliperidone LAI in terms of discontinuation rate and adverse reactions (Naber et al., 2015). A meta-analysis of controlled clinical trials published between January 2002 and May 2013 showed that the fewest relapses occur with aripiprazole LAI and risperidone LAI, and discontinuations for any reason are lower with aripiprazole LAI. Compared with placebo, all LAIs increased the risk of weight gain and EEP; the extremes for weight gain are aripiprazole LAI and risperidone LAI, and for EEP olanzapine LAI and risperidone LAI, respectively (Majer et al., 2015).

3.3.5 Relapse and prevention of relapses

San et al concluded that, in univariate analysis, poor family support, disease duration greater than 5 years, number of previous hospitalizations, cocaine and cannabis use, and number of different classes of previous antipsychotic drugs, were risk factors for relapse. In multivariate analysis, the number of previous hospitalizations and the number of different antipsychotics previously used were significant predictors of relapse. Absence of cannabis use was a protective factor. Neither adherence to treatment in the past 3 years nor type of antipsychotic regimen was significantly associated with relapse (San et al., 2013). A cohort study published in 2020 mapped four predictors of relapse; treatment adherence was considered grade I and the strongest predictor of relapse (relapse rate for adherence vs. nonadherence: 22.9 vs. 55.7%, $p < 0.001$). The second-degree factor was occupational status (employed versus unemployed: 19.7 versus 42.7%, $p < 0.001$); the third-degree factors were daily living skills and household income (Mi et al., 2020).

For an effective relapse prevention, clinicians and the therapeutic team should consider the individual risk factors of each patient and address each one individually. In practice, treatment non-adherence is considered to be the most important modifiable factor influencing disease progression, on which therapeutic effort is focused. LAI treatments may reduce relapse rates in patients with schizophrenia. However, recent studies also show that, in patients stabilized on LAI treatment, who are in remission, the transition to the oral formulation is followed by a high rate of relapse (A.-A. Miron et al., 2022).

3.3.7 Cost-efficiency of LAI treatments

The annual costs of schizophrenia are £400 million in England and over $10 billion in the US (Weiden & Olfson, 1995). 40% of treatment-related costs for patients with schizophrenia are attributed to non-adherence to treatment (Byerly et al., 2007). Although LAIs have significantly higher costs than oral medication, patients who start this type of treatment will incur lower costs than those who receive oral treatment (J. Lin et al., 2013). In addition to the direct impact on hospitalization costs, reduced relapse rates and length of hospitalization may allow patients using LAI to have better social functioning, maintain employment with less absenteeism, and decrease substance abuse; all of which can contribute to lower indirect costs related to the disease, which in 2002 in the US were estimated at $32.4 billion (Wu et al., 2005).

A cost-effectiveness study from France concluded that paliperidone LAI is a cost-effective option in the treatment of schizophrenia (Druais et al., 2016). In Germany, a cohort study highlighted that initiation of LAI treatment resulted in reduced hospitalization rates and total costs (Mahlich et al., 2020). A recent meta-analysis demonstrated that LAI antipsychotics were associated with improved medication adherence and significant clinical benefits, such as reduced hospitalizations and emergency room admissions compared with oral antipsychotics. Lower medical costs offset higher pharmacy costs, resulting in a nonsignificant difference in total healthcare costs (D. Lin, Thompson-Leduc, et al., 2021).

3.4 LAI IN EARLY PHASE SCHIZOPHRENIA

A longer duration of untreated psychosis (DUP) correlates with poor clinical outcome, more severe positive and negative symptoms, lower likelihood of remission, reduced social functioning, and poorer global outcome. Long DUP does not correlate with employment, quality of life, or hospital treatment. The small but consistent correlation between long DUP and poor outcome indicates that early intervention in psychosis may have positive effects on the long-term course of the illness (Penttilä et al., 2014).

Most of the clinical and psychosocial impairments, cognitive decline, and progressive structural changes that occur in brain volume (Brugger et al., 2011) occur within the first 5 years after disease onset (Rocca et al., 2013). In this initial phase, early pharmacological intervention favorably affects symptomatic control and functional outcomes (Viala et al., 2012). Therefore, the primary goal of treatment during this period is to prevent further relapse and restore socio-occupational functioning to the premorbid level (S.-W. Kim et al., 2013).

3.5 LAI DURING PREGNANCY AND POSTPARTUM

Most of the data related to LAI use in pregnancy and postpartum come from case reports or case series, and the conclusions are still divided. According to Reutfors' 2020 study, the most frequently used antipsychotic in pregnancy was quetiapine, followed by olanzapine and risperidone (Reutfors et al., 2020). The research carried out in the Clinical Hospital of Psychiatry and Neurology Brașov by Assoc. prof. Dr. Teodorescu and Prof. Dr. Ifteni showed that olanzapine is safe for mother and fetus during pregnancy (Teodorescu et al., 2017), and in severe cases, the use of clozapine was also reported, with good results (Teodorescu et al., 2021). Cohort studies show minimal risks of atypical antipsychotic treatment to the mother and the absence of substantial teratogenic risks to the fetus (Damkier & Videbech, 2018; Habermann et al., 2013; Vigod et al., 2015). Discontinuation of treatment, on the other hand, leads in most cases to relapse (Ifteni et al., 2014).

Clinicians tend to discontinue LAI antipsychotics during pregnancy, even in patients at extremely high risk of relapse. In the cases reported to date, no major complications in the mother or newborn have been identified (O'Sullivan et al., 2022). Recently, the first series of 6 cases of pregnant women treated with aripiprazole LAI was published, showing good results (Fernández-Abascal et al., 2021).

According to a guideline published in 2020, the appropriate patient to receive an LAI during pregnancy should not differ significantly from the appropriate patient to receive an LAI when not pregnant. In summary, it is recommended that a patient on LAI treatment who wants pregnancy or becomes pregnant can continue treatment if there is no major contraindication, and factors suggestive of a benefit of LAI are non-adherence to treatment, frequent and prolonged hospitalizations, decompensations during previous pregnancies or postpartum, and illicit substance use (Reinstein et al., 2020).

3.6 LAI DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic generated major effects on the entire medical system. Globally, changes in psychotropic prescribing have undergone significant changes during the COVID-19 pandemic (Leong et al., 2022; Maguire et al., 2022). Prof. Dr. Ifteni et al. reported that administration of LAI has been suspended or decreased in some areas, even though it is a necessary treatment that should be continued (Ifteni et al., 2020). A minor decrease in LAI treatment administrations was found in Pittsburgh (Gannon et al., 2020). In Canada, LAI prescription rates remained stable during the COVID-19 pandemic and transitions from PP1M to PP3M increased significantly during the pandemic (McKee et al., 2021). In Romania, the restrictions imposed by the COVID-19 pandemic caused a significant decrease in the number of LAI initiations (A. A. Miron et al., 2022).

3.7 CONCLUSIONS

Evidence of the superiority of LAI treatments is continuously accumulating in the literature, yet controversy persists around them (Kane et al., 2021). As a result, globally, this type of treatment is still under-utilized (Parellada & Bioque, 2016). Implementation of standardized tools in the selection of the target population, such as the ROLIN index (Ifteni et al., 2021) and appropriate education of clinicians (by increasing awareness of the evidence regarding the potentially favorable benefit-risk ratio for LAI antipsychotic drugs compared to oral formulations) may lead to greater use of this type of treatment (Paton, Okocha, et al., 2022).

CHAPTER 4- PRACTICAL PART

4.1 WORKING HYPOTHESES/ OBJECTIVES

As shown in the previous chapters, in the current state of knowledge regarding the treatment of LAI, many controversies persist and, for various reasons, the treatment is prescribed to a small percentage of patients with schizophrenia. As a result, the doctoral thesis aims to, through 4 studies, bring additional data in this field. The first study starts from the hypothesis that LAI treatment is superior in relapse prevention compared to oral treatment and aims to analyze the long-term effectiveness of LAI. The second study starts with the question What is the evolution of patients after switching from LAI treatment to oral treatment? The objective of the second study is to highlight the therapeutic switch effect from LAI to oral treatment. The third study started from the hypothesis that an effective antipsychotic treatment should be sufficient in monotherapy to control the symptoms of the disease; therefore, the primary objective was to evaluate concomitant mood stabilizer and benzodiazepine treatments in patients stabilized on LAI antipsychotics versus those stabilized on oral antipsychotics. The fourth study started from the reality of the fact that the COVID-19 pandemic significantly affected the entire health system, in Romania and worldwide. The objective of the study was to investigate the impact of the COVID-19 pandemic on LAI treatments.

4.2 GENERAL METHODOLOGY

The studies carried out in the present thesis were of a non-interventional type. All patients in the four studies were diagnosed with schizophrenia according to DSM-5 criteria. All patients included in the research were over 18 years old; the studies did not establish a maximum age as an inclusion/exclusion criterion; all were admitted voluntarily and signed an informed consent regarding participation in the study. Inclusion and exclusion criteria were clearly defined for each study and were met by all participants. All the research within the thesis was approved by the Ethics Committee of the Clinical Hospital of Psychiatry and Neurology Brașov (Opinion no. 3/26.09.2018). For the calculation of statistical significance, t-test, F-test, or Chi-square test were used as appropriate. The results were analyzed using SPSS version 20.00. Adjusted odds ratio (AOR) was calculated with 95% confidence interval using the t-test method. Multivariable logistic regression was used to indicate significant associations where appropriate. p values below 0.05 were considered statistically significant.

4.3 Study 1. HIGHLIGHTING THE LONG-TERM EFFECTIVENESS OF LAIs

4.3.2 Working hypothesis/objectives

The present study started from the hypothesis that LAI type antipsychotic treatments are superior to oral ones in terms of treatment adherence and relapse prevention. The primary objective of the study was to assess the efficacy, safety profile and sustained remission in patients diagnosed with schizophrenia treated with SGA-LAI antipsychotics. The secondary objective was to evaluate the actual percentage of patients who are prescribed LAI treatments.

4.3.3 Materials and methods

4.3.3.1 Study design

We conducted an observational study with a retrospective design with a follow-up period of 60 months. The study included patients diagnosed with schizophrenia according to DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM., 2013). The patients were enrolled in the study from January 1, 2012, to December 31, 2013. During the 2 years, data were collected from the general clinical observation sheets of patients admitted to the Brașov Clinical Hospital for Psychiatry and Neurology, Psychiatry II, and Clinical Psychiatry III wards. The patients were subsequently followed for a period of 5 years. Among the SGA-LAIs existing at the time, olanzapine, risperidone, and aripiprazole were selected for the final analysis, since FGA-LAIs are not the subject of the present thesis and the number of patients treated with paliperidone LAI was too small to be included in the final analysis.

4.3.3.8 Statistical analysis

Demographic, clinical, and biochemical characteristics of patients treated with the study LAI antipsychotics (SGA-LAI group) and their oral counterparts (OAP group) were compared using

analysis of variance. The primary outcome was the time in months to relapse in the SGA-LAI group compared with the OAP group. To compare means, we used t-test to calculate statistical significance. To compare proportions, we used the Chi-square test. A p-value below 0.05 is considered statistically significant.

4.3.4 Results

Between 01.01.2012 and 31.12.2013, a total of 560 patients diagnosed with schizophrenia were admitted to the Psychiatry II and Clinical Psychiatry III departments of the Brașov Clinical Hospital for Psychiatry and Neurology. Among them, 102 patients (18.21%), who were offered SGA-LAI treatment (olanzapine LAI, risperidone LAI or aripiprazole LAI), met the inclusion-exclusion criteria in our study. Among them, 52 patients (50.98%) agreed to LAI treatment (defined as the SGA-LAI group), and 50 patients (49.02%) preferred to continue oral antipsychotic treatment (defined as the OAP group). The demographic characteristics of the two groups are detailed in Table 2.

Table 2. Demographic characteristics of the SGA-LAI and OAP groups

Parameters		SGA-LAI (N=52)	OAP (N=50)	p value
Male (N, %)		22 (43.3%)	24 (48%)	0.93
Age (years; mean±SD)		44.75±11.22	42.32±4.12	0.76
Age of onset (years; mean±SD)		23.44±4.17	24.20±6.78	0.88
Duration of illness (years; mean±SD)		16.22±15.33	17.29±16.65	0.92
Reason for admission	Non-adherence (N, %)	36 (69.2%)	33 (66%)	0.89
	Alcohol abuse (N, %)	12 (23.1%)	11 (22%)	0.91
Number of hospitalizations (all life) (N, SD)		10.67±5.38	12.60±3.65	0.7
Number of hospitalization days (all life) (days, SD)		456.56±120.20	444.20±140.76	0.11
Duration of evaluation (months, mean ±SD)		55±5.6	52±7.8	0.62
Educational status	Under 8 years	8.82%	6.66%	0.74
	9- 12 years	70.58%	76.66%	0.58
	Over 12 years	20.60%	16.68%	0.69
Marital status	Married	23.52%	20%	0.73
	Necăsătorit	70.58%	50%	0.09
	Divorced	5.90%	23.33%	0.04
	Widow	0.00%	6.66%	0.12
Professionall status	Employed	8.82%	6.66%	0.74
	Retired	88.23%	83.33%	0.57
	No occupation	2.95%	0.00%	0.34
	Unemployed	0.00%	3.33%	0.28

Smokers		32.35%	40%	0.52
Comorbidities	Arterial hypertension	5.88%	20%	0.09
	Diabetes mellitus	8.82%	0.00%	0.09
	Cardiovascular disease	0.00%	23.33%	0.003
	Inflammatory disease	5.88%	3.33%	0.63

The distribution of the two groups, both in number and in average age and sex, is relatively uniform. There is no statistically significant difference between the mean ages in the SGA-LAI group compared to the OAP group (p= 0.76). The age of onset of the disease, as well as the duration of the disease, is also similar in the two groups (23.44±4.17 in the SGA-LAI group versus 24.20±6.78 in the OAP group, p=0.88, respectively 16.22±15.33 in the SGA-LAI group compared to 17.29±16.65 in the OAP group, p=0.92).

In most cases, patients were hospitalized for psychotic relapses due to non-adherence to treatment, both in the SGA-LAI group (69.2%) and in the OAP group (66%), without showing a statistically significant difference in the rate of non-adherence between the two lots. A smaller percentage of patients in both groups were readmitted for episodes related to alcohol abuse (23.1 in the SGA-LAI group, 22% in the OAP group respectively).

Also, no statistically significant differences were observed in total lifetime hospitalizations or lifetime total hospital days between the two study groups.

In the SGA-LAI group, 20 patients continued treatment with olanzapine LAI, 22 patients with risperidone LAI, and 10 patients with aripiprazole LAI. The distribution of patients in the SGA-LAI group according to the type of antipsychotic is illustrated in Figure 4.

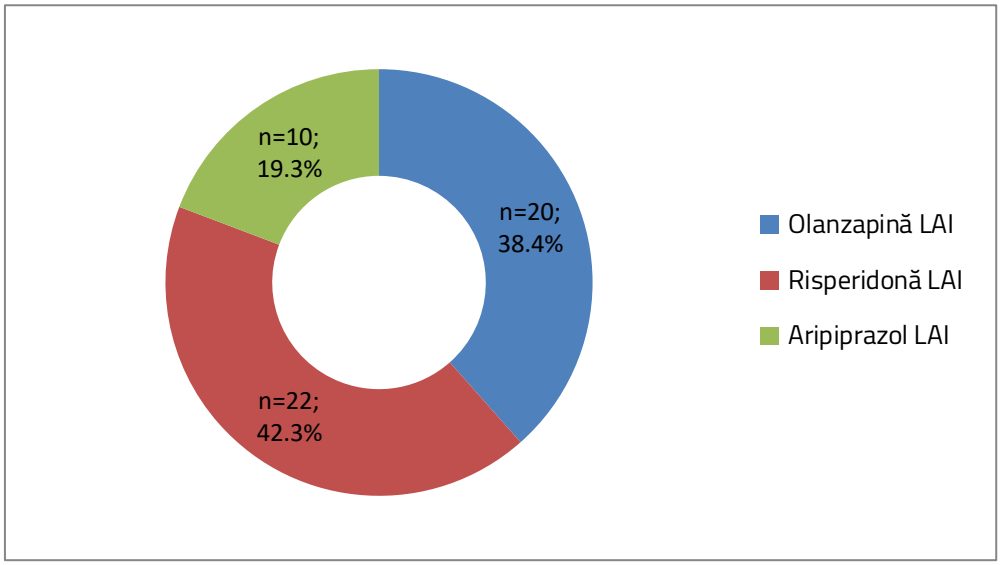

Figure 4. Distribution of patients in the SGA-LAI group according to the type of antipsychotic

In the OAP group, 16 patients continued treatment with oral olanzapine, 20 patients with oral risperidone, and 14 patients with oral aripiprazole. The distribution of patients in the OAP group according to the type of antipsychotic is illustrated in Figure 5.

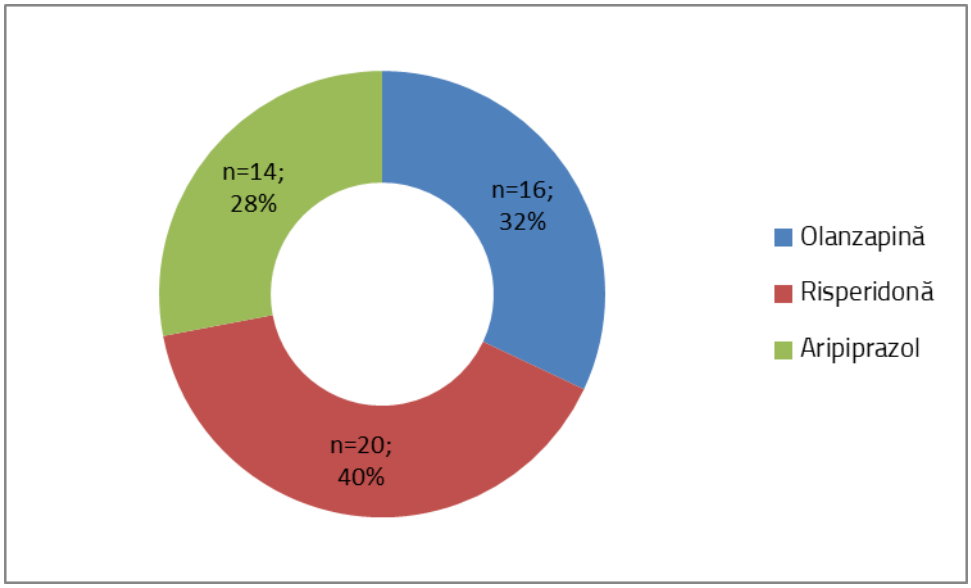

Figure 5. Distribution of patients in the OAP group according to the type of antipsychotic

There was no statistically significant difference between the proportions of patients who accepted LAI treatments versus those who remained on oral treatment, for any of the three antipsychotics studied.

The antipsychotic treatment history of the patients in the two study groups is detailed in Table 6.

Table 6. Previous treatments of patients in the study groups

Previous treatment	SGA-LAI	OAP	p value
olanzapine (N, %)	44 (84.16%)	43 (86%)	0.96
risperidone (N, %)	10 (19.23%)	12 (24%)	0.15
aripiprazole (N, %)	3 (6%)	4 (8%)	0.12
number of previous antipsychotics (mean)	4.3	5.2	0.8

There were no statistically significant differences between the two groups regarding the type of previous medication or the number of previous antipsychotics.

We noted that patients in the SGA-LAI group had significantly less concurrent treatment with mood stabilizers and/or benzodiazepines compared to the OAP group. Also, in the case of the other evaluated concomitant medications (antipsychotics, anticholinergics, hypnoinducers, antidepressants), the percentages were lower in the SGA-LAI group, but without statistical significance. The concomitant treatments of patients in the SGA-LAI group compared to the OAP group are illustrated in Table 7.

Table 7. Concomitant treatment in the study groups

Concomitent treatment type	SGA-LAI	OAP	P value
Mood stabilizers (%)	17.64%	60%	0.0005
Benzodiazepines (%)	11.76%	63.33%	< 0.0001
Anticholinergics (%)	5.88%	26.66%	0.0234
Antipsyhotics (%)	8.82%	13.33%	0.56
Hypnotics (%)	11.76%	20%	0.36
Antidepressants (%)	8.82%	0.00%	0.09

The number of all-cause psychiatric relapses and hospitalizations observed during the follow-up period is detailed in Table 8.

Table 8. Relapses and hospitalizations in the study groups

	SGA-LAI group (N=52)	OAP group (N=50)	P value
Relapses (N, %)	12 (23.07%)	23 (46%)	**0.0152**
Hospitalizations (N, %)	15 (28.84%)	30 (60%)	**0.0016**

The uniqueness of the study lies in the fact that the patients were followed for a period of 60 months after enrollment. We noted that in the SGA-LAI group, both the number of relapses and psychiatric hospitalizations during the 5-year follow-up period is significantly lower compared to the OAP group ($p < 0.05$).

4.3.6 Conclusions

To date, this is the only long-term (5-year) efficacy study of extended-release injectable olanzapine, risperidone, and aripiprazole compared with oral antipsychotics. The study confirmed the working hypothesis, i.e., demonstrated the superior effectiveness of the SGA-LAI studied compared to oral antipsychotics in the prevention of relapses and hospitalizations. In addition, the study showed that SGA-LAI-treated patients had fewer concomitant treatments with anticholinergics, mood stabilizers, and benzodiazepines, which may suggest their superiority in tolerability over oral antipsychotics. Further research, namely controlled clinical trials, is needed to clarify this assumption.

4.4 Study 2. HIGHLIGHTING THE EFFECT OF SWITCH FROM LAI TO ORAL ANTIPSYCHOTICS

4.4.2 Working hypothesis/objectives

The present study started from the premise that LAI treatments provide superior adherence to oral antipsychotics, as a result patients will benefit from a longer period of remission under LAI treatment. The working hypothesis of the study is that, when switching from LAI treatment to oral treatment, patients will experience psychotic relapses, mainly due to the recurrence of the non-adherence phenomenon. The primary objective of the present study is to evaluate the transition effect (or therapeutic switch) from an SGA-LAI type treatment to an oral antipsychotic treatment, with a focus on olanzapine LAI.

4.4.3 Materials and methods

4.4.3.1 Study design

We conducted an observational study with a prospective design, which included patients diagnosed with schizophrenia, according to DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM., 2013), registered in the documents of the Clinical Hospital of Psychiatry and Neurology Brasov. The enrollment period was between 01.03.2020 and 31.03.2020. The patients registered in March 2020, who satisfied the inclusion-exclusion criteria in the study, were divided into two study groups: those who remained on olanzapine LAI - the OLZ-LAI group, and those who preferred to switch to oral olanzapine - the O-OLZ group. Both groups were followed for 12 months.

4.4.3.7 Statistical analysis

Demographic, clinical and olanzapine-related characteristics of patients treated with OLZ-LAI and O-OLZ were calculated using basic statistics. Variable scores before and after exposure to OLZ-LAI were compared using the variance ratio test (F test). For calculation of statistical significance, comparison of proportions, t-test and Chi-square test were used. Statistical significance was set at $p < 0.05$ bilaterally.

4.4.4 Results

Between 01.03.2020 and 31.03.2020, a total of 231 patients were registered in the documents of the Clinical Hospital for Psychiatry and Neurology of Brașov. Of these, 27 patients were stabilized on olanzapine LAI treatment. On March 15, 2020, a state of emergency was declared on the territory of Romania, as a result of which access to hospitals was strictly limited to emergencies, the compartment that ensured the free administration of LAI treatments was closed, and the hospital administration of LAI treatments was suspended. Patients were referred for LAI administrations to other locations (e.g. private clinics). Due to the impossibility of continuing administration under these conditions (in private clinics, the cost of an injection can reach 100 RON, the working hours in private offices, longer distances, the anxiety generated by the new situation), 21 of the patients preferred to be switched from OLZ-LAI to oral olanzapine (group O-OLZ). Only 6 patients agreed to continue treatment with the long-acting formula (OLZ-LAI group). Demographic and clinical characteristics of the patients are shown in Table 9.

Table 9. Demographic and clinical characteristics of the study groups

Characteristics	O- OLZ group (n=21)	OLZ-LAI group (n=6)	P value
Age (years, mean, SD)	42.52 ± 10.15	49.5 ± 11.29	0.15
Male (n, %)	9 (42.85%)	2 (33.3%)	0.68
Smokers (n, %)	11 (52.38%)	3 (50%)	0.94
Age of onset (years, mean, SD)	24.52 ± 4.45	23.45 ± 4.66	0.61
Duration of illness (years, mean, SD)	18 ± 9.70	19.3 ± 11.1	0.78
Duration of illness before OLZ-LAI (years, mean, SD)	11.42 ± 8.26	9.06 ± 7.99	0.54
Number of episodes before initiating OLZ-LAI (mean ± SD)	7.38 ± 2.15	8.41 ± 2.04	0.77
Number of episodes after initiating OLZ-LAI (mean ± SD)	0.57 ± 0.67	0.53 ± 0.74	0.12

The mean age of the patients, as well as the gender distribution, is similar in the two study groups. More than 50% of patients are smokers. The total duration of illness is similar in the two groups. It is noted that the duration of illness before initiation of OLZ-LAI is longer in the O-OLZ group, but without statistical significance. The number of disease episodes before initiation of OLZ-LAI was also similar in the two groups, but a statistically significant difference was observed in the number of episodes recorded before and after initiation of olanzapine LAI in both groups.

The 21 patients in the O-OLZ group started oral olanzapine treatment 30 days after the last OLZ-LAI administration according to the model shown in Table 12. The patients in the OLZ-LAI group continued the treatment without changing their doses.

Table 12. OLZ-LAI and O-OLZ doses

OLZ-LAI dose (mg/month)	Oral dose equivalent (mg/day)	Switch dose O-OLZ (mg/day)
600 (300 mg every 2 weeks)	20	20
420 (210 mg every 2 weeks)	15.55	15
405 (405 mg every 4 weeks)	15	15
300 (300 mg every 4 weeks)	10	10

The most commonly used dose in the study groups was 300 mg every 4 weeks. Group characteristics by initiation, duration and doses of OLZ-LAI are detailed in Table 13.

Table 13. Characteristics related to olanzapine-LAI in the study groups

Parameters		O-OLZ group (n=21)	OLZ-LAI group (n=6)	P value
Reason for initiating OLZ-LAI	Non-adherence (n, %)	17 (80.95%)	5 (83.3%)	0.90
	Adverse effects to other antipsychotics	3 (14.28 %)	1 (16.7%)	0.94
	Switch from clozapine	1 (4.77 %)	-	-
Age of initiation OLZ-LAI (years, mean, SD)		36.42 ± 10.09	33.56 ± 9.2	0.53
Duration of OLZ-LAI (years, mean, SD)		6.09 ± 1.51	5.56 ± 1.88	0.52
OLZ-LAI doses	210 mg every 2 weeks (n, %)	2 (9.52%)	-	-
	300 mg every 4 weeks (n, %)	11 (52.38%)	3 (50%)	0.91
	300 mg every 2 weeks (n, %)	6 (28.58%)	1 (16.7%)	0.81
	405 mg every 4 weeks (n, %)	2 (9.52%)	2 (33.3%)	0.61

During our study period, the most unchanged dose over time was 300 mg every 2 weeks. During the entire treatment period, the LAI group received more than 1000 injections, and only seven PDSS of mild intensity (sedation, confusion, slurred speech) were recorded, all of which recovered completely. All but one patient continued treatment with olanzapine LAI after the mentioned event.

The outcomes of patients who were switched from OLZ-LAI to oral olanzapine were not favorable; these are illustrated in Figure 8.

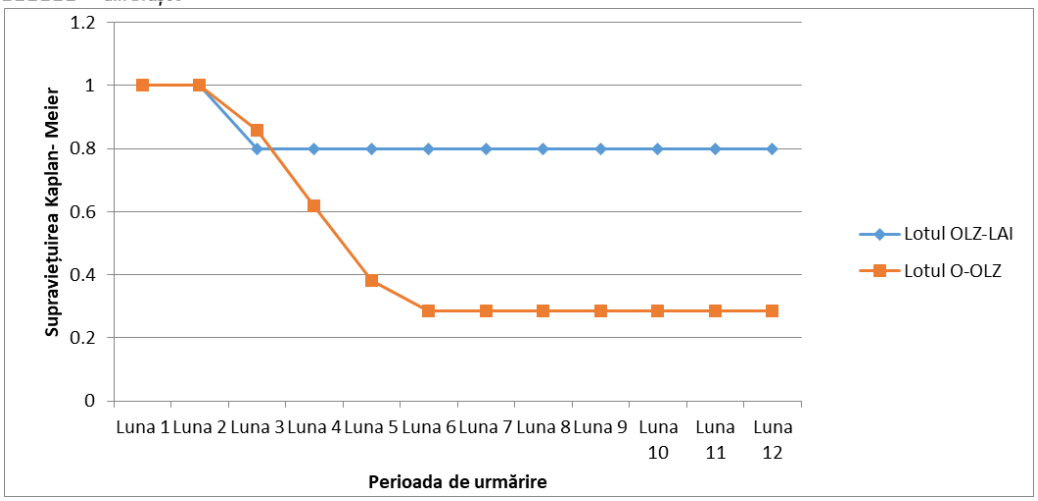

Figure 8. Kaplan-Meier survival curve

During the following 12 months of follow-up, 15 patients (71.4%) in the O-OLZ group had relapses, all occurring in the first 6 months of follow-up. Moreover, 12 patients (80%) required psychiatric hospitalization for the management of the psychotic episode. In the OLZ-LAI group, there was only one patient relapse, in the third month of follow-up (16.6%). From the sixth month until the end of the 12-month follow-up period, there were no further relapses in either group.

There was no statistically significant difference in the doses administered to patients who relapsed compared to the doses of the 6 patients who remained in remission (mean dose 361.1 mg ± 102.4 SD vs. 417.5 mg ± 134.9, p = 0.27).

The main limitation of the study is the small sample size. The strengths of the study lie in the patient characteristics (quality and long remission and long duration of olanzapine LAI treatment) and the long follow-up period.

4.4.6 Conclusions

The study confirmed the working hypothesis, namely the fact that, regardless of the duration of the previous period of remission, patients who switched from the LAI antipsychotic on which they were stabilized, respectively olanzapine LAI, to the oral antipsychotic, relapsed in the vast majority of cases. Our study demonstrates that nonadherence can recur at any time during the course of the disease, and long periods of remission cannot be considered a protective factor for relapses. The COVID-19 pandemic has had a significant impact on the healthcare system, globally, and has had dire consequences on current medical practice. One of the consequences of the restrictions during the pandemic was the abandonment of LAI treatments on which patients were stable, which led to patients with long periods of stable remission relapsing after being switched to oral treatment.

4.5 Study 3. CONCOMITANT TREATMENT OF PATIENTS STABILIZED ON LAIs

4.5.2 Working hypothesis/objectives.

The study's working hypotheses are that the need for concurrent treatment for schizophrenic patients stabilized on antipsychotics derives from insufficient control of symptoms by antipsychotic monotherapy and the fact that LAI treatments have a superior therapeutic benefit compared to oral ones. Therefore, we could assume that patients stabilized on LAI-type antipsychotic treatments have a lower need for concomitant treatments. Based on these hypotheses, the primary objective was to assess whether there is any difference in the use of concomitant medication between patients stabilized on LAI antipsychotics versus those stabilized on oral antipsychotics. The secondary objective of the study was to assess the actual percentage of schizophrenic patients, stabilized on an antipsychotic, who are on long-term concomitant treatments.

4.5.3 Materials and methods

4.5.3.1 Study design

We conducted an observational study with a cross-sectional design, which included patients diagnosed with schizophrenia, according to DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM., 2013). The study was designed as a prevalence study, and its primary aim was to assess the prevalence of concurrent psychotropic medication use among patients stabilized on LAI antipsychotics versus oral antipsychotics. The enrollment period was between 01.06.2021 and 01.06.2022.

4.5.3.7 Statistical analysis

For the calculation of equivalent doses of chlorpromazine we used equivalence tables (Atkins et al., 1997; Inada & Inagaki, 2015) and the consensus method of Gardner et. al (Gardner et al., 2010; S. Leucht et al., 2015). In the case of atypical LAI, we converted to the equivalent oral dose, then to chlorpromazine. To compare means, we used t-test to calculate statistical significance. To compare proportions, we used the Chi-square test. A p-value below 0.05 is considered statistically significant.

4.5.4 Results

Between 01.06.2021 and 01.06.2022, a total of 315 patients who met the inclusion-exclusion criteria were enrolled. Among them, 77 (24.44%) patients were stabilized on LAI treatment (LAI sub-group) and 238 (75.56%) patients on oral treatment (OAP sub-group); The characteristics of the LAI and OAP batches are summarized in Table 15.

Table 15. Characteristics of LAI and OAP lots

Parameters	LAI	OAP	P value
Total patients (n, %)	77 (24.44%)	238 (75.56%)	p< 0.0001
Male (n, %)	34 (44.15%)	96 (40.34%)	p=0.55
	52.92	51.32	p=0.28

Mean age (±SD)		(±12.24 SD)	(±11.10 SD)	
Patients receiving benzodiazepines (nr, %)	Total	29 (37.66%)	90 (37.81%)	p= 0.98
	Male	11 (37.93%)	34 (37.77%)	p= 0.98
	Female	18 (62.07%)	56 (62.23%)	p= 0.93
Patients receiving mood stabilizers (nr, %)	Total	16 (20.77%)	68 (28.57%)	p= 0.17
	Male	8 (50%)	32 (47.05%)	p= 0.83
	Female	8 (50%)	36 (52.95%)	p= 0.83
Patients receiving benzodiazepines and mood stabilizers (nr, %)	Total	10 (12.98%)	29 (12.18%)	p= 0.85
	Male	5 (50%)	15 (51.72%)	p= 0.92
	Female	5 (50%)	14 (48.28%)	p= 0.92
Antipsychotic type	olanzapine (n, %)	5 (6.49%)	70 (29.41%)	p<0.0001
	risperidone (n, %)	16 (20.77%)	31 (13.02%)	p= 0.09
	paliperidone (n, %)	9 (11.68%)	17 (7.14%)	p= 0.20
	aripiprazole (n, %)	9 (11.68%)	24 (10.08%)	p= 0.69
	quetiapine (n, %)	-	24 (10.08%)	-
	amisulpride (n, %)	-	20 (8.40%)	-
	ziprasidone (n, %)	-	1 (0.42%)	-
	haloperidol (n, %)	0	22 (9.24%)	-
	flupenthixol (n, %)	36 (46.75%)	-	-
	zuclopenthixol (n, %)	2 (2.59%)	-	-
	levomepromazine (nr, %)	-	3 (1.26%)	-
	tiapridal (nr, %)	-	1 (0.42%)	-
	clozapine (nr, %)	-	66 (27.73%)	-

In the FGA-LAI group, the maximum number of females is found in the 50-59 age group (8 patients), and the maximum number of males is recorded in the over 60 age group (9 patients). In the SGA-LAI group, the maximum number of males are found in the 30-39 age group (7 patients), and the maximum number of females are in the 50-59 age group (9 patients). In the OAP group, the maximum number of females is found in the 40-49 age group (48 patients), and the maximum number of Males in the 50-59 age group (28 patients).

18 patients (5.71%) were stabilized on combined antipsychotic, LAI and oral treatment. In the LAI group, 39 patients (50.64%) were stabilized with second-generation LAI antipsychotics (SGA-LAI group), and 38 patients (49.36%) with first-generation LAI antipsychotics (FGA-LAI group). Patients stabilized on SGA-LAI treatment represent 12.38% of all patients in the study (Figure 14).

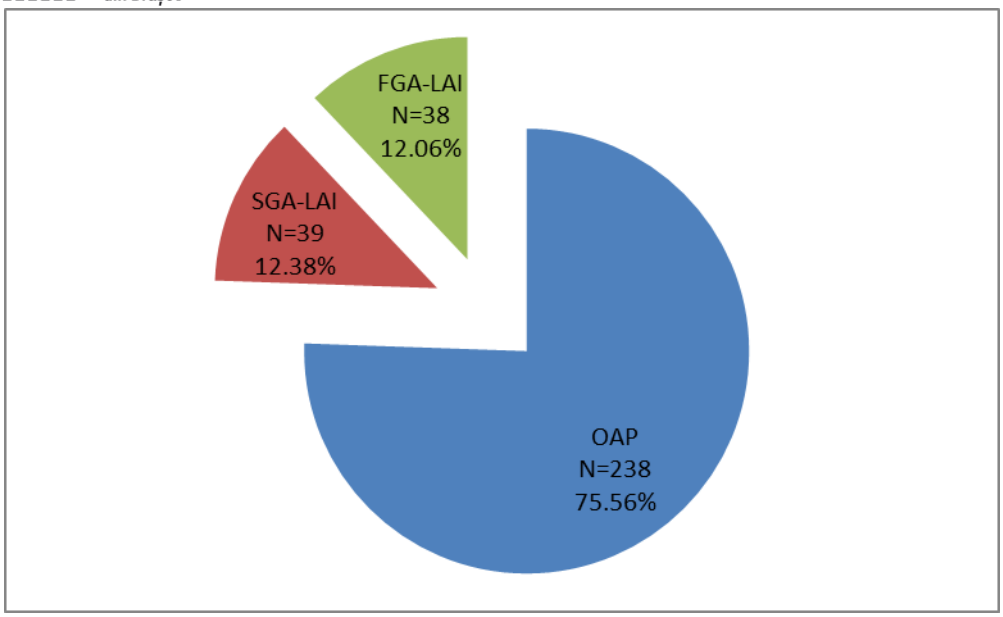

Figure 14. Percentage of patients stabilized with SGA-LAI, FGA-LAI and OAP

The distribution of patients by type of LAI antipsychotic treatment is illustrated in Figure 15.

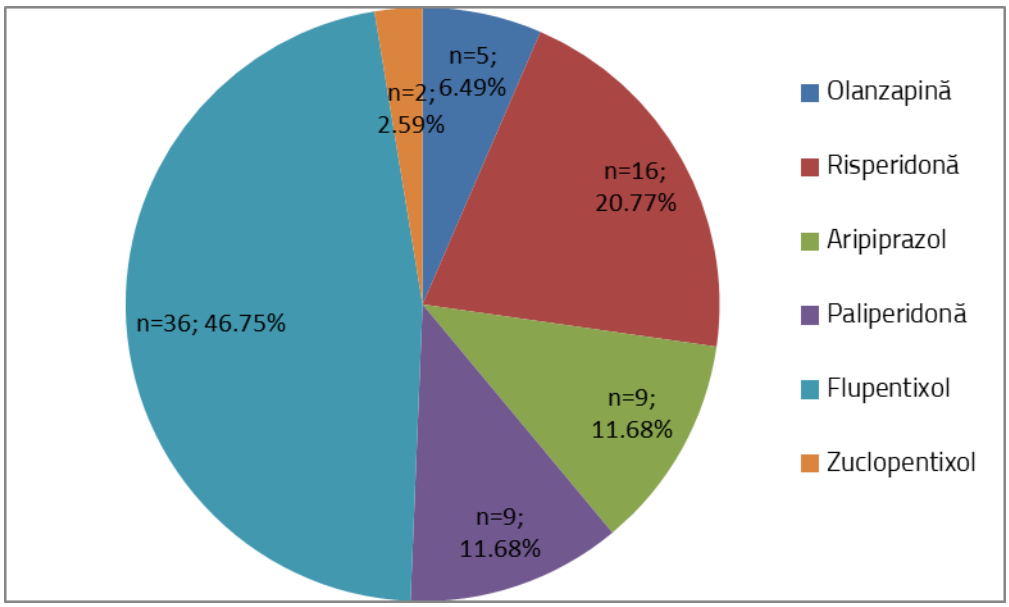

Figure 15. Distribution of patients in the LAI group according to the type of antipsychotic

Among oral antipsychotics, olanzapine is most frequently prescribed (29.41%), followed by clozapine (27.73%).

The distribution of patients according to the type of oral antipsychotic treatment is illustrated in Figure 16.

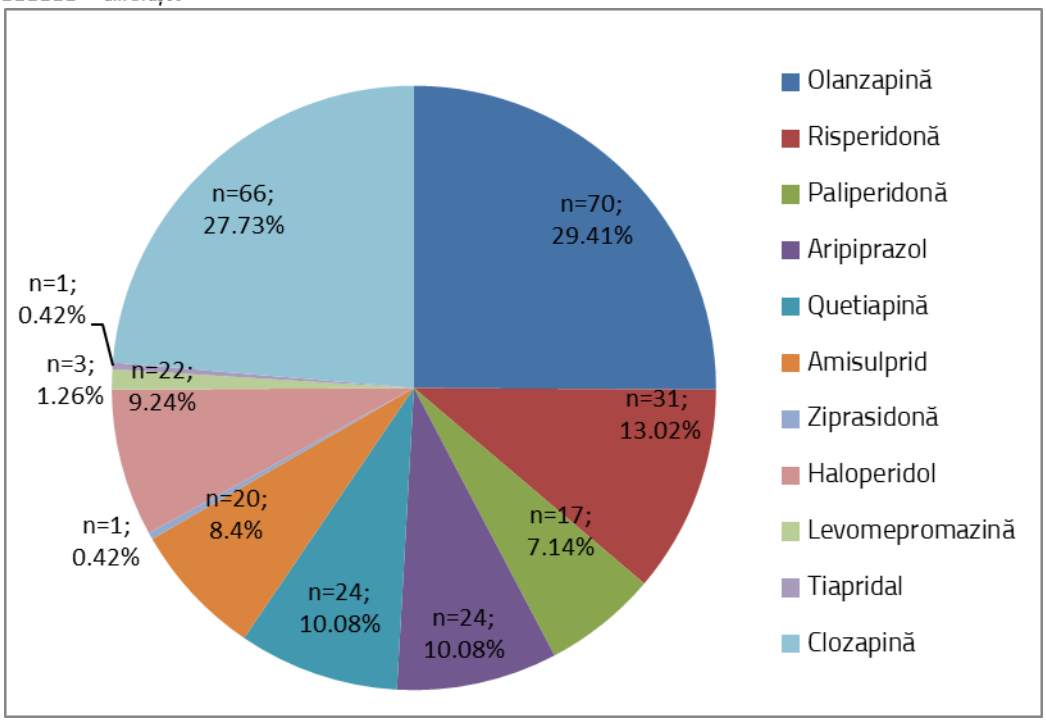

Figure 16. Distribution of patients in the OAP group according to the type of antipsychotic

In the FGA-LAI group, 36 patients (94.73%) were stabilized on flupenthixol treatment, and 2 patients (5.27%) on zuclopenthixol treatment.

In the SGA-LAI group, the distribution of patients by antipsychotic is illustrated in Figure 17.

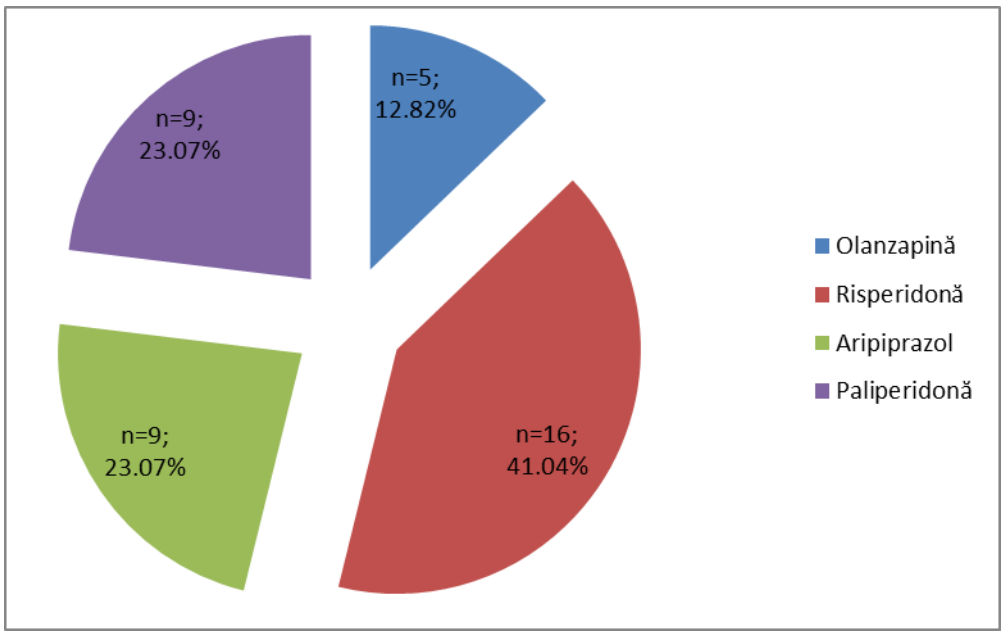

Figure 17. Distribution of patients in the SGA-LAI group according to antipsychotic

For oral antipsychotics that have corresponding LAIs, the comparison of proportions was calculated separately for each antipsychotic. The only statistically significant difference observed was in the case of olanzapine, which is used in a significantly higher proportion in its oral form compared to the LAI form ($p < 0.0001$).

Mean doses used in the LAI and OAP groups were calculated for each type of antipsychotic. In order to be able to make a comparison between average doses, the equivalent of chlorpromazine is used. The doses of antipsychotics used in the two groups are shown in Table 20.

Table 20. Average doses of antipsychotics

Antipsyhotic (type, formulation)		Number of cases	Mean dose (mg)	Equivalent oral dose (mg)	Chlorpromazine equivalent (mg)	P value
olanzapine	LAI	5	480 (± 164.31)	16 (± 5.47)	320	p= 0.66
	OAP	70	15 (±5)	15 (±5)	300	
risperidone	LAI	16	76.56 (±24.94)	3.06 (±0.99)	306	p =0.21
	OAP	31	3.58 (±1.50)	3.58 (±1.50)	358	
aripiprazole	LAI	9	400	20	266.66	p =0.22
	OAP	24	16.875 (±7.49)	16.875 (±7.49)	225	
paliperidone	LAI	9	180.55 (± 152.97)	9.66 (±1.32)	483	p =0.0050
	OAP	15	7.4 (±1.91)	7.4 (±1.91)	370	
quetiapine	LAI	-	-	-	-	NA
	OAP	24	491.66 (±224.89)	-	655	
amisulpride	LAI	-	-	-	-	NA
	OAP	20	500 (±247.08)	-	290	
ziprasidone	LAI	-	-	-	-	NA
	OAP	1	120	-	200	
haloperidol	LAI	-	-	-	-	NA
	OAP	22	3.52	-	176	

			(±1.61)			
flupenthixol	LAI	36	35 (±8.78)	-	100	NA
	OAP	-	-	-	-	
zuclopenthixol	LAI	2	200	-	100	NA
	OAP	-	-	-	-	
levomepromazine	LAI	-	-	-	-	NA
	OAP	3	54.16 (±7.21)	-	54.16	
tiapridal	LAI	-	-	-	-	NA
	OAP	1	100	-	100	
clozapine	LAI	-	-	-	-	NA
	OAP – Total	66	272.72 (±126.51)	-	272.72	
	OAP – Clozapine alone	53	297.64 (±128.56)		297.64	

A statistically significant difference between the dose of the oral antipsychotic and its LAI form was observed only for paliperidone. It is also noted, comparing the equivalent doses of chlorpromazine, that in the case of FGA-LAI antipsychotics the doses are lower. The highest equivalent dose of chlorpromazine is quetiapine.

Of the 315 patients, a total of 84 patients (26.66%) were under treatment with mood stabilizers, respectively sodium valproate; no patient with concomitant treatment with carbamazepine, lamotrigine or other mood stabilizers was identified. From the LAI group, 16 patients (20.77%) received mood stabilizers, and from the OAP group, 68 patients (28.57%) were identified. The prevalence of the use of mood stabilizers in the two groups and the Odds Ratio (OR) were calculated from the corresponding contingency tables, resulting as follows: prevalence of mood stabilizers in the LAI group = 0.20, prevalence of mood stabilizers in the OAP group = 0.28, OR = 0.65.

We applied the Chi-square test to calculate the p-value and to detect any statistically significant difference. Taking into account the prevalences of the use of mood stabilizers between the OAP group and the group of patients stabilized on LAI (regardless of its type), we did not observe a statistically significant difference between the prevalences of the use of mood stabilizers in the two groups.

We also verified the existence of significant differences in mood stabilizer treatment between the SGA-LAI, FGA-LAI and OAP groups. In the SGA-LAI population, 9 patients (23.07%) received mood stabilizer, and in the FGA-LAI population, 7 patients (18.42%) were identified. Comparing the percentages, we found that the differences are not statistically significant neither between the SGA-LAI population compared to the FGA-LAI (p=0.61; OR= 1.32), nor between the SGA-LAI population compared to the OAP (p=0.47; OR=0.75).

Of the 315 patients, 119 (37.77%) were on benzodiazepine treatment. 8 patients (2.53%) had concurrent treatment with more than one benzodiazepine. There is no statistically significant difference between the prevalence of benzodiazepine use in the two groups. Although it is noted that there were fewer patients with concomitant benzodiazepine treatment in the SGA-LAI group compared to the FGA-LAI group, the difference is not statistically significant. We also compared the prevalence of benzodiazepines in the SGA-LAI sub-group (28.20%) versus the OAP group (37.80%), but here too no statistical significance was revealed (p = 0.24; OR = 0.64).

Seven types of benzodiazepines (diazepam, alprazolam, lorazepam, clonazepam, bromazepam, nitrazepam and cinolazepam) were used in the study population. No patients treated with medazepam, temazepam, tetrazepam or midazolam were identified. The types of benzodiazepines, with the related percentages, used in the LAI and OAP groups, respectively, are illustrated in Table 28.

Table 28. Types of benzodiazepines

	diaze-pam	alprazo-lam	loraze-pam	clonaze-pam	bromaze-pam	nitraze-pam	cinolaze-pam
SGA-LAI (nr, %)	4 (10.25%)	1 (2.56%)	3 (7.69)	2 (5.12%)	1 (2.56%)	1 (2.56%)	1 (2.56%)
FGA-LAI (nr, %)	8 (21.05%)	0	8 (21.05%)	1 (2.63%)	1 (2.63%)	0	1 (2.63%)
OAP (nr, %)	43 (18.06%)	4 (1.68%)	49 (20.58%)	16 (6.72%)	2 (0.84%)	0	1 (0.42%)

We noted that in the subgroup SGA-LAI there are fewer patients who have concomitant treatment with diazepam or lorazepam compared to the subgroup FGA-LAI (Figure 18).

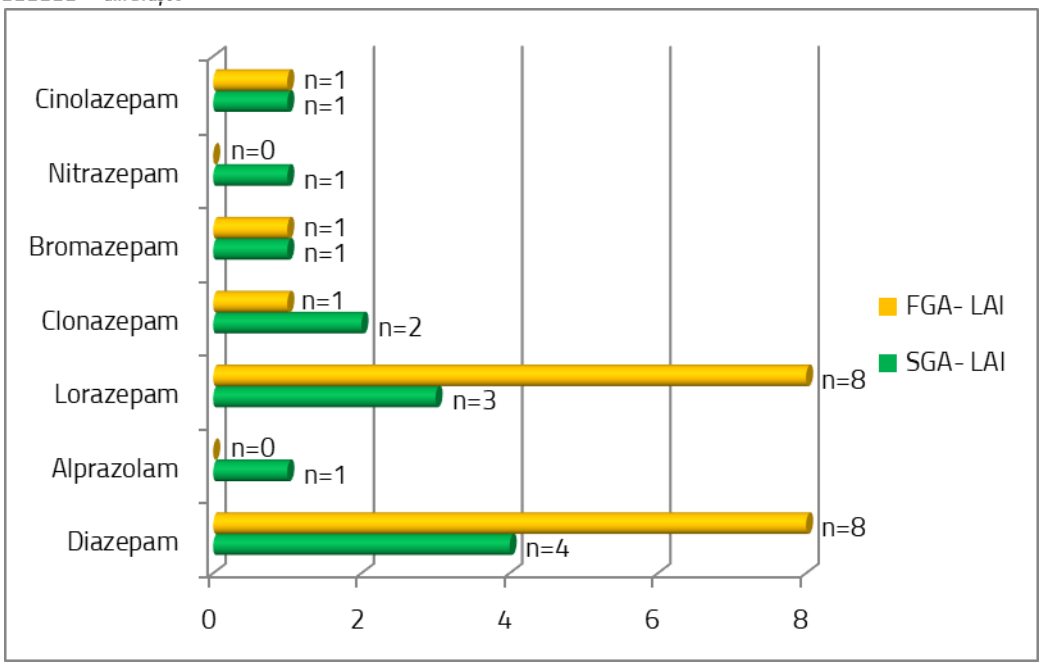

Figure 18. Distribution of SGA-LAI and FGA-LAI groups by benzodiazepine type

For diazepam and lorazepam, where the difference is visible, the comparison of proportions was performed, but the calculation does not indicate statistical significance either in the case of diazepam (p = 0.1943) or in the case of lorazepam (p = 0.0961). Differences observed in diazepam and lorazepam between the SGA-LAI subgroup and the OAP group were also verified. No statistical significance was revealed either in the case of diazepam (p= 0.2292) or in the case of lorazepam (p= 0.0564).

In the SGA-LAI group we identified a number of 6 patients (15.38%) who had concurrent treatment with a combination of mood stabilizer and benzodiazepine, while in the FGA-LAI group we found 4 patients (10.52%). The difference is not statistically significant (p= 0.52). In the OAP group, 29 patients (12.18%) were identified with concomitant combined treatment; comparing the proportions of the SGA-LAI group with the OAP group, no statistical significance is revealed (p= 0.57).
In the SGA-LAI group, we checked whether there were significant differences in the use of mood stabilizers or benzodiazepines between LAI antipsychotics and their oral counterpart (Table 29).

Table 29. Concomitant treatment by type of antipsychotic

Antipsychotic type	For-mulation	Mood stabilizers (n, %)	p value	Benzodiaze-pines (n, %)	p value	Mood stabilizers and benzodiazepines (nr, %)	p value
olanzapine	LAI n=5	n=1 (20%)	p=0.77	n=0	p=0.10	n=0	p=0.42
	OAP n=70	n=18 (25.71%)		n=25 (35.71%)		n=8 (11.42%)	

risperidone	LAI n=16	n=4 (25%)	p=0.47	n=6 (37.50%)	p=0.93	n=3 (18.75%)	p=0.96
	OAP n=31	n=11 (35.48%)		n=12 (38.70)		n=6 (19.35%)	
aripipra-zole	LAI n=9	n=2 (22.22%)	p=0.69	n=2 (22.22%)	p=0.54	n=2 (22.22%)	p=0.49
	OAP n=24	n=7 (29.16%)		n=8 (33.33%)		n=3 (12.50%)	
paliperi-done	LAI n=9	n=2 (22.22%)	p=0.57	n=3 (33.33%)	p=0.73	n=1 (11.11%)	p=0.70
	OAP n=15	n=5 (33.33%)		n=4 (26.66%)		n=1 (6.66%)	

We observed that among SGA-LAI antipsychotics, risperidone has the highest percentages of associated mood stabilizers (25%) and associated benzodiazepines (37.5%) (Figure 19).

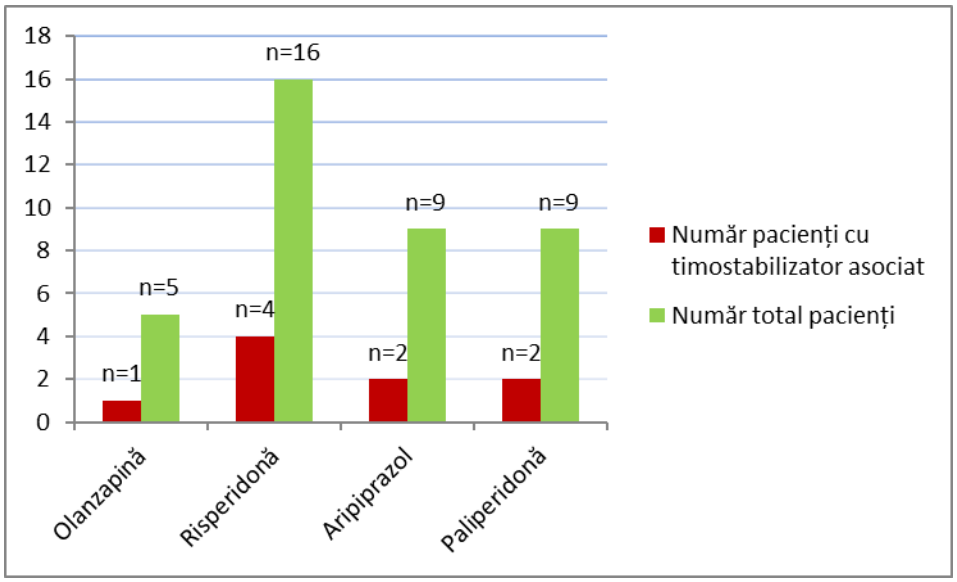

Figure 19. Distribution of the SGA-LAI group according to the use of mood stabilizers

Also, in the OAP group, also in the case of risperidone, we found the highest proportions of patients with associated mood stabilizer (35.48%) and associated benzodiazepines (38.70%). In the case of concomitant combined treatment (mood stabilizer and benzodiazepine), the highest percentage of

patients was registered with aripiprazole LAI (22.2%) and oral risperidone (19.35%). The distribution of the SGA-LAI group according to benzodiazepine use is illustrated in Figure 20.

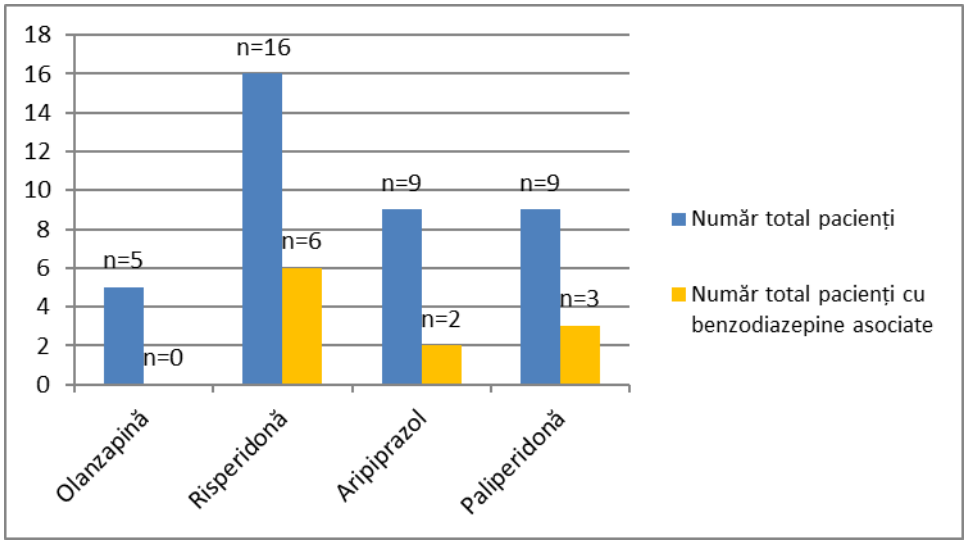

Figure 20. Distribution of SGA-LAI group according to benzodiazepine use

No statistically significant differences were observed for any of the four antipsychotics.
Analysis of data from the SGA-LAI group also identified a number of patients who were on LAI antipsychotic and associated oral antipsychotic treatment, according to Table 30.

Table 30. Patients under treatment with SGA-LAI and OAP

Number of patients	SGA-LAI type	SGA-LAI dose (mg)	OAP type	OAP dose (mg)
2	aripiprazole	400	clozapine	100
1	aripiprazole	400	aripiprazole	15
1	risperidone	100	clozapine	100
1	risperidone	75	olanzapine	10
1	risperidone	100	risperidone	3
1	risperidone	100	risperidone	1
1	risperidone	25	risperidone	2
1	paliperidone	100	clozapine	50

A total of 39 patients are stabilized on a combination of two or more antipsychotics (12.38%). In the SGA-LAI group we identified 9 patients (23.07%); in the FGA-LAI group there are also 9 patients (23.68%), while in the OAP group we identified 21 patients (8.82%) under treatment with combinations of antipsychotics. There is no statistical significance when comparing the proportions of the SGA-LAI groups with FGA-LAI (p= 0.94), but the difference is statistically significant when comparing the percentages of the total LAI group (18 patients, 23.37%) with the OAP group

(p=0.0008) , as well as when comparing the groups SGA-LAI with OAP (p=0.0080), and FGA-LAI with OAP (p= 0.0064).

The distribution of cases stabilized on monotherapy, respectively polytherapy, in the two groups, is illustrated in Figure 21.

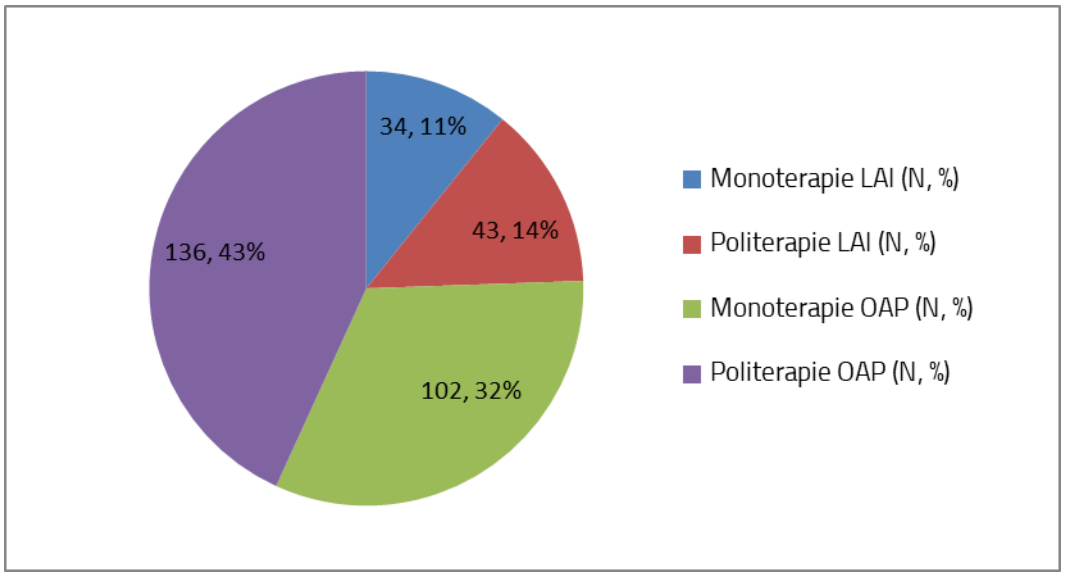

Figure 21. Distribution of cases with monotherapy and polytherapy

The percentage of patients stabilized with monotherapy is significantly lower than those stabilized with polytherapy in the OAP group (p= 0.0133), but in the LAI group the difference is not statistically significant (p= 0.5748). We applied the Chi-square test to calculate the statistical significance of the difference in the percentages of patients treated with monotherapy found between the LAI (11%) and OAP (32%) groups. Patients stabilized on LAI received significantly less monotherapy than those stabilized on OAP (p= 0.0003).

136 patients (43.17%) are stabilized on antipsychotic monotherapy. Their distribution by antipsychotic is detailed in Table 31.

Table 31. Patients stabilized on antipsychotic monotherapy

Antipsyhotic (typ, formulation)		Total number of patients	Patients on monotherapy (nr, %)	P value
olanzapine	LAI	5	4 (80%)	p = 0.18
	OAP	70	32 (45.71%)	
risperidone	LAI	16	8 (50%)	p = 0.24
	OAP	31	10 (32.25%)	
aripiprazole	LAI	9	5 (55.55%)	p = 0.25
	OAP	24	8 (33.33%)	

paliperidone	LAI	9	4 (44.44%)	p = 0.83
	OAP	15	6 (40%)	
quetiapine	OAP	24	6 (24%)	-
amisulpride	OAP	20	9 (45%)	-
ziprasidone	OAP	1	1 (100%)	-
haloperidol	OAP	22	3 (13.63%)	-
flupenthixol	LAI	36	13 (36.11%)	-
zuclopenthixol	LAI	2	0	-
levomepromazine	OAP	3	0	-
tiapridal	OAP	1	0	-
clozapine	OAP	66	27 (40.90%)	-
Total			136 (43.17%)	-

The distribution of cases stabilized on monotherapy in the LAI group by antipsychotic is illustrated in Figure 22.

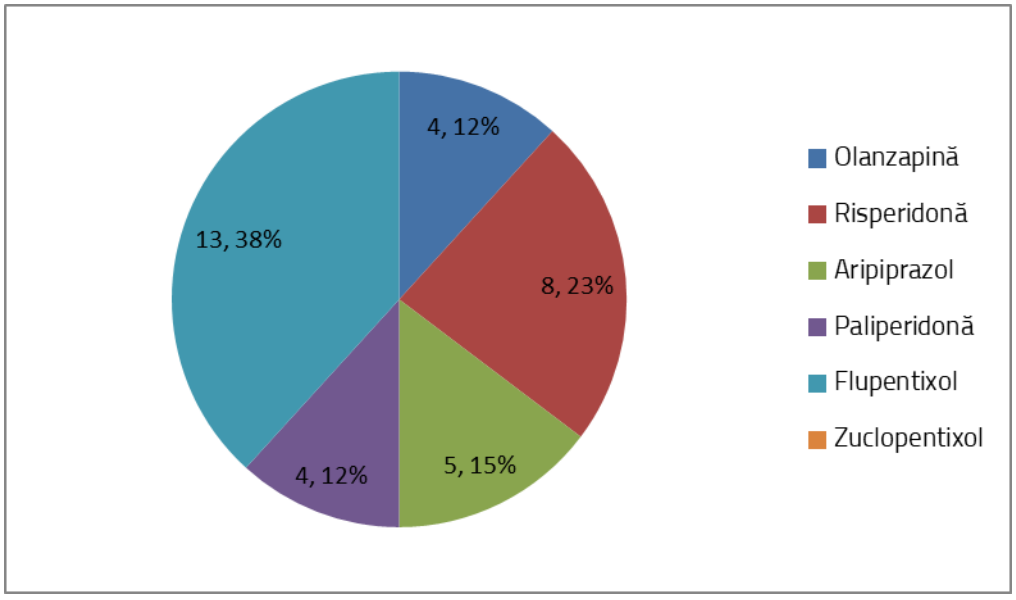

Figure 22. Distribution of monotherapy cases in the LAI group

The distribution of cases stabilized on monotherapy in the OAP group by antipsychotic is illustrated in Figure 23.

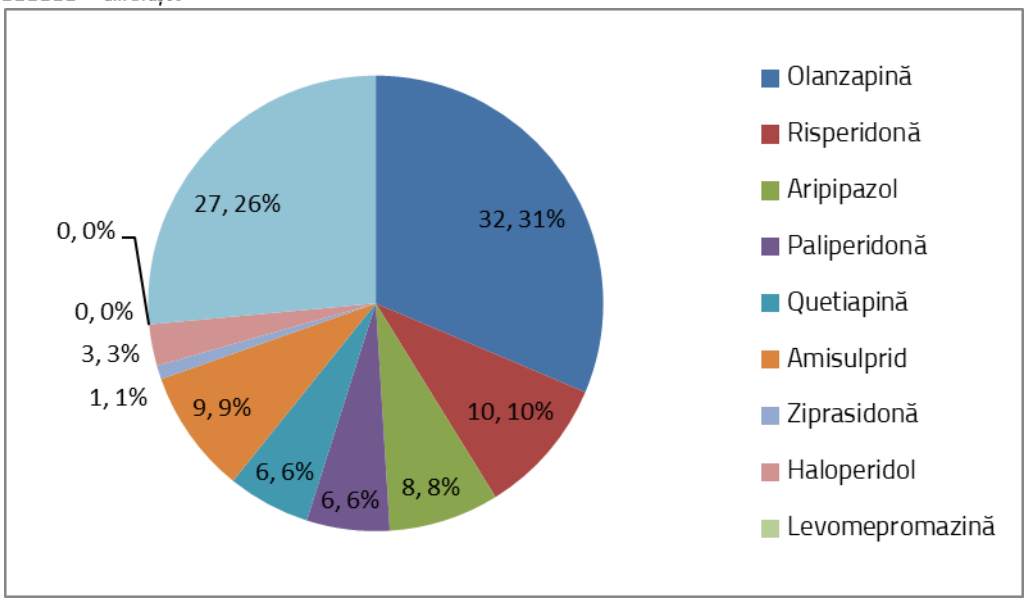

Figure 23. Distribution of monotherapy cases in the OAP group

We observed that the percentages of patients stabilized on monotherapy are in most cases below 50%. No statistical significance was revealed when comparing SGA-LAI antipsychotic subgroups with their oral counterpart. The highest percentage of patients in monotherapy is observed with olanzapine LAI (80%), followed by aripiprazole LAI (55.55%).

4.5.6 Conclusions

The actual percentage of patients who are stabilized on antipsychotic and concomitant treatment with benzodiazepines and mood stabilizers is higher than could be justified by reasonable presumptions (ineffectiveness of antipsychotic monotherapy, inadequate antipsychotic dosage, treatment of antipsychotic adverse reactions). No significant differences were found regarding concomitant treatment with mood stabilizers and/or benzodiazepines between patients stabilized on LAI versus OAP. Study results did not support the starting hypothesis that patients stabilized on LAI antipsychotics should have fewer concurrent treatments compared to those stabilized on oral antipsychotics. Our results draw the attention of clinicians to the need for more frequent and careful evaluation of the risk-benefit balance regarding long-term concomitant treatment. Benzodiazepines, proven useful in the acute management of psychotic episodes, and mood stabilizers, with limited utility in schizophrenia, may have undesirable effects as maintenance treatment. We also draw attention to the need for accurate assessments of treatment-resistant schizophrenia, which may be present in a higher percentage than previously estimated. More detailed research is needed to confirm or deny the benefits of current drug polypharmacy trends.

4.6 Study 4. HIGHLIGHTING THE IMPACT OF THE COVID-19 PANDEMIC ON LAI TREATMENTS

4.6.2 Working hypothesis/objectives.

The present study started from the hypothesis that, due to the restrictions imposed by the COVID-19 pandemic, the prescriptions, and initiations of LAI antipsychotic treatments for patients with

schizophrenia will be significantly affected. Therefore, the objective of the study was to evaluate SGA-LAI treatment initiations before and after the declaration of the COVID-19 pandemic.

4.6.3 Materials and methods

4.6.3.1 Study design

We conducted an observational, retrospective, mirror-type study in which we analyzed and compared LAI treatment initiations in the 12 months before the declaration of the COVID-19 pandemic with those in the following 12 months after the declaration of the pandemic. The data were collected from March 11, 2019 to March 12, 2021, for all patients with schizophrenia who were admitted to the Clinical Hospital of Psychiatry and Neurology Brașov. The COVID-19 pandemic was declared by the WHO on March 11, 2020, so the period studied was divided into the pre-COVID comparator period, from March 11, 2019 to March 11, 2020, and the period of the COVID-19 pandemic, from March 12, 2020 to March 12, 2021.

4.6.3.7 Statistical analysis

The results were analyzed using SPSS version 20.00. The adjusted odds ratio (AOR) was calculated with 95% confidence interval using the t-test method. p-values below 0.05 were considered statistically significant. Multivariable logistic regression was used to indicate a significant association. The Chi-square test was used to compare proportions.

4.6.4 Results

During the comparator pre-pandemic period (March 11, 2019-March 11, 2020), a total number of 1,500 patients were admitted to the Brașov Clinical Hospital for Psychiatry and Neurology, of which 224 patients (14.9%) had a diagnosis of schizophrenia in accordance with the DSM criteria -5 (Figure 24).

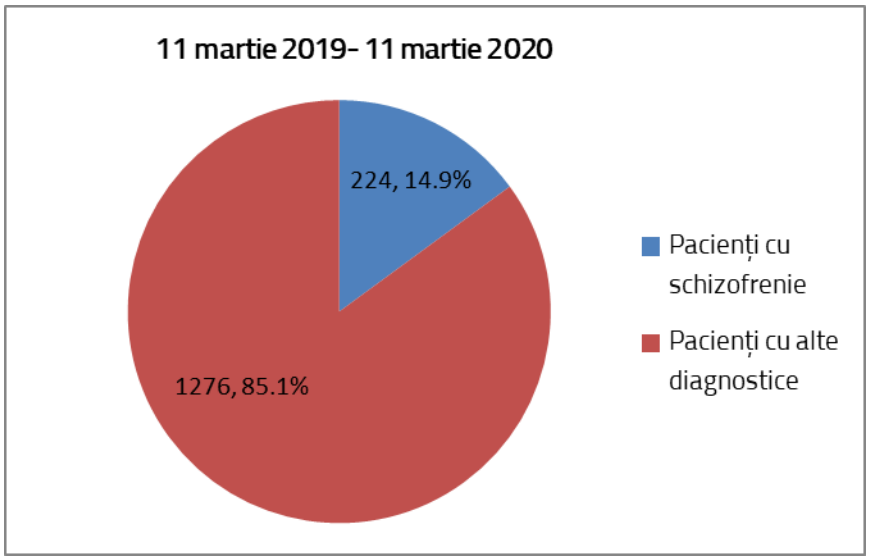

Figure 24. Hospitalized patients in the pre-pandemic period

During the pandemic period (March 12, 2020-March 12, 2021), a total of 1,100 patients were admitted to the Brașov Clinical Hospital for Psychiatry and Neurology, of which 218 patients (19.8%) were diagnosed with schizophrenia according to the DSM-5 criteria (Figure 25).

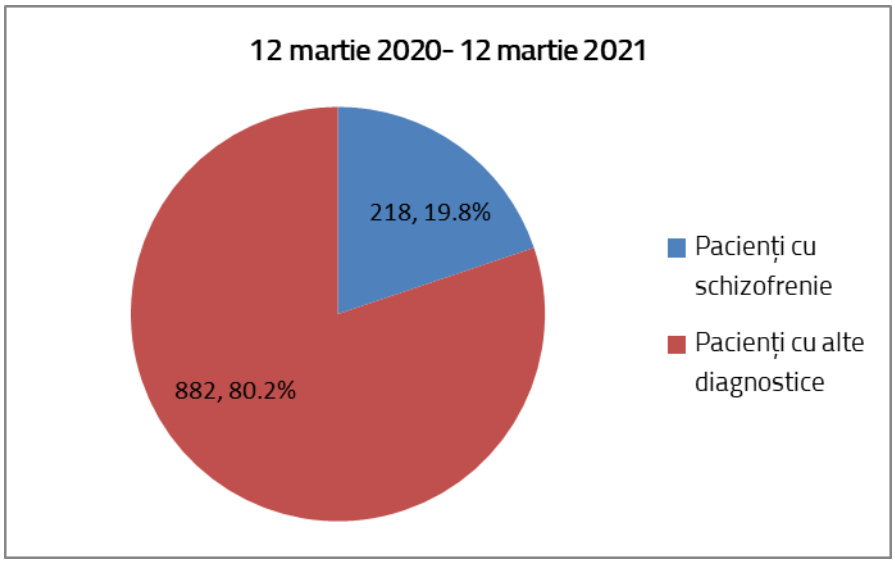

Figure 25. Hospitalized patients during the pandemic

The evolution of the total number of admissions and the number of admissions with schizophrenia is illustrated in Figure 26.

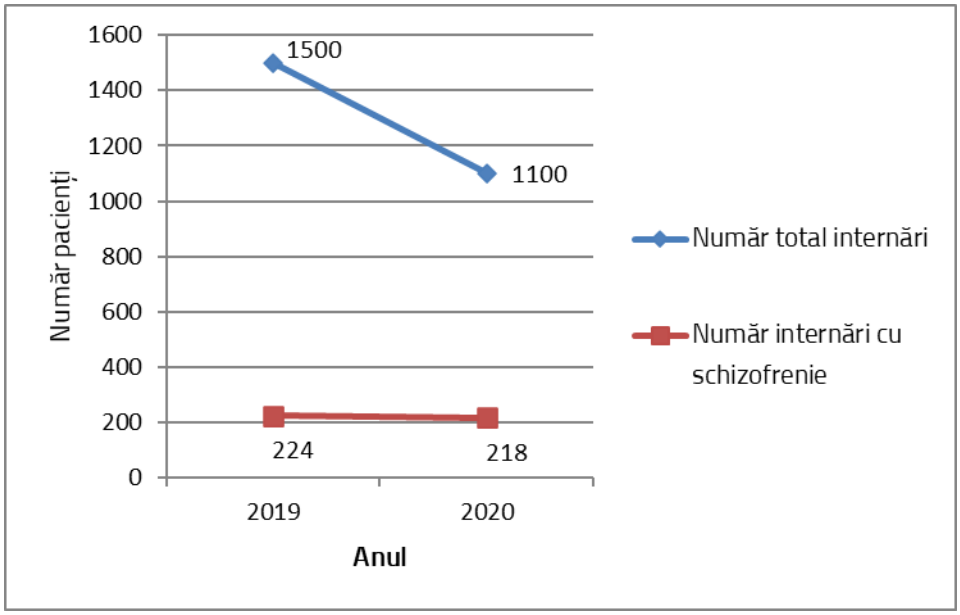

Figure 26. Evolution of hospitalizations before and after the declaration of the pandemic

We noted that although the total number of hospitalizations decreased in the year following the declaration of the pandemic by 26.6%, the number of hospitalizations for schizophrenia registered a decrease of only 2.67%. However, the proportion of hospitalized patients with schizophrenia increased significantly (p=0.0010) during the pandemic.

In the pre-pandemic period, there were 29 LAI initiations (12.9%), and in the pandemic period only 15 (6.9%), meaning a decrease of 48.3% (Figure 27).

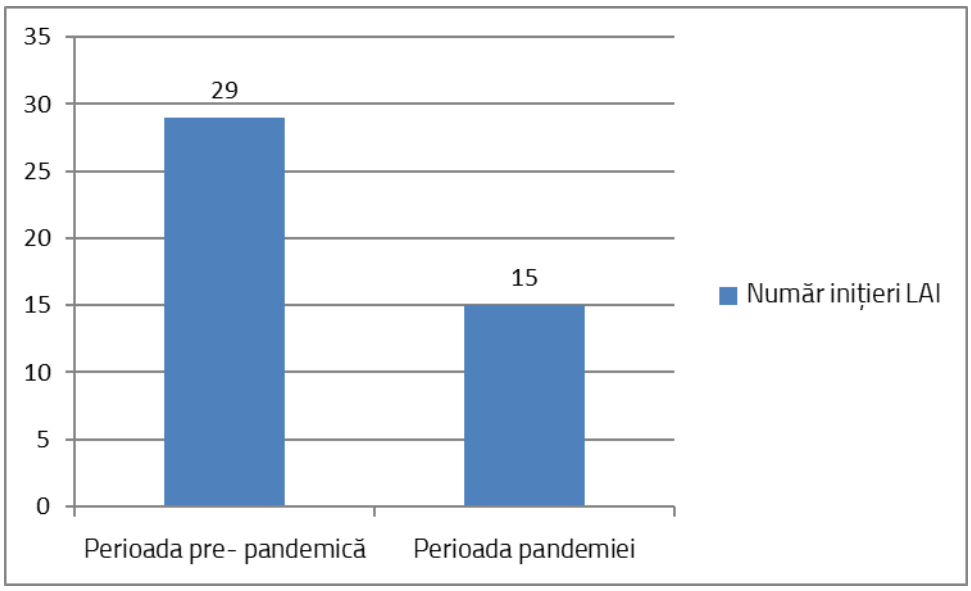

Figura 1. Numărul inițierilor LAI pre- și post-pandemie

The decrease in the number of LAI initiations is statistically significant (p=0.0353).
Demographic and clinical characteristics of patients initiated on LAI are detailed in Table 34.

Table 34. Demographic and clinical characteristics of patients initiated on LAI

	LAI initiations		
	Pre- pandemic	**During the pandemic**	**P value**
	N = 29	N = 15	
Male	14 (48.2%)	4 (26.6%)	0.17
Age (years, ±SD)	42.3 (±7.8)	44.4 (±8.3)	0.41
Age of onset (years, ±SD)	28.6 (±8.6)	25.2 (±6.6)	0.18
Duration of illness (years, ±SD)	13.8 (±9.2)	19.2 (±6.2)	0.0476
Duration of hospitalization (years, ±SD)	14.1 (±8.6)	16.7 (±6.6)	0.31

It is interesting to note that during the pandemic, the number of male patients who underwent LAI decreased, from 48.2% pre-pandemic to 26.6% during the pandemic; the decrease is not statistically significant.

The comparison between the treatments initiated pre-pandemic versus the pandemic period, and the level of statistical significance are detailed in Table 36.

Table 36. Pre- and post-pandemic antipsychotic treatments

Antipsyhotic type	Pre-pandemic (N, %)	During the pandemic (N, %)	P value
SGA-LAI	29 (12.9%)	15 (6.9%)	0.0353
FGA-LAI	18 (8.2%)	14 (6.5%)	0.49
other oral antipsychotics	133 (59.3%)	151 (69.2%)	0.0302
clozapine	44 (19.6%)	38 (17.4%)	0.55

Figure 28 illustrates the distribution of the pandemic patient cohort according to the type of treatment used.

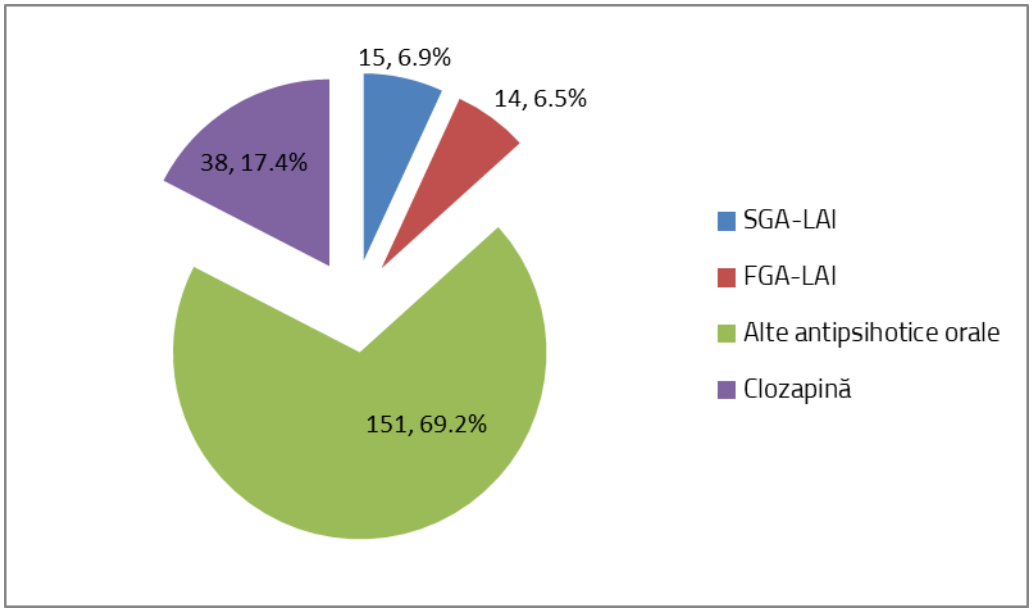

Figure 28. Distribution of patients according to the recommended treatment in the pandemic

In the pre-pandemic period, out of the 224 patients, 29 patients (12.9%) were initiated on SGA-LAI. 133 patients (59.3%) received oral antipsychotics (other than clozapine) and 44 patients (19.6%) received clozapine and the remaining 18 patients (8.2%) received FGA-LAI, as illustrated in Figure 29.

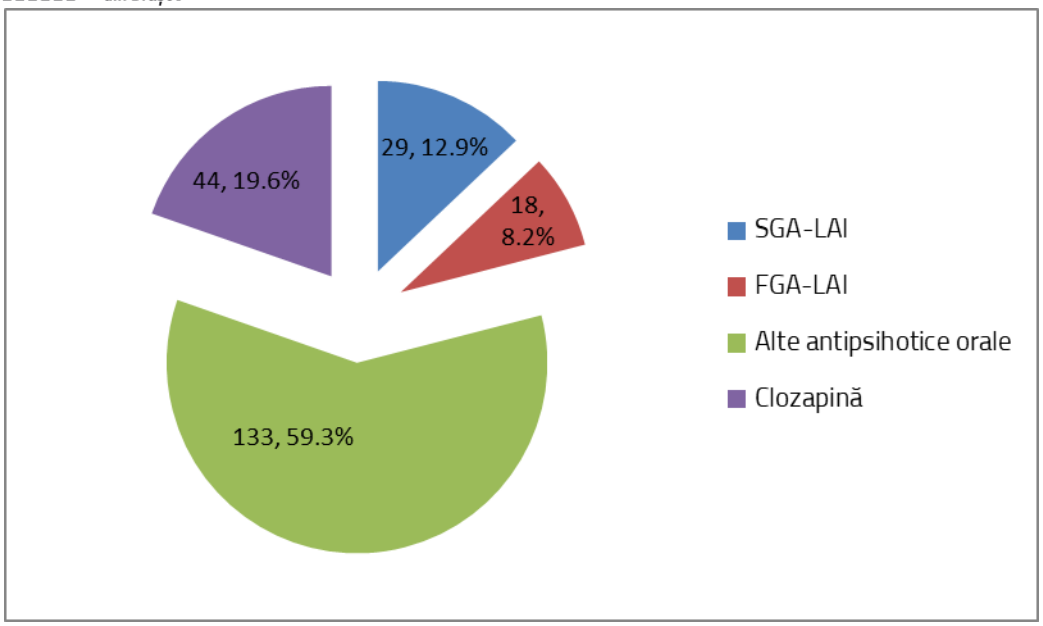

Figure 29. Distribution of patients according to pre-pandemic recommended treatment

We observed, in addition to the significant decrease in SGA-LAI initiations, a small decrease, without statistical significance, also in the case of FGA-LAI. In parallel, there has been a significant increase in the number of oral antipsychotics (other than clozapine). In the particular situation of clozapine, there was a decrease, but not statistically significant.

The SGA-LAIs used for initiations during the study periods are detailed in Table 37.

Table 37. Initiations of atypical LAI antipsychotics

	SGA-LAI initiations		
	Pre-pandemic	**During the pandemic**	**P value**
SGA-LAI type (N, %)	N = 29 (12.9%)	N = 15 (6.9%)	
aripiprazole (N, %)	9 (31%)	2 (13%)	0.19
olanzapine (N, %)	3 (10%)	0	0.50
risperidone (N, %)	8 (28%)	11 (73%)	0.0048
paliperidone (N, %)	9 (31%)	2 (13%)	0.19

After the declaration of the pandemic, LAI olanzapine initiations decreased by 100%, but due to the small sample size (3 patients in the pre-pandemic group), the resulting statistical significance cannot be considered valid. Aripiprazole and paliperidone LAI initiations both decreased by 77.8%. Surprisingly, in the case of risperidone there was an increase of 27.3%, statistically significant (p=0.0048).

To test whether initiations were related to poor use of a particular antipsychotic, we also analyzed the two cohorts in terms of oral antipsychotic initiations in the two study periods. Oral antipsychotics recommended for outpatients are detailed in Table 38.

Table 38. Oral antipsychotics used in the study groups

	Pre-pandemic	During the pandemic	P value
oral antipsyhotics (N, %)	177 (79%)	189 (86.7%)	0.0322
olanzapine (N, %)	61 (34.5%)	69 (36.5%)	0.68
quetiapine (N, %)	18 (10.2%)	24 (12.7%)	0.45
risperidone (N, %)	18 (10.2%)	23 (12.2%)	0.54
paliperidone (N, %)	3 (1.7%)	7 (3.7%)	0.24
aripiprazole (N, %)	8 (4.5%)	6 (3.2%)	0.51
amisulpride (N, %)	14 (7.9%)	10 (5.3%)	0.31
haloperidol (N, %)	11 (6.2%)	12 (6.3%)	0.96
clozapine (n, %)	44 (24.8%)	38 (20.1%)	0.28

Our data indicates a 6.4% increase in oral antipsychotic prescriptions in the period following the declaration of the pandemic. Small, non-statistically significant decreases in oral treatment recommendations were seen for aripiprazole and amisulpride. In the case of clozapine, there was also a 13.6% decrease in prescriptions during the pandemic. For olanzapine, the number of OAP initiations is the highest in both study periods (61 pre-pandemic initiations and 69 pandemic initiations respectively), which indicates the high level of use in clinical practice. The next OAP in terms of use is clozapine. Our results show that the level of use of an oral antipsychotic does not correlate with the level of use of its LAI counterpart.

4.6.6 Conclusions

Our study confirmed the working hypothesis; results demonstrated that the COVID-19 pandemic and the restrictions imposed in this context caused considerable changes in the pattern of antipsychotic initiations in patients with schizophrenia. Furthermore, our research was the first to show that SGA-LAI initiations decreased significantly after the pandemic was declared. Our results showed the major impact of the pandemic on the health system in Romania, and the consequences on patients and their treatments, and draw attention to the need to develop psychiatric treatment management strategies in the event of another pandemic.

CHAPTER 6 - FINAL CONCLUSIONS. ORIGINAL CONTRIBUTIONS. DISSEMINATION OF RESULTS. FUTURE DIRECTIONS OF RESEARCH

6.1 FINAL CONCLUSIONS

The first study of the present thesis concluded that LAI-type antipsychotic treatments are more effective than oral ones in preventing psychotic relapses and hospitalizations and are at least similar to oral treatments in terms of tolerability. This first research took place at a time when the literature showed that LAI treatments have similar efficacy to oral ones (Kishimoto et al., 2014). The results of our study (Fodor et al., 2018) were preliminary and contributed to the current state of knowledge, which indicates a superiority of LAI antipsychotics over oral ones in the prevention of relapses and hospitalizations (Kishimoto et al., 2021).

LAI treatments are under-utilized in our country, something highlighted during all the research in the thesis. This result confirms the finding that, globally, clinicians' fears, patients' perceptions (Kane et al., 2021; Kane & Correll, 2019; Sajatovic, Ross, Legacy, Correll, et al., 2018), as well as the lack of a unified vision on the initiation of LAI, causes too small a percentage of patients to benefit from these types of treatments. These findings highlight the significant need to increase and improve the current level of knowledge and education regarding LAI treatments, both among patients and healthcare professionals. Access to information about LAIs, including their benefits in relapse prevention, could increase acceptance and use of this formulation among patients with schizophrenia (Potkin et al., 2013; Sugawara et al., 2019).

Our research highlighted two phenomena: the late initiation of LAI treatments, a fact also found by other authors (Kane et al., 2014), and the typical profile of the patient for whom an LAI is chosen or proposed: a non-adherent patient, with repeated relapses in the antecedents, most likely several years after the onset and already associating degradations in the functional areas. This patient selection process was visible both in the study conducted before the COVID-19 pandemic and in the studies conducted after the declaration of the pandemic. In this sense, we propose the development of national information programs, intended for medical professionals (psychiatrists, family doctors) and patients with schizophrenia, which will increase the level of awareness of the benefits of LAI and their initiation as early as possible after the onset of the condition (Kane et al., 2020; Lian et al., 2022).

We also propose, as a future direction, the implementation, at the local and national level, of the routine use of standardized tools for the assessment of patients with schizophrenia in order to establish the need and usefulness of introducing an LAI. In this sense, it should be mentioned that in our clinic, Professor Ifteni and his collaborators undertook a pioneering work, proposing the ROLIN index (Ifteni et al., 2021), a tool that helps clinicians in the decision-making process of initiating a treatment LAI.

The doctoral thesis has the advantage of carrying out research over a period of 8 years, thus capturing essential aspects in the therapeutic approach of patients with schizophrenia in the pre-pandemic period and in the period that followed the declaration of the COVID-19 pandemic.

Moreover, the thesis captured the evolution over time of attitudes towards the treatment of patients with schizophrenia. It has been noted that the percentage of patients receiving concomitant treatments with benzodiazepines and/or mood stabilizers has increased significantly over the last 10 years. It was also found that, although initially these adjunctive medications were prescribed significantly more to patients on oral treatment, currently the percentages are similar for patients stabilized on LAI or oral antipsychotics (A. A. Miron et al., 2022). Further studies are needed to determine whether there is a real benefit of concomitant treatments with benzodiazepines and/or mood stabilizers in schizophrenia, treatments that are widely used although currently lacking the support of therapeutic guidelines and no sound scientific basis.

We note, despite the current recommendations, the tendency of antipsychotic polypharmacy to increase over time, at the expense of monotherapy. This phenomenon has also been observed worldwide (S.-K. Lin, 2020). Some authors recommend, based on the ever-accumulating evidence, that guidelines should change their categorical recommendations discouraging any antipsychotic polypharmacy in the maintenance treatment of schizophrenia. More randomized trials investigating the potential benefits and risks of polypharmacy in schizophrenia are needed.

The particular epidemiological context of the COVID-19 pandemic offered the opportunity to carry out a unique study, switching from LAI treatment to oral treatment, which would not have been possible under other conditions, due to ethical considerations. Our results showed that patients stabilized on LAI treatment, who during the pandemic were switched to oral treatment, relapsed in most cases, most likely due to the recurrence of non-adherence (A.-A. Miron et al., 2022) . We therefore emphasize the fact that this phenomenon, frequently underestimated in clinical practice, is maintained at high levels in the population of patients with schizophrenia, and that LAI-type treatments are also effective in preventing or reducing non-adherence, as others have found authors (Sajatovic, Ross, Legacy, Byerly, et al., 2018). From this perspective, the originality and uniqueness of our study lies in the fact that it provides incontrovertible evidence that non-adherence can reappear at any time, if favorable conditions are created for it.

The doctoral thesis also highlighted the effect of the COVID-19 pandemic on LAI treatment initiations. Although there were alarm signals in this regard (Ifteni et al., 2020), our study was the first to show a significant decrease in LAI antipsychotic initiations during the pandemic (A.-A. Miron et al., 2022) . This phenomenon was not noticed in other states, where the health system had the ability to substitute LAI administration in the hospital with that at home, or to offer alternative treatment schemes to patients (Alevizopoulos & Nystazaki, 2021; Barlati et al., 2022; Gannon et al., 2020; MacLaurin et al., 2021; McKee et al., 2021).

Our research shows that the impact of the COVID-19 pandemic on the entire health system in Romania was probably much deeper than initially estimated and affected all levels, including hospitals, day care systems, public and private outpatient clinics. The doctoral thesis particularly draws attention to the negative consequences of the pandemic on a vulnerable population of patients, namely those diagnosed with schizophrenia, for whom an unfavorable epidemiological context represents an additional destabilizing factor, and for whom it is imperative to ensure the continuity of access to treatment . We therefore emphasize the major importance of the need to

develop national strategies for the management of psychiatric treatments in the event of another pandemic.

6.2 ORIGINAL CONTRIBUTIONS

The doctoral thesis presents a unique study evaluating patients diagnosed with schizophrenia and in remission, stabilized on LAI antipsychotic treatment, who switched to an oral antipsychotic. The research also includes the first study in the literature to highlight a decrease in LAI antipsychotic initiations during the COVID-19 pandemic. Another original contribution is the unique assessment of treatment prescribing trends in schizophrenia, and their evolution over time.

6.3 DISSEMINATION OF RESULTS

The results of the thesis research were published in prestigious national and international journals, and presented as papers at national conferences, thus contributing significantly to the current state of knowledge regarding antipsychotic treatments in schizophrenia (Table 39, Appendix 1, Appendix 2).

Table 39. Dissemination of research results

	Lucrări pe tema tezei de doctorat	Lucrări pe teme conexe
Număr articole	4	6
Număr lucrări prezentate în cadrul conferințelor	4	2

6.4 FUTURE RESEARCH DIRECTIONS

Starting from the results of the research within the doctoral thesis, I propose the following as future research directions:

◘ Active involvement in the research of new forms of long-acting antipsychotics, with oral or subcutaneous administration
◘ Involvement in researching the effects of other types of LAI
◘ Tracking the evolution of patients who received LAI from the first episode of schizophrenia
◘ Implementation of programs to educate patients, families and medical staff about LAI, with the aim of increasing their acceptability and use in the treatment of patients with schizophrenia
◘ At the local and national level, the development and implementation of psychiatric treatment management strategies in the event of another pandemic.

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APPENDIX

APPENDIX 1. LIST OF PUBLICATIONS

1. Fodor AA, Pascu AM, Poroch V, Ifteni PI, Burtea V, Tom, S, Teodorescu A. Long Term Efficacy of the Treatment with Olanzapine Pamoate, Risperidone and Aripiprazole Monohydrate. Revista de Chimie. 2018; 69(3), 650-653. Link: https://doi.org/10.37358/RC.18.3.6168

2. Miron AA, Ifteni PI, Teodorescu A, Petric PS. Long-Acting Injectable Antipsychotics (LAIs) Prescribing Trends during the COVID-19 Pandemic in Romania. Healthcare (Basel). 2022 Jul 7;10(7):1265. doi: 10.3390/healthcare10071265. PMID: 35885792; PMCID: PMC9316377. Link: Long-Acting Injectable Antipsychotics (LAIs) Prescribing Trends during the COVID-19 Pandemic in Romania - PMC (nih.gov)

3. Miron AA, Teodorescu A, Ifteni P, Irimie CA, Dima L, Petric PS. Switch from Olanzapine Long-Acting Injectable to its Oral Equivalent during COVID-19 Pandemic: a Real World Observational Study. Psychiatr Q. 2022 Jun;93(2):627-635. doi: 10.1007/s11126-021-09924-9. Epub 2022 Mar 2. PMID: 35235126; PMCID: PMC8888267. Link: Switch from Olanzapine Long-Acting Injectable to its Oral Equivalent during COVID-19 Pandemic: a Real World Observational Study - PMC (nih.gov)

4. Miron AA, Petric PS, Teodorescu A, Ifteni P, Chele G, Szalontay AS. Benzodiazepines and Mood Stabilizers in Schizophrenia Patients Treated with Oral versus Long-Acting Injectable Antipsychotics—An Observational Study. *Brain Sciences*. 2023; 13(2):173. Link: https://doi.org/10.3390/brainsci13020173

5. Andreea T, Petru I, Miron AA, Paula-Simina P, Lorena D. Clozapine for Treatment-Refractory Aggressive Behavior. Psychiatr Q. 2021 Jun;92(2):721-733. doi: 10.1007/s11126-020-09839-x. Epub 2020 Sep 12. PMID: 32918660 Link: Clozapine for Treatment-Refractory Aggressive Behavior - PubMed (nih.gov)

6. Teodorescu A, Ifteni P, Dragan A, Moga MA, Miron AA, Dima L. Clozapine Efficacy in a Case of Severe Treatment-Resistant Postpartum Psychosis. Risk Manag Healthc Policy. 2021 Feb 12;14:555-559. doi: 10.2147/RMHP.S294249. PMID: 33603521; PMCID: PMC7886290. Link: Clozapine Efficacy in a Case of Severe Treatment-Resistant Postpartum Psychosis - PMC (nih.gov)

7. Moga S, Teodorescu A, Dragan A, Miron AA, Ifteni P. Neutropenia in Patients With Clozapine-Treated Schizophrenia: An Effect of Clozapine or a Consequence of SARS-CoV-2 Infection? A Systematic Review. Am J Ther. 2022 Sep-Oct 01;29(5):e544-e552. doi: 10.1097/MJT.0000000000001532. Epub 2022 Jun 24. PMID: 35749754. Link: Clozapine And Neutropenia In Patients With Schizophrenia | NDT (dovepress.com)

8. Moga S, Teodorescu A, Ifteni P, Petric PS, Miron AA. Clozapine and Neutropenia in Patients with Schizophrenia and SARS-CoV-2 Infection. Neuropsychiatr Dis Treat. 2022 May 4;18:977-983. doi: 10.2147/NDT.S361405. PMID: 35547265; PMCID: PMC9081886. Link: Clozapine and Neutropenia in Patients with Schizophrenia and SARS-CoV-2 Infection - PMC (nih.gov)

9. Duca L, Roman NA, Miron A, Teodorescu A, Dima L, Ifteni P. WHODAS Assessment Feasibility and Mental Health Impact on Functional Disability in Systemic Lupus Erythematosus. Healthcare (Basel). 2022 Jun 6;10(6):1053. doi: 10.3390/healthcare10061053. PMID: 35742104; PMCID: PMC9222861. Link: WHODAS Assessment Feasibility and Mental Health Impact on Functional Disability in Systemic Lupus Erythematosus - PMC (nih.gov)

10. Moga S, Petric PS, Miron AA, Ifteni P, Teodorescu A. Outcome of COVID-19 mRNA Vaccination in Patients Treated With Clozapine WHO Previously Went Through SARS-COV-2 Infection. Am J Ther. 2023 Apr 24. doi: 10.1097/MJT.0000000000001633. Epub ahead of print. PMID: 37097999. Link: Outcome of COVID-19 mRNA Vaccination in Patients Treated With Clozapine WHO Previously Went Through SARS-COV-2 Infection. - Abstract - Europe PMC

APPENDIX 2. LIST OF CONFERENCES PAPERS

1. Miron AA, Teodorescu A, Ifteni PI. Tratamentul antipsihotic în sarcină- provocare etică și medico-legală. Conferința de Psihiatrie și Psihologie Medico- Legala Sibiu, 10-11 decembrie 2021

2. Miron AA, Ifteni PI, Teodorescu A. Eficacitatea clozapinei în episoadele maniacale severe. Congresul Național de Psihiatrie, Cluj- Napoca, 12-17 iulie 2022

3. Miron AA, Teodorescu A, Popa A, Chifor M. Pot oferi antipsihoticele de tip LAI protecție împotriva suicidului? Conferința de Psihiatrie și Psihologie Medico- Legala Sibiu, 8-10 decembrie 2022

4. Miron AA, Popa A, Ifteni PI. Implicațiile utilizării benzodiazepinelor în inițierea tratamentului cu antipsihotice de tip LAI. Conferința Națională No Addict, Iași, 4-6 mai 2023

5. Miron AA, Ifteni PI, Popa A, Petric PS, Teodorescu A. Provocări ale inițierii LAI la pacienții cu tratament concomitent cu antipsihotice și benzodiazepine. Zilele Medicale și Științifice ale Spitalului Clinic de Psihiatrie "Prof. Dr. Al. Obregia", București, 16-20 mai 2023

6. Ifteni PI, Teodorescu A, Popa A, Petric PS, **Miron AA.** Algoritm decizional în vederea inițierii tratamentelor de tip LAI. Zilele Medicale și Științifice ale Spitalului Clinic de Psihiatrie "Prof. Dr. Al. Obregia", București, 16-20 mai 2023