

REHOSPITALIZATION RATES AMONG PATIENTS WITH PSYCHOTIC DISORDERS DURING COVID-19 PANDEMIC: ORAL VERSUS LONG-ACTING INJECTABLE ANTIPSYCHOTICS

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Abstract

Objective: The superiority of long-acting injectable antipsychotics (LAIs) versus oral antipsychotics is often emphasized, even in terms of adherence and rehospitalization rates. As such, LAIs are particularly recommended during the COVID-19 pandemic. The goal of our research was to determine whether there are differences in the number of rehospitalizations in patients treated for schizophrenia, schizophrenia-like disorders, and delusional states (psychotic disorders) with LAI antipsychotics versus oral antipsychotics.

Method: Subjects with schizophrenia, schizophrenia-like disorders and delusional states participated in our retrospective study. 124 subjects were treated with oral antipsychotics, while 72 received LAIs along with oral antipsychotics. We collected their sociodemographic data and psychiatric history data. Our main outcome measure was the number of rehospitalizations.

Results: Statistical analysis showed that the studied groups did not differ according to sociodemographic parameters, except that in the group of patients with LAIs there was a significantly higher percentage of men (65 (52.4) vs 50 (69.4), $p=0.029$). Also, the groups do not differ according to the psychiatric history data. There is no difference in the duration of the current hospitalization nor in the composition of the patients, considering the order of the current hospitalization. The difference in the number of rehospitalizations is not significant neither in the first year of follow-up ($p=0.144$), nor in the second ($p=0.142$), nor after two years of follow-up ($p=0.083$).

Conclusions: Our research has shown that there is no difference in the number of rehospitalizations in patients with schizophrenia, schizophrenia-like disorders and delusional states, considering whether they take oral antipsychotics or they also take LAIs along with them. We can therefore conclude that it is particularly important to work on improving patient adherence. We must make psychiatrists aware that the pandemic, like other threats, can be our ally in improving adherence ("perceived threat as a health belief").

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1. Introduction

The COVID-19 pandemic brought numerous challenges to psychiatry (Borovina et al., 2021). The introduced anti-pandemic measures and the change in the organization and priorities of health care made adequate psychiatric treatment more difficult (Mutlu & Anil Yağcıoğlu, 2021). The same changes contributed to the deterioration of mental health (Borovina et al., 2022). Patients with schizophrenia, disorders similar to schizophrenia and delusional states (psychotic disorders) are a particularly vulnerable group whose problem is cooperation, i.e. taking the prescribed therapy

(adherence). Long-acting injectable antipsychotics (LAIs) are normally, and especially in times of a pandemic, seen as a possible solution to that problem (Mutlu & Anil Yağcıoğlu, 2021). The results of research into the effect of LAIs, in relation to oral antipsychotics, on the number of rehospitalizations of patients with psychotic disorders are currently unclear (Kirson et al., 2013; Marcus et al., 2015). Data on this topic for the period of the pandemic are extremely scarce (Mutlu & Anil Yağcıoğlu, 2021).

The aim of our study is therefore to determine whether there is a difference in the number of rehospitalizations

during the COVID-19 pandemic in patients with psychotic disorders, considering whether they use LAIs in addition to oral antipsychotics or they take only oral antipsychotics.

2. Subjects and methods

The research was approved by the Ethics Committee of Clinical Hospital Center (CHC) Split.

This is a retrospective study, which includes subjects who were hospitalized at the Clinic for Psychiatry of CHC Split in the period from October 1, 2019 until January 31, 2020 (on that date The World Health Organization International Health Regulation Emergency Committee reconvenes and declares the coronavirus outbreak a Public Health Emergency of International Concern) (Centers for Disease Control and Prevention, 2022). All of them were treated for psychotic disorders, i.e. under diagnosis F20-F29. They meet the criteria according to ICD-10 and DSM-5 (American Psychiatric Association, 2013; World Health Organization, 1992). In the mentioned period, 228 patients with a diagnosis of psychotic disorder were discharged from hospital treatment at our Clinic. 196 respondents (86%) were included in the research. These are only those patients that we could monitor in the hospital IT system and/or contact by phone over the next two years (up to the period from October 1, 2021 to January 31, 2022). They were treated with the same form of therapy throughout the entire period, even after rehospitalization. Based on this, they were divided into two groups: 124 subjects with oral therapy and 72 subjects with oral therapy and LAIs. After one year, due to death, the group with oral therapy had 120 subjects, and the group with LAIs and oral therapy had 71 respondents. 32 patients were not included because they could not be contacted or because they stopped taking therapy completely or they stopped/started LAIs after rehospitalization. Sociodemographic data were taken from all respondents: gender, age, education (Didn't finish elementary school, Elementary school, High school, Bachelor's degree, Master's degree), marital status (Married, Single), cohabitation (Doesn't live alone, Lives alone), employment (Retirement pension/

employed/student, Disability pension/unemployed). We also recorded psychiatric comorbidities: F43.1, F60.3, F70, F33/F32, F63.3. We checked psychiatric heredity and the use of psychoactive substances, including alcohol, and what type it was (F10, F11, F12, F19). Then we checked how long the respondents have been treated (shorter or longer than 5 years) and how many days their current hospitalization lasted (the one with which we started observation) and which hospitalization in order it was (1st hospitalization, 2nd or 3rd hospitalization, 4th or more hospitalization). For all subjects, we checked the number of rehospitalizations during the first year of follow-up, during the second year and the total number of rehospitalizations after two years.

Statistical analysis of the collected data was performed using the statistical program MedCalc (Medcal Software, Ostend, Belgium, version 20.112). Quantitative continuous variables are presented as arithmetic mean \pm standard deviation, and non-continuous variables as median (interquartile range). Qualitative variables are presented as whole number and percentage. The assessment of the normality of the distribution of variables was performed using the Kolmogorov-Smirnov test. Comparison between continuous quantitative variables was performed using the t-test for independent variables, while comparison between qualitative variables was performed using the chi-square test or Fisher's exact test. The level of statistical significance was set at $P < 0.05$.

3. Results

The study included 196 respondents who are being treated for schizophrenia, schizophrenia-like disorders, and delusional states. 72 subjects receive LAIs, in addition to oral therapy. 124 respondents take only oral therapy. After one year, due to the death of the respondents, there are 71 respondents in the first group and 120 respondents in the second group.

Statistical analysis showed that the examined groups did not differ according to sociodemographic parameters, except that in the group of patients with LAIs there was a significantly higher percentage of men (65 (52.4) vs 50 (69.4), $p=0.029$) (table 1).

Table 1. Baseline Sociodemographic Parameters of the Study Population

Parameter	Study sample N=196	Pills group N=124	Depo group N=72	<i>p</i> *
Male gender (N, %)	115 (58.7)	65 (52.4)	50 (69.4)	0.029
Age (years)	44.7 \pm 12.6	45.3 \pm 13.3	43.8 \pm 11.4	0.420
Education (N, %)				
Didn't finish elementary school	10 (5.1)	7 (5.6)	3 (4.2)	
Elementary school	19 (9.7)	14 (11.3)	5 (6.9)	
High school	146 (74.5)	89 (71.8)	57 (79.2)	0.775
Bachelor's degree	19 (9.7)	13 (10.5)	6 (8.3)	
Master's degree	2 (1.0)	1 (0.8)	1 (1.4)	
Marital status (N, %)				
Married	36 (18.4)	27 (21.8)	9 (12.5)	
Single	160 (81.6)	97 (78.2)	63 (87.5)	0.154
Living situation (N, %)				
Doesn't live alone	140 (71.4)	89 (71.8)	51 (70.8)	
Lives alone	54 (27.6)	35 (28.2)	21 (29.2)	0.923
Employment (N, %)				
Retirement pension / employed / student	56 (28.6)	33 (26.6)	23 (31.9)	
Disability pension / unemployed	140 (71.4)	91 (73.4)	49 (68.1)	0.527

Note. All data is presented as whole number (percentage) or mean \pm standard deviation.

* chi-square test or t-test for independent samples

Also, the groups do not differ according to the psychiatric history data (table 2).

Figure 1 shows us that there is no difference in the duration of the current hospitalization (from which we observe the respondents) between the examined groups.

Table 3 shows that the studied groups do not differ in the composition of patients, considering the order of the current hospitalization.

Statistical analysis showed that there is no significant difference between patients treated for schizophrenia, schizophrenia-like disorders and delusional states in the number of rehospitalizations in the first year of follow-up, nor in the second nor after two years of follow-up, regardless of whether they were treated with oral antipsychotics or oral and LAIs (table 3).

delusional states (Marcus et al., 2015). Therefore, in the challenging times of the COVID-19 pandemic, they are imposed as a logical choice (Borovina et al., 2021; Lazzari et al., 2020; Nystazaki & Karanikola, 2022). However, we have found only one paper comparing LAIs and oral antipsychotics on the basis of the frequency of disease relapse (schizophrenia/schizoaffective disorder, bipolar disorder) during the COVID-19 pandemic. In that paper, Mutlu et al. did not establish the superiority of LAI antipsychotics (Mutlu & Anıl Yağcıoğlu, 2021). This corresponds to the results of our research. Our examined groups do not differ in any way, except that there is a significantly higher proportion of men among the subjects with LAIs. Adherence is generally weaker in men, which could explain why LAIs did not prove to

Table 2. Psychiatric Anamnesis of the Study Population

Parameter	Study sample N=196	Pills group N=124	Depo group N=72	p*
Main psychiatric diagnosis (N, %)				
Schizophrenia	83 (42.3)	48 (38.7)	35 (48.6)	0.219
Delusional disorders	3 (1.5)	2 (1.6)	1 (1.4)	
Brief psychotic disorder	50 (25.5)	33 (26.6)	17 (26.3)	
Schizoaffective disorders	29 (14.8)	19 (15.3)	10 (13.9)	
Unspecified psychosis	20 (10.2)	11 (8.9)	9 (12.5)	
Other psychotic disorder	3 (1.5)	3 (2.4)	0 (0)	
Schizotypal disorder	8 (4.1)	8 (6.5)	0 (0)	
Psychiatric comorbidity (N, %)				
None	156 (79.6)	94 (75.8)	62 (86.1)	0.154
Post-traumatic stress disorder	19 (9.7)	15 (12.1)	4 (5.6)	
Borderline personality disorder	11 (5.6)	7 (5.6)	4 (5.6)	
Mild mental retardation	8 (4.1)	6 (4.8)	2 (2.8)	
Depressive episode/disorder	1 (0.5)	1 (0.8)	0 (0)	
Trichotillomania	1 (0.5)	1 (0.8)	0 (0)	
Psychiatric heredity (N, %)				
Negative	153 (78.1)	97 (78.2)	56 (77.8)	0.915
Positive	43 (21.9)	27 (21.8)	16 (22.2)	
Psychoactive drugs and alcohol (N, %)				
Uses	35 (17.9)	23 (18.5)	12 (16.7)	0.890
Doesn't use	161 (82.1)	101 (81.5)	60 (83.3)	
Type of psychoactive drug (N, %)				
None	161 (82.1)	101 (81.5)	60 (83.3)	0.890
Alcohol	20 (10.2)	13 (10.5)	7 (9.7)	
Cannabinoids	4 (2.0)	2 (1.6)	2 (2.8)	
Multiple drug use	10 (5.1)	7 (5.6)	3 (4.2)	
Opioids	1 (0.5)	1 (0.8)	0 (0)	
Duration of therapy (N, %)				
< 5 years	43 (21.9)	27 (21.8)	16 (22.2)	0.923
> 5 years	153 (78.1)	97 (78.2)	56 (77.8)	

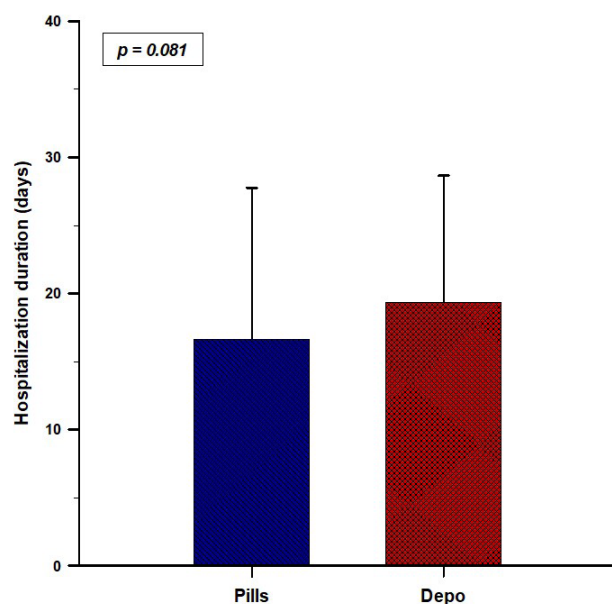
Note. All data is presented as whole number (percentage) or mean ± standard deviation.

* chi-square test

4. Discussion

Good patient adherence is always cited as an advantage of long-acting injectable antipsychotics (Jakovljević, 2014; Marcus et al., 2015). Also, their superiority over oral antipsychotics is highlighted when it comes to the risk of rehospitalization of patients with schizophrenia, schizophrenia-like disorders and

be superior (Smith et al., 1997). However, in the study by Marcus and colleagues, which is about the better effectiveness of LAIs compared to oral antipsychotics, there are also significantly more male subjects (Marcus et al., 2015). Sociodemographic parameters that could possibly influence adherence and thus the frequency of rehospitalization are the same here for both groups of examined patients (Higashi et al., 2013; Kuwabara et

Figure 1. Difference of the Hospitalization Duration Between the Depo Group (N=72) and Pills Group (N=124)

Note. DATA: Pills – 16.63 ± 11.12 vs Depo – 19.36 ± 9.29

Table 3. Hospitalization Data of the Study Population

Parameter	Study sample	Pills group	Depo group	p*
	N=196	N=124	N=72	
<u>Current hospitalization number (N, %)</u>				
1 st hospitalization	32 (16.3)	23 (18.5)	9 (12.5)	0.350
2 nd or 3 rd hospitalization	21 (10.7)	11 (8.9)	10 (13.9)	
4 th or more hospitalization	143 (73.0)	90 (72.6)	53 (73.6)	
<u>Rehospitalization number during 1st year (N, %)</u>	0.76 ± 1.18	0.85 ± 1.22	0.59 ± 1.10	0.144
<u>Rehospitalization number during 2nd year (N, %)</u>	0.51 ± 0.99	0.60 ± 1.08	0.38 ± 0.83	0.142 [†]
<u>Total rehospitalization number during 2 years (N, %)</u>	1.28 ± 1.85	1.46 ± 1.97	0.98 ± 1.61	0.083 [†]

Note. All data is presented as whole number (percentage) or mean ± standard deviation.

* chi-square test or t-test for independent samples

† four patients from pills group and one patient from depo group died after 1st year

al., 2015). Of these, only age can be singled out as a possible explanation for the lack of superiority of LAIs. Namely, LAIs have so far proven to be more effective in patients younger than 40 years (Mutlu & Anıl Yağcıoğlu, 2021). In our study, the mean age was 43.8 ± 11.4 years (table 1). The groups do not differ even in the psychiatric history data, which could otherwise affect the rate of rehospitalization (Higashi et al., 2013). A possible explanation for the lack of difference in the number of rehospitalizations between the examined groups can be in the concept of "perceived threat as a health belief". Today, it is known that the perception of health risks can positively influence patient adherence (Carpenter, 2005). Perhaps the state of global health threat, i.e. the pandemic, led to an improvement in adherence in both groups of patients and thus erased the differences in the number of rehospitalizations (Borovina et al., 2021; Lazzari et al., 2020; Mutlu & Anıl Yağcıoğlu, 2021).

Research is otherwise unclear, even from pre-pandemic times, when comparing the effectiveness of oral antipsychotics and LAIs. Kirson et al. in their meta-analysis stated that RCTs did not show an advantage of LAIs when the data were adjusted for gender and age.

On the other hand, LAIs show benefits in observational studies (Kirson et al., 2013). In the study by Marcus and colleagues, which confirms better adherence and lower rehospitalization rates in subjects with LAIs compared to oral antipsychotics, the mean and median age of the subjects were less than 40 years (Marcus et al., 2015). We can wonder about the value of these results if we know that LAIs are more effective in people younger than 40 (Mutlu & Anıl Yağcıoğlu, 2021). Kazgan et al. present data on the better functionality of patients with schizophrenia on LAIs, but not on the rate of rehospitalization (Kazgan et al., 2021). In addition to the above, Misawa et al. showed in their meta-analysis, in which they compared the same LAIs and oral antipsychotics, that they did not differ in serious side effects nor in more than 90% of side effects (Misawa et al., 2016).

5. Strengths, novelty and clinical implications

We believe that our study is significant because so far only one study dealing with this issue has been published. In that study, Mutlu et al. monitored the respondents for 3 months, while we monitored them for

2 years (Mutlu & Anil Yağcıoğlu, 2021). Also, there are no significant differences between the examined groups, except for gender, the role of which we discussed, which gives credibility to the results. From the results of our research, as well as from the available medical literature, it is clear how important adherence, i.e. a good therapeutic relationship, is, regardless of the form of therapy (Higashi et al., 2013).

6. Limitations

Limitations of our study certainly exist. In addition to the number of respondents, telephone follow-up of respondents is also a limitation, as there is a possibility of giving desirable answers. In addition to LAIs, our subjects also take oral antipsychotics, as in most other studies, but for a more precise discussion about LAIs, more studies are needed in which part of the subjects receive only this form of therapy. Our subjects received different antipsychotics, in both groups, and it would be useful to compare the data for the same antipsychotics. The shortcoming of the study is that we do not know the clear causes of rehospitalizations, but we can assume that the majority of them are due to discontinuation of therapy. The cause can also be the consumption of psychoactive substances, including alcohol. It is equally present in both groups, but we do not know how it changed during the two years of follow-up.

7. Conclusion

Our research has shown that there is no difference in the number of rehospitalizations in patients with schizophrenia, schizophrenia-like disorders and delusional states, considering whether they take oral antipsychotics or they take LAIs along with them. We can therefore conclude that it is particularly important to work on improving patient adherence, for which there are proven methods (Smith et al., 1997). We must make psychiatrist aware that the pandemic, like other threats, can be our ally in improving adherence ("perceived threat as a health belief") (Carpenter, 2005). Additional research is certainly needed on the effectiveness of LAI antipsychotics compared to oral antipsychotics, especially with subjects receiving one form of therapy (LAIs or oral) and the same antipsychotic.

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