Psychiatry Research 332 (2024) 115676

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Impact of long-acting injectable antipsychotics vs. oral medication on relapses of patients with psychosis and bipolar disorder

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ARTICLE INFO

Keywords:
Hospital admissions
Voluntary admissions
Involuntary admissions
First-generation LAIs
Second-generation LAIs
Adherence

ABSTRACT

Relapse associated with multiple hospital readmissions of patients with chronic and severe mental disorders, such as psychosis and bipolar disorder, is frequently associated with non-adherence to treatment. The primary aim of the study was to compare the effectiveness of long-acting injectable (LAI) treatment, vs. oral medication in reducing readmissions of patients with psychotic or bipolar disorder in a community sample of 164 patients with psychosis and 29 patients with bipolar disorder ($n = 193$), with poor adherence to oral medication. The mean follow up period was 5.6 years and the number of readmissions were compared for an equal-length period of oral treatment preceding the onset of LAI administration. We observed a significant decrease of 45.2 % in total hospital readmissions after receiving LAIs treatment. The effect was significant both for patients with a pre-LAI treatment history of predominantly voluntary hospitalizations and with predominantly involuntary admissions. In addition, we observed equal effectiveness of first- vs. second-generation LAIs in reducing total hospital readmissions regardless of type of pre-treatment admission history (voluntary vs. involuntary). LAIs appear to be effective in reducing both voluntary and involuntary hospital readmissions in patients with psychosis and bipolar disorder with a history of poor adherence to treatment.

1. Introduction

1.1. Prevalence and economic burden of psychosis and bipolar disorder

Schizophrenia and bipolar disorder are chronic severe mental illnesses affecting patients' lives in many aspects (Grant et al., 2001; Vieta et al., 2018). The life-time prevalence of both is about 1 % (Bebbington and Ramana, 1995; Moreno-Küstner et al., 2018; Pini et al., 2005; Saha et al., 2005). Despite its relatively low prevalence (Baxter et al., 2013), psychosis contributes highly to the global burden of disease (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). The economic burden of schizophrenia was found to be very high not only for patients but also for caregivers and society, while it was estimated to range from 0.02 % to 1.65 % of the gross domestic product (Chong et al., 2016). Similarly, economic burden is extremely high for bipolar disorder, while it is estimated that the total annual economic cost in US is more than $195 billion and 25 % is attributed to medical expenses (Bessonova et al., 2020).

Psychosis and bipolar disorder due to chronicity and persisting symptoms (American Psychiatric Association, 2013; Peritogiannis et al., 2020) require long-term treatment with antipsychotic medication, which appear to be efficacious for relapse prevention (Kusumakar, 2002; Leucht et al., 2003; Lindström et al., 2017; Marcus et al., 2015).

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https://doi.org/10.1016/j.psychres.2023.115676
Received 29 July 2023; Received in revised form 7 December 2023; Accepted 14 December 2023
Available online 24 December 2023

1.2. Noncompliance to treatment and the potential role of LAIs

Adherence to medication is often remarkably low in chronic mental disorders, such as schizophrenia and bipolar disorder (García et al., 2016), estimated at 42 % (Cramer and Rosenheck, 1998) and 41 %, respectively (Lingam and Scott, 2002). Poor insight, perceived risk of treatment (e.g. medication side effects), cognitive impairment and poor therapeutic alliance are key factors contributing to noncompliance (García et al., 2016; Perkins, 2002), which is associated with increased relapse rate and poor long-term illness outcome (Hui et al., 2013; Lindström et al., 2017).

Continuity of oral antipsychotic medication could protect patients with psychosis (Hui et al., 2013) or with bipolar disorder (Lindström et al., 2017) from relapses. Long-acting injectable antipsychotics (LAIs; also referred to as depot antipsychotics), have been reported to improve continuity of treatment in patients with poor adherence and insight by reducing dosing frequency and offering predefined medication delivery, stable pharmacokinetics (Kane, 2006; Park et al., 2013) and better tolerability (Schneider-Thoma et al., 2022). Huang et al. (2021) have concluded that prescription of LAIs in early stages of psychosis could significantly decrease the risk of mortality and suicidality.

1.3. Effectiveness of LAIs in preventing clinical relapses

Meta-analyses of randomized, cohort and pre-post studies (Kishimoto et al., 2021) and meta-analyses of mirror-image studies (Kishimoto et al., 2013b) have shown that LAIs are superior compared to oral antipsychotics in preventing relapses and in reducing the number of hospitalizations in patients with schizophrenia. Lambert et al. (2011) reported a reduction in hospitalizations of over 50 % in patients with schizophrenia using LAI treatment across four countries (US, Spain, Australia and Belgium). Also, it has been reported that prescription of LAIs in patients with poor prognosis in first-episode psychosis could be beneficial in decreasing hospital readmissions and relapses by preventing deterioration of their functionality (Abdel-Baki et al., 2020; Barrio et al., 2013; Schreiner et al., 2014; Tiihonen et al., 2011). However, a meta-analysis of randomized clinical trials (RCTs) failed to find evidence of LAI superiority over oral medication in reducing risk of relapse in patients with schizophrenia (Kishimoto et al., 2014).

Similar results have been reported for the usefulness of LAIs in patients with affective disorders. Individual studies and systematic reviews comparing different treatment formulations (LAIs vs. placebo and LAIs vs. oral antipsychotics) concluded that prescription of LAIs in patients with bipolar disorder or schizoaffective disorder was an effective and well-tolerated maintenance treatment option (Gigante et al., 2012; El-Mallakh, 2007; Vieta et al., 2008, 2012; Pacchiarotti et al., 2019; Kishi et al., 2016).

1.4. First- vs. second-generation LAIs: are they different?

Typically, LAI antipsychotics are divided into first (typical) and second (atypical) generation agents (FGA vs. SGA). The two types of medication are distinguished in terms of their clinical availability by a period of three decades and are different in terms of chemical structure and pharmacological properties (Park et al., 2013). First-generation antipsychotics include haloperidol and zuclopenthixol mostly used in Europe and fluphenazine in US, while second-generation antipsychotics include risperidone, paliperidone, olanzapine and aripiprazole (Park et al., 2013). Second-generation antipsychotics appear to be preferred by clinicians as they have minimal or no extrapyramidal side effects (Leucht et al., 2003; Park et al., 2013). Studies comparing effectiveness between first- and second-generation medication treatments report inconsistent results. Some studies reported comparable effectiveness in reducing time-to-readmission between patients with schizophrenia using SGA LAIs vs. those using FGA LAIs (Stone et al., 2018; Patel et al., 2018), whereas others have found that SGA LAIs are more effective in preventing readmissions (Grimaldi-Bensouda et al., 2012). Furthermore, it has been found that SGA LAIs are superior in preventing manic relapses without worsening depression compared to FGA LAIs (Gigante et al., 2012).

1.5. Aims of the study

The main objective of the study is to examine the effectiveness of long-acting injectable (LAI) treatment vs. oral medication in terms of hospital readmissions of patients with psychotic or bipolar disorder based on data from the Depot Clinic, Department of Psychiatry, University of Crete General Hospital and the affiliated Mobile Mental Health Unit (MMHU). Specifically, we hypothesized that patients diagnosed with psychosis or bipolar disorder, who receive LAI antipsychotic medication would have fewer hospital readmissions compared to an equal-length period preceding the onset of LAIs administration when they were treated solely with oral antipsychotics. A secondary aim is to compare the effectiveness of LAIs in reducing hospital readmissions in two patient subgroups: those with a history of predominant voluntary hospitalizations before the onset of LAI treatment and those with a history of mainly involuntary hospitalizations. Finally, we examined and compared the effectiveness of first vs. second generation LAIs in terms of hospital readmissions.

2. Materials and methods

2.1. Patient sample

To be eligible for the study patients had to be: >18 years old; diagnosed with psychosis or bipolar disorder; to have received LAIs treatment for more than two years at the time of entering the study; and to have had at least one hospital admission in the Psychiatric Inpatient Unit prior to initiation treatment with LAIs. Exclusion criteria included: age >65 years; psychosis as a result of organic causes or substance use; comorbidity with moderate/severe mental impairment.

A sample of 382 patients, diagnosed with psychosis or bipolar disorder according to the International Classification of Diseases, Tenth Version (ICD-10) and receiving LAIs were identified in our database. The sample that met our inclusion/exclusion criteria comprised of 193 patients diagnosed with psychosis or bipolar disorder, of which 149 were men (77.2 %) and 44 were women (22.8 %), with a mean age of 48.1 years (S.D. = 11.35). The large majority of the sample consisted of patients with psychosis (n = 164, 85 %), whereas only 29 (15 %) of patients were diagnosed with bipolar disorder. LAIs were prescribed to this group of patients due to noncompliance to oral treatment medication. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of University of Crete (protocol code 34/09.11.2018, 10 December 2018 date of approval and protocol code 27/08.02.2023, 13 February 2023 date of approval).

2.2. Treatment settings

Patients living in urban Heraklion were receiving LAIs antipsychotics at a specialized Depot Clinic of the Department of Psychiatry, University of Crete General Hospital (n = 97). Patients diagnosed with psychosis or bipolar disorder living in rural and remote areas of Heraklion were receiving mental healthcare by the Mobile Mental Health Unit of Heraklion and injections were administered by the nursing staff of the Community Health Centers (CHC). LAIs were classified as first generation vs second generation medications based on the time they became clinically available. First-generation antipsychotics used in our participants included haloperidol and zuclopenthixol; second-generation antipsychotics included risperidone, paliperidone, olanzapine, and aripiprazole. Second-generation antipsychotics appear to be preferred by clinicians due to their minimal or no extrapyramidal side effects

(Leucht et al., 2003; Park et al., 2013).

2.3. Procedure

The clinical diagnoses were based on International Classification Diagnoses 10 edition (ICD-10), using a semi-structured clinical interview by board-certified psychiatrists. Demographic and clinical data (age, sex, diagnosis, substance abuse, living conditions, substance and type of medication (first generation antipsychotics vs. second generation vs. a combination of both) admissions (voluntary/involuntary) were retrieved from the electronic database of the MMHU and the Department of Psychiatry, University of Crete General Hospital.

2.4. Statistical analysis

Descriptive statistics for the demographic variables were summarized as means± standard deviations for continuous variables and frequencies and proportions for categorical variables.

The first research aim of the study involved comparing the pre- and an equal post-depot period determined individually for patient on the number of total, voluntary and involuntary admissions. Given that the distributions of the six variables displayed serious deviation from normality (as indicated by skewness > 2.8 and kurtosis > 11.7) Wilcoxon Signed-Rank Tests were used.

The main dependent variable in the context of the second research aim was change in the number of admissions that took place during the individually-defined period prior to LAI-treatment onset vs the number of admissions that took place after LAI prescription. Depot delay was determined as the time interval between the first hospitalization pre-treatment and the first LAI medication. Pre-depot period was determined as the time interval pre-treatment equal to the length time of depot treatment (measured up to January 2023). Depot duration was defined as the time period that patients were receiving LAI medication. Although the distribution of values was quite symmetric (as indicated by skewness values $< |1|$ for total number, involuntary and voluntary admissions), distributions were highly leptokurtic. Accordingly, we performed non-parametric univariate analyses using the Mann-Whitney U test to compare various patient subgroups on the magnitude of change in hospital admissions. Subgroups were formed according to the relative preponderance of voluntary over involuntary admissions prior to LAI treatment. Patients were assigned to the predominantly voluntary admissions group if they had a higher number of voluntary admissions compared to involuntary admissions. The reverse was true for patients assigned to the predominantly involuntary admissions group. The effectiveness of LAI treatment was further assessed at the patient level by categorizing patients into three additional subgroups: those who had more, less, or the same number of hospitalizations in the post-LAI period as compared to an equal-length pretreatment period. A three-by-two chi-square test was performed to test overall differences in proportions between the three groups (defined on the direction of change in admissions) and the two groups formed according to the predominant type of pre-LAI hospitalization (voluntary or involuntary).

Two sets of supplementary multivariate analyses were performed after transforming the dependent variables (change in number of admissions) using the Box-Cox method resulting in distributions that presented acceptable similarity to the normal distribution as indicated by skewness and kurtosis values $< |1|$ (Box & Cox, 1964). Initially we compared the predominantly voluntary and predominantly involuntary hospitalizations groups on the degree of change in post-LAI treatment by controlling for potentially important clinical (history of substance abuse) and demographic variables (age, gender) through ANCOVA. In addition, we conducted three multiple linear regression models to assess the contribution of treatment history (delay from diagnosis to the onset of LAI treatment), history of substance abuse) and demographic variables (age, gender) on the change in total, voluntary and involuntary admission frequency. The statistical analysis was performed in IBM SPSS v. 26 and the significance level was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics of patients

The final sample consisted of 193 patients diagnosed with psychotic or bipolar disorder (Table 1). More than half of the patients were living in rural and remote areas and were receiving mental healthcare by MMHU ($N = 95$, 54.9 %), while 78 patients (45.1 %) were living in urban areas in Heraklion. Twenty patients were missing information about their exact residence. All patients were receiving LAI medication for at least 2 years. First generation LAIs were prescribed to 27.1 % ($n = 52$) of the patient sample, while 58.9 % ($n = 113$) of the sample was receiving second generation LAIs. A combination of first and second generation LAIs were prescribed to 14.1 % ($n = 27$) of the patients. The mean duration of LAIs treatment was 5.56 years (S.D. = 2.50), while the mean pre-treatment interval, which was equal to depot duration, was 5.56 years (S.D. = 2.50).

3.2. Change in inpatient admissions before and after LAI treatment

Regarding the first research aim of the study, the average number of hospitalizations before and after prescription of LAIs are presented in Table 2 for the total sample, revealing a statistically significant decrease of 45.2 % after starting LAI antipsychotic medication compared to the patient-adjusted, pre-treatment period ($z = -6.39$, $p < 0.001$). This effect was similar for voluntary ($z = -3.76$, $p < 0.001$, 42.3 %) and involuntary hospitalizations ($z = -5.68$, $p < 0.001$, 46.1 %).

3.3. Change in inpatient admissions before and after LAI treatment as a function of predominant, pretreatment type of hospitalization

The second aim of the present study involved computing change in the number of hospitalizations separately for patients with a history of predominantly voluntary vs. predominantly involuntary admissions prior to LAI treatment (see Table 3). Both patient groups showed statistically significant reduction in the total number of admissions (predominantly voluntary hospitalizations group: $z = -4.48$, $p < 0.001$, predominantly involuntary hospitalizations group: $z = -4.48$, $p < 0.001$). The magnitude of reduction in total readmissions was higher for the former (60.8 %) than for the latter group (34.6 %) although this difference did not approach significance (U (63,122) = 3415.00, $p = 0.204$). The ANCOVA model confirmed that the degree of change in the total number of admissions did not vary between predominantly voluntary and predominantly involuntary patient subgroups even after controlling for age, gender, and history of substance abuse ($p = 0.8$).

Table 1
Descriptive and clinical characteristics of study participants ($n = 193$).

Variables	N	%	Variables	M	S.D.
Gender			Age	48.08	11.35
Men	149	77.2	*Men*	48.54	10.72
Women	44	22.8	*Women*	46.55	13.25
Diagnoses			Pre-depot period	5.56	2.50
Psychosis	164	85.0	Depot duration	5.56	2.50
Bipolar disorder	29	15.0			
Place of residence					
Urban- Hospital	78	45.1			
Rural- MMHU	95	54.9			
LAI generation					
1st generation	52	27.1			
2nd generation	113	58.9			
1st & 2nd generation	27	14.1			

Pre-depot period: time interval pre-treatment equal in terms of the length time of depot treatment.
Depot duration: time period that patients were receiving LAI medication.

Table 2
Average number of admissions prior and after LAI treatment in the total sample ($n = 193$).

Hospitalizations	Period	M	SD	Range	Z	p
Total	Pre	2.63	2.52	1–19	−6.39	<0.001
	Post	1.44	2.85	0–23		
Voluntary	Pre	1.04	1.72	0–12	−3.76	<0.001
	Post	0.60	1.35	0–9		
Involuntary	Pre	1.56	1.79	0–9	−5.68	<0.001
	Post	0.84	2.12	0–17		

Table 3
Average number of admissions prior to and after LAI treatment for patients with a history of predominantly voluntary or mainly involuntary hospital admissions before treatment with LAIs ($n = 185$).

		Patients with a pre-LAI history of predominantly voluntary hospitalizations ($n = 63$)				
Hospitalizations	Period	M	SD	Range	Z	p
Total	Pre	2.76	3.21	1–19	−4.48	<0.001
	Post	1.08	1.92	0–9		
Voluntary	Pre	2.30	2.28	1–12	−5.77	<0.001
	Post	0.65	1.24	0–6		
Involuntary	Pre	0.46	1.16	0–7	−0.55	0.580
	Post	0.46	1.40	0–9		
		Patients with a pre-LAI history of predominantly involuntary hospitalizations ($n = 122$)				
Total	Pre	2.54	2.10	1–10	−4.45	<0.001
	Post	1.66	3.25	0–23		
Voluntary	Pre	0.38	0.78	0–4	−1.26	0.206
	Post	0.60	1.43	0–9		
Involuntary	Pre	2.14	1.81	1–9	−6.02	<0.001
	Post	1.07	2.43	0–17		

Moreover, the percentage of patients who showed increased, decreased or identical number of total admissions in the pre- vs. post-LAI treatment periods were similar in the two subgroups (Table 4; $x^2 = 0.91$, df = 2, $p = 0.6$).

In supplementary analyses, we compared the two subgroups on the treatment effect (pre- vs. post-LAI treatment) according to the type of hospitalizations experienced. During the entire study period patients assigned to the predominantly voluntary admission group had 83.3 % voluntary and 16.7 % involuntary hospitalizations. This group displayed a significant reduction in the number of voluntary readmissions in the order of 71.1 % ($z = -5.77$, $p < 0.001$), with minimal change in the number of (the less frequent overall) involuntary readmissions ($z = -0.55$, $p = 0.580$). During the same period patients assigned to the predominantly involuntary admission group had 15.8 % voluntary and 84.2 % involuntary hospitalizations. This group displayed a significant reduction in the number of involuntary readmissions (50 %; $z = -6.02$, $p < 0.001$), and a non-significant increase in voluntary readmissions (averaging 0.38 pre-LAI vs. 0.60 hospitalizations post LAI treatment; $z = -1.26$, $p = 0.206$).

Table 4
Distribution of patients according to the direction of change in the number of post treatment readmissions and the predominant type of pre-treatment hospitalizations ($n = 180$).

	Predominant type of pre-LAI treatment hospitalizations						
	Voluntary		Involuntary				
Direction of change in the number of hospitalizations	n	%	n	%	Chi-square	df	p
No change	8	13.1	18	15.1	0.91	2	0.6
Increase	7	11.5	19	16.0			
Decrease	46	75.4	82	68.9			

Note. *No change*: patients had the same number of hospitalizations in the pre- and post-LAI periods; Assignment to the Increase or Decrease subgroups required corresponding change in at least one admission.

Finally, the magnitude of reduction in total hospital admissions was similar for patients treated at the University Hospital Depot Clinic vs. the MMHU (predominantly voluntary: U (32,26) = 399.00, $p = 0.787$, predominantly involuntary: U (66,52) = 1601.00, $p = 0.524$).

When we repeated the previously described analyses based only in patients with psychosis the results were similar (see supplement material). Analysis restricted to patients with bipolar disorder was not possible due to the small sample size.

3.4. Differences in readmission rate between patients receiving first or second LAIs medication

The comparisons reported in this section are between those receiving only first generation or only second generation LAIs. The decrease in total readmissions post-LAI medication was 59.5 % for the patient group receiving first-generation LAIs and 58.6 % for the patient group receiving second-generation LAIs (U (52,112) = 2829.00, $p = 0.763$).

Also, we found no differences in voluntary readmission rates after LAI treatment between patients receiving either first-generation or second-generation antipsychotics for both patient groups having either predominantly voluntary admissions ($x^2 = 1.321$, df = 1, $p = 0.307$) or having predominantly involuntary admissions pre-treatment ($x^2 = 0.158$, df = 1, $p = 0.787$). Similarly, there were no significant differences in terms of involuntary readmission rates between the patient group receiving first-generation LAIs vs. the patient group receiving second-generation LAIs (predominant voluntary: $x^2 = 1.239$, df = 1, $p = 0.406$, predominant involuntary: $x^2 = 0.383$, df = 1, $p = 0.773$) (Tables 5a and 5b). We should note that our sample size had sufficient power to reject the null hypothesis for the group with predominantly involuntary admissions (statistical significance at α=0.05, with at least 85 % power), whereas our sample size for the total group and the group with predominantly voluntary admissions did not have sufficient power.

3.5. Impact of pre-LAI treatment history on LAI treatment response

Results of multiple linear regression models indicated that the delay in starting LAI medication (in years following diagnosis) was negatively associated with the degree of reduction in total and involuntary post-LAI admissions controlling for age, gender, diagnosis, and history of substance abuse: B=−0.157, *95 %CI* = −0.228 to −0.086, $p < 0.001$ and B=−0.093, *95 %CI* = −0.145 to −0.040, $p = 0.001$). Notably, none of the other variables in the models approached significance ($p > 0.2$).

Table 5a
Differences in readmission rates between first and second generation LAIs in patients with predominantly voluntary readmissions pre-treatment ($n = 55$).

LAI Generation	Decrease		No change/Increase			
	N	%	N	%	Chi-square	p
Total hospitalizations						
First	14	77.8	4	22.2	0.344	0.7
Second	26	70.3	11	29.7		
Voluntary hospitalizations						
First	16	88.9	2	11.1	1.321	0.3
Second	28	75.7	9	24.3		
Involuntary hospitalizations						
First	1	5.6	17	94.4	1.239	0.4
Second	6	16.2	31	83.8		

Note: Chi-square tests for proportions with 1 degree of freedom.

Table 5b
Differences in readmission rates between first and second generation LAIs in patients with predominantly involuntary readmissions pre-treatment ($n = 104$).

LAI Generation	Decrease		No change/Increase			
	N	%	N	%	Chi-square	p
Total hospitalizations						
First	24	77.4	7	22.6	0.051	1
Second	55	75.3	18	24.7		
Voluntary hospitalizations						
First	5	16.1	26	83.9	0.158	0.8
Second	14	19.4	58	80.6		
Involuntary hospitalizations						
First	27	87.1	4	12.9	0.383	0.8
Second	60	82.2	13	17.8		

Note: Chi-square tests for proportions with 1 degree of freedom.

4. Discussion

Our data indicate that the prescription of LAIs in noncompliant patients with psychosis or bipolar disorder is an effective treatment in reducing hospital readmissions by almost 50 %. Also, LAIs were equally effective in reducing hospital readmissions between those with predominant voluntary vs. those with predominant involuntary admissions pre-treatment (71 % vs. 50 %). Finally, our data showed that the two types of LAIs, i.e. FGA vs. SGA, were equally effective in reducing total hospital readmissions, as well as in those with either predominant voluntary or involuntary admissions pre-treatment.

Previous research has shown that LAIs is a more effective treatment for patients with poor adherence and a high risk of relapses (Lieslehto et al., 2022; Olivares et al., 2009; Savas et al., 2006; Tiihonen et al., 2011; Vieta et al., 2008) Also, several studies have shown that LAIs are more effective in reducing hospital readmissions for either bipolar disorder (Vieta et al., 2012) or psychosis (Beauclair et al., 2007; Maestri et al., 2018; Pappa et al., 2023) and in delaying time-to-relapse (Hough et al., 2010; Gaebel et al., 2010) compared to oral antipsychotic medication. Also, a meta-analysis in pre-post studies indicated significant lower risk of readmission in patients with schizophrenia using LAIs as compared to oral antipsychotics (Kishimoto et al., 2021). Our results are consistent with these findings, showing that prescription of LAIs to non-compliant patients could decrease significantly both voluntary and involuntary hospital readmissions. Further, consistently with previous findings (Abdel-Baki et al., 2020; Lambert et al., 2011; Pacchiarotti et al., 2019), our results suggest that LAIs are superior to oral medications both in short-term and long-term use. In contrast, two previous meta-analyses based on randomized controlled clinical trials reported that LAIs were not superior to oral antipsychotics in relapse prevention, with the possible exception in the prevention of relapses among rapid cycling patients with bipolar disorder (Kishi et al., 2016; Kishimoto et al., 2014). Major methodological differences between the two types of studies are that in a cohort study like ours, the selection of the sample consists of noncompliant patients to oral medication and reflects better the "real world" clinical practice and that every subject is a control of him/herself reducing variance. In randomized controlled trials by the nature of the study design, patients are assigned based on their demographic and clinical similarities, and not on whether they are compliant to the treatment. Also, in most randomized controlled clinical studies the average length of treatment is between 6 and 24 months, whereas in cohort studies like our study the mean duration is much longer, e.g. 5.6 years.

Our study showed that there was an overall reduction of involuntary readmissions independent of the status of predominant voluntary or involuntary pre-treatment. This is consistent with a retrospective observational mirror-image study in Japan that concluded that SGA LAIs had significantly reduced involuntary readmissions in patients with schizophrenia (Horikoshi et al., 2022). Our study confirms and expands these findings in a larger sample and for a longer follow-up period.

Research on the potential differential effectiveness of LAIs treatment in those who were admitted pre-treatment voluntarily vs. involuntarily is lacking. Our study, based on a large sample that was followed for a long period (5.6 years), showed that LAIs treatment was equally effective in those admitted pre-treatment voluntarily vs. involuntarily. This indicates that LAI treatment is effective even in those that they have the worst non-compliant record and therefore prognosis.

Our findings indicated no differences in the effectiveness of first- and second-generation LAIs in decreasing overall as well as voluntary and involuntary readmissions. Also, no differences were observed between patient groups that pre-treatment were admitted predominantly voluntarily vs. predominantly involuntarily. These results are consistent with previous research that concluded there was no differences in effectiveness between FGA LAIs and SGA LAIs in reducing readmissions (Patel et al., 2018) and in time-to-readmission (Stone et al., 2018). In contrast, two studies suggested that SGA LAIs treatment compared with FGA LAIs was superior in preventing relapses and readmissions (Grimaldi--Bensouda et al., 2012; Kishimoto et al., 2013a). However, our sample was based on non-adherent patients with psychosis or bipolar disorder with a mean follow-up period of about 6 years compared to the mean follow-up period of only 12 months of the previous studies (Grimaldi--Bensouda et al., 2012; Kishimoto et al., 2013a).

4.1. Strengths and limitations

Our research has some noteworthy strengths. First, our sample is large and recruited from patients living both in urban and rural areas of Crete. Second, our study has one of the longest follow-up periods, with a mean period of 5.6 years. Third, our study examined and compared the effectiveness of LAIs between patients admitted predominantly voluntarily vs. those admitted predominantly involuntarily. Fourth, our study with its naturalistic design reflects better the "real world" clinical practice, compared to studies such as RCTs which are not representative of typical clinical practice (Kane et al., 2013). Finally, to our knowledge, this is the first study in Greece that examines the effectiveness of LAIs in decreasing readmissions in non-compliant patients.

Despite the strengths of our study, some limitations that should be noted. Our study did not include a control parallel comparative group on oral antipsychotic medication. Also, our study is based on a single-center population, compared to a multi-centered population. In addition, the sample size of patients with bipolar disorder was small not allowing for a separate analysis. Finally, our results comparing the effectiveness of the first- and second-generation LAIs should be considered tentative since we had sufficient power to test the statistical significance only in the group with predominantly involuntary admissions.

4.2. Clinical implications

This study suggests that LAIs are effective in reducing the risk and the number of readmissions, both voluntary and involuntary, in patients with severe and chronic mental disorders and a history of poor compliance to treatment. Also, LAIs are effective in decreasing readmissions compared to oral medication treatment regardless of whether patients were admitted predominantly voluntarily vs. predominantly involuntarily pre-treatment. Furthermore, due to the equal effectiveness of both FGA and SGA LAIs in decreasing of readmission, the prescription of LAIs should be based on each patient's needs and clinical profile. Finally, our tentative results suggest that they should be administered early during the course of illness. Our University Mobile Unit prescribes regularly LAIs in about 45 % in patients with psychosis or bipolar disorder, which is higher than the percentage reported by other Mobile Units in Greece. For example, Peritogiannis et al. (2023) reported that only 30 % of patients treated by MMHU-I (Mobile Mental Health Unit of

Ioannina) were prescribed LAIs medication and 76.9 % of them were receiving a second-generation LAI.

Our data support the clinical usefulness of LAIs in patients with severe mental disorders and suggest the need for education of both clinicians and patients and their families about the long-term effectiveness and safety of this treatment approach (Paton et al., 2022). Finally, given that LAI antipsychotic medications may be a key modality for lowering expenses, alleviating symptoms, and promoting quality of life outcomes in patients with psychosis and bipolar disorder, the findings of this study may have implications in terms of public mental health policies.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of University of Crete (protocol code 34/09.11.2018 and 10–12–2018 date of approval & protocol code 27/08.02.2023, 13 February 2023 date of approval).

Informed consent statement

Not applicable.

Funding

"This research was partially funded by the Region of Crete, grant number 152721/05-07-2018"

CRediT authorship contribution statement

Alexandros N. Vgontzas: Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing, Validation. **Anna Paschalidou:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Panagiotis G. Simos:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Validation. **Maria Anastasaki:** Investigation, Writing – original draft, Writing – review & editing. **Avgi Zografaki:** Investigation, Writing – original draft, Writing – review & editing. **Emmanouil Volikos:** Investigation, Writing – review & editing. **Katerina Koutra:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Maria Basta:** Investigation, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Authors declare no conflict of interest.

Data availability

The clinical data used for the study are kept in the Department of Psychiatry and MMHU Medical charts and are confidential

Acknowledgments

The support of the attending and in-training psychiatrists of Department of Psychiatry of the University Hospital in Heraklion who rotated through MMHU is greatly appreciated.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115676.

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