



# Comparing re-hospitalization rates in a real-world naturalistic 24-month follow-up of psychotic patients with different treatment strategies: oral versus LAI antipsychotics

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Abstract

**Aim & background:** Non-adherence to antipsychotic treatment is a major issue in the management of severe psychiatric disorders, because it is usually related to future relapses and re-hospitalizations. Long-Acting-Injection (LAI) antipsychotics can be useful to increase treatment adherence in these patients. The aim of the present study was to compare the re-hospitalization rates of psychotic patients discharged from a psychiatric ward and then divided into three groups upon the treatment received: LAI antipsychotic, oral antipsychotic at home, or oral antipsychotic administered daily by psychiatric nurse staff as patients lived in a long-term care facility.

**Methods:** Data on all inpatients consecutively admitted to the Psychiatric Unit of the Nuovo Ospedale Apuano (Massa, Italy), between January 2017 and December 2018, were obtained by the registration record system. Information about eventual re-hospitalizations of these patients, occurred within a 24-month timeframe since discharge, were collected from the same database.

**Results:** In a Kaplan-Meier analysis, patients treated with LAI antipsychotics showed significantly lower re-hospitalization rates in the first 24 months after discharge than those treated with oral ones.

**Conclusions:** This study highlights the impact of LAI antipsychotics in preventing re-hospitalization in severe psychotic patients at high risk in a naturalistic setting. The benefits appear relevant also with respect to a controlled long-term oral antipsychotic treatment, however further studies are needed to develop more tailored intervention strategies in such complex psychiatric population.

**Keywords:** psychosis, schizophrenia, antipsychotic, LAI, long-term care facility, hospitalization, relapse

### What is already known about this topic?

Non-adherence to antipsychotic treatment is a major issue in the treatment of severe psychiatric disorders, because it is usually related to future relapses and re-hospitalizations. Long-Acting-Injection antipsychotics can be useful in increase treatment adherence in such patients.

## **'What does this article add?'**

This study highlights the advantage of LAI antipsychotics with respect with oral ones administered at home or in long-term care facility in preventing re-hospitalization.

### **1. Introduction**

Relapses occur frequently in the course of severe mental illnesses, such as Bipolar Disorder (BD), Schizophrenia (SCH) or Schizoaffective Disorder (SAD)<sup>1,2</sup>. In both clinical trials and naturalistic studies on individuals with SCH, one-year relapse rates result to be around 30%<sup>1,3</sup>, while lifetime rates reach up to 70%<sup>4</sup>. Despite the lack of a global consensus on the definition of what represents a “relapse” in SCH, “hospitalization” is the most frequently used hallmark among studies<sup>5</sup>. It is also noteworthy that hospitalizations represent the greater contributor to the direct costs related to SCH, especially in western countries<sup>6,7</sup>. Data on BD showed a similar but maybe more complex picture, considering that the recurrence of both manic and depressive episodes during the illness course represents the rule rather than the exception<sup>8</sup>. Despite hospital admissions and relapses are less frequently overlapping in BD than in SCH, even in this case hospitalizations represent a robust proportion of direct BD-related costs for the healthcare system, as well as a severe complication for the patient<sup>9</sup>. Moreover, there is a robust evidence linking the number of relapses in both affective or psychotic disorders and several negative outcomes, such as higher risk of further episodes<sup>10-12</sup>, treatment resistance<sup>13,14</sup>, functional impairment<sup>15,16</sup>, besides increased suicide risk<sup>14,17</sup>.

Long-term sustained antipsychotic treatment has a pivotal role in the relapse prevention in SCH and is relevant in BD for mood episodes prevention, particularly of manic ones<sup>4,18-21</sup>. Nevertheless, non-adherence to antipsychotic treatment represents a major issue in the treatment of these severe psychiatric disorders and is usually related to future relapses or hospitalizations<sup>22-24</sup>. In a systematic review, Garcia et al.<sup>24</sup> found that main risk factors for medication non-adherence are younger age, minority ethnicity, low socio-economic status and education level, poor therapeutic alliance, substance abuse, poor insight, cognitive impairments and high levels of delusional symptoms. Previous data showing mean treatment adherence rates to be far from reaching at least 50% in patients with SCH or BD, highlight the importance implementing effective therapeutic strategies in such patients. Long-Acting-Injection (LAI) antipsychotics can represent a useful tool for increasing treatment adherence<sup>25,26</sup> besides having a proven ability to decrease relapse risk.

Two studies on large Swedish samples of patients affected by SCH, conducted by Tiihonen et al.<sup>27,28</sup>, demonstrated the superiority of LAI antipsychotics, with respect to oral ones, in reducing re-hospitalization rates in a real-world setting. Recently, Lähteenvuo et al.<sup>29</sup> reported similar findings in a large population-based study on the hospitalization prevention in BD. In recent studies, LAI antipsychotics were also associated to better outcomes in treatment adherence, psychopathology levels, quality of life, subjective experience of the psychotropic medication, substance craving, and violent behaviors when compared to oral formulations<sup>30-32</sup>. However, other studies failed at finding a superiority in LAI formulation compared to the oral one<sup>33,34</sup>, hence further research is needed, especially in real-world settings.

The development of long-term care facilities have been gradually increased in Italy, since the shutdown of the large government operated hospitals for the mentally ill population over 50 years ago, in the framework of the re-organization of the national health system born in 1978. To date, such facilities are widely spread all over the country and frequently used to assist patients with stabilized clinical conditions who may require a long-term assistance, because of the chronicity of their severe psychiatric disorders. Residents are referred to the long-term care facilities by their psychiatrists, who work in the public health service. Typically, residents with SCH or BD come directly from inpatient ward and are addressed to the residential setting because they have a long history of repeated or prolonged hospitalizations and have not been able to live in the community either alone or with their families<sup>35</sup>. These structures represent a useful strategy to address several clinical and social aspects of the patients, in order to reducing re-hospitalization risk, increase medication adherence<sup>36,37</sup>, and improve functional levels. However, the selection of patients for these healthcare structures needs to be particularly pondered. The public health system usually covers all costs related to treatment in the long-term care facilities, which are much lower than the costs of inpatient treatment in public psychiatric hospitals. Their annual cost ranges between 20000 and 40000€ for patients<sup>38</sup>, representing a large proportion of the economical budget of the psychiatric departments. Previous studies demonstrated, in fact, that the economic burden of patients in long-term healthcare facilities is the highest among the cost of the Italian healthcare psychiatric service<sup>38-40</sup>.

In light of existent data on the relevance of re-hospitalization in patients with severe psychotic disorders, such as SCH, SAD or BD, and on the possible treatment strategies to reduce the risk of such event, the aim of present study was to examine the differences in the re-hospitalization rates

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of a sample of patients with a diagnosis of psychotic disorder dismissed from a Psychiatric Inpatient Unit in Italy and followed for 24 months while treated with an antipsychotic in one of the following contexts: with a LAI antipsychotic; while living in a long-term care facility, and thus receiving oral antipsychotics administered by health care operators; or in out-patient care programs while living at home. In our hypothesis, patients receiving a LAI antipsychotics or an oral antipsychotic in long-term care facilities will present, lower re-hospitalization rates than those treated with oral antipsychotics at home, where daily medication supervision cannot be assured.

## **2. Methods**

### **2.1 Study sample**

The present study presents a longitudinal retrospective naturalistic design. The study sample included all patients admitted to the psychiatric ward (Servizio Psichiatrico Diagnosi e Cura, SPDC) of the Nuovo Ospedale Apuano (Massa, Tuscany, Italy) between January 2017 and December 2018, with an ICD-9 diagnosis of SCH, SAD, BD (particularly manic or mixed episode with psychotic features) or unspecified psychosis (UNP) and who received an antipsychotic medication. Subjects were divided into three groups depending on they were treated with a LAI antipsychotic, an oral one at home, or an oral one while living in a long-term care facility (where medications were administered by health care operators). Patients from the first two groups periodically attended psychiatric visits at the psychiatric unit, as part of the treatment plan for patients affected by psychotic disorders. LAI antipsychotic were administered in the framework of this visit. Inclusion criteria were age 18 years old at the time of hospital admission, being hospitalized in the psychiatric unit for a diagnosis of SCH, SAD, BD or UNP, receiving treatment with a LAI antipsychotic, an oral one at home or in long-term care facility. Exclusion criteria were the following: age younger than 18 years old, a concomitant diagnosis of Dementia or other organic disorder, and being resident in different areas than that of managed by the present psychiatric unit. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Area Vasta Nord Ovest Toscana (Italy).

### **2.2 Assessment procedure**

The Authors obtained data of the present study examining the registration records regarding all the inpatients admitted to the psychiatric ward. For each patient we obtained information about age, gender, psychiatric diagnosis, substance abuse, and first/new episode. Data on the type of antipsychotic medication and on the re-hospitalization of the subjects enrolled in the following 24 months after the discharge from the psychiatric ward (until March 2020) were collected too. Medication type and dosage at discharge were established by clinicians of the Psychiatric Clinic, based on patient's characteristics, symptoms severity and tolerance. Data on the exact antipsychotic dosages were not available in the record system.

### **2.3 Statistical analysis**

Continuous variables were reported as mean  $\pm$  standard deviation (SD), whereas categorical variables were reported as percentages. All tests were two-tailed and a p value  $<.05$  was considered statistically significant.

Chi-square tests (or Fisher test if appropriate) were computed in order to compare the sociodemographic and clinical characteristics of subjects treated with oral antipsychotic, LAI ones, or residential facilities program. The relative risks of re-admission were examined by survival analysis, using the time-to-readmission (months) as the variable of interest. Comparison of re-hospitalization rates between groups were obtained by computing Chi-square test. The survival function and cumulative re-hospitalization rates during follow-up were examined using Kaplan-Meier survival analysis, comparing the three treatment groups (LAI antipsychotic, oral antipsychotic and oral antipsychotics administered in long-term care facility). All statistical analyses were carried out using the Statistical Package for Social Science, version 20.0 (SPSS Inc.).

### **3. Results**

From an initial sample of 736 patients, hospitalized in the psychiatric ward, 555 were excluded because presented not psychotic disorders and 35 because met any of the exclusion criteria. The final sample included 135 patients, 70 males (51.9%) and 65 females (48.1%). The mean ( $\pm$ SD) age was  $42.8 \pm 14.0$  years (min 18, max 77). In the total sample, 48 patients (35.6%) received a diagnosis of SCH, 14 of SAD (10.4%), 41 of BD (30.4%) and finally 32 of UNP (23.7%). Furthermore, 32 (23.7) patients reported a first psychotic episode. Alcohol or substance abuse comorbidity was present in 38 patients (28.1%), particularly: 6 (4.4%) with alcohol use disorder, 10 (7.4%) with cannabis use disorder, 2 (1.5%) with opioid use disorder and 20 (14.8%) with polysubstance use disorder.

The three treatment groups were a first group treated with oral antipsychotics at home including 59 (43.7%) patients, a second receiving a LAI antipsychotic including 55 (40.7%) patients, and a third treated with oral antipsychotics administered in long-term care facility including 21 (15.6%) patients. Only psychiatric diagnoses differed significantly between patients from the three groups (see table 1). Table 2 shows the types of antipsychotics prescribed among the three groups.

The re-hospitalization rates at 12 months was 31.1%. In figure 1 and table 3 were reported the Kaplan-Meier survival estimates of the proportion of patients who remained free from re-

hospitalization during the first 12 months follow-up period. In the comparison of the three treatment groups the LAI antipsychotic one showed significantly higher survival rates than the oral antipsychotic one ( $p=.043$ ). No significant differences emerged for the comparison of the oral antipsychotics administered in long-term care facility group with respect to the other two treatment modalities.

The re-hospitalization rates at 24 months was 38.5%. In figure 2 and table 3 were reported the Kaplan-Meier survival estimates of the proportion of patients who remained free from re-hospitalization during the 24 months follow-up period. Comparing the three treatment groups: patients on LAI antipsychotics showed significantly higher survival rates than those on oral antipsychotics ( $p=.019$ ). No significant differences emerged when comparing patients on oral antipsychotics administered in long-term care facilities with respect to those on one of the other two treatment modalities.



#### 4. Discussion

To the best of our knowledge, this is the first long-term naturalistic study conducted in Italy comparing the re-hospitalization rates of patients with psychotic disorders, treated with LAI antipsychotics with respect to self-administered oral antipsychotics and antipsychotics administered by psychiatric nurse staff in the context of psychiatric residential facilities. The findings of our study showed that cumulative re-hospitalization rates during the follow-up were significantly lower among subjects treated with LAI antipsychotic than in those treated with oral formulation at home. Therefore, LAI formulation seems to be advantageous with respect to oral one in re-hospitalization prevention, while no significant difference emerged for the residential facility. Furthermore, results were confirmed by both 12 and 24-months follow-up analyses.

Several clinical trial and real-world studies on both psychotic and affective patients have shown how LAIs use is associated with a lower risk of relapse and re-hospitalization<sup>27-29,41</sup>. Our study corroborates these previous findings, in a real-world sample treated in a mental health department in central Italy. The relevance of this data is due to the current controversies on the real superiority of LAI formulation with respect to the oral one<sup>42,43</sup>. A meta-analysis of RCTs by Kishimoto et al.<sup>44</sup> failed, in fact, in demonstrating a significant difference between LAIs and oral antipsychotics in preventing relapse or hospitalization. Some authors have suggested that other methodological type of studies, than standard RCT, might be more correct in order to compare these two kind of medications. In particular, several characteristics of patients enrolled in RCT studies, such as better treatment adherence or lower illness severity, may affect results<sup>45</sup>. In this perspective, real-world findings may furnish data closer to routinely clinical practice<sup>46</sup>, despite the bias related to their naturalistic no randomized nature. Moreover, the importance of this field of research in real-world settings is supported by the increasing trend of prescription of LAIs in more severe patients in daily routine, with low adherence levels and a history of several relapses<sup>25,31</sup>.

Re-hospitalization rates reported in the present research appear to be particularly high, and almost 40% of patients discharged were readmitted to the hospital within 24 months. Several typical aspects of patients from real-world settings can affect this negative outcome, not only the severity psychopathology, but substance or alcohol abuse, socio-economic difficulties, unemployment, lack of support, medical comorbidities and legal problems.<sup>47-52</sup>. Hence, the selection of the most effective treatment strategy in reducing such risk appear to be an even more important issue. Interestingly, patients in residential facilities did not differ significantly in re-hospitalization rates

with respect to the other two-treatment group. Obviously, this kind of facilities in clinical practice are usually selected for the most complex patients, who present not only lack of medication adherence, but above all social difficulties, low functioning levels or medical and psychiatric comorbidities. However, our data suggest that taking advantage of LAI antipsychotics may be more appropriate than such residential facilities in order to reduce re-hospitalization rates. Grunebaum et al.<sup>37</sup>, in a study on 74 patients with SCH described how medication adherence was not perfect in a facilities treatment setting, with higher, although not absolute, adherence rates with medication supervision. Residential facilities should represent the treatment strategy, in fact, for patient with manifold clinical situation that go beyond medication non-adherence.

The results of the present study must be analyzed keeping in mind several limitations. First, the bias due to the naturalistic nature of the study that does not include a randomization protocol. Despite in our study treatment strategies were not randomly allocated, psychiatrists commonly prescribe LAI or residential facility programs in more severe or complex patients. Second, the small sample size, characterized by a not uniformity in the three treatment groups. Third, the lack of distinction among psychiatric disorders. Moreover, other possible confounders that may affect results were not included in our analysis, particularly possible concomitant treatments, including psychotherapy interventions such as Cognitive Behavioral Therapy (CBT). Fourth, the absence of specific analysis on the different oral or LAI antipsychotics. Finally, data on medication dosage or treatment adherence (for oral antipsychotic medications) were not evaluated.

In conclusion, LAI antipsychotics with respect to oral ones significantly decrease the re-hospitalization rates after 12 and 24 months from discharge in psychotic patients from a real-world setting. These results, taken together with previous findings on the issue<sup>28,29,53</sup>, suggest how taking advantage of LAI antipsychotic could be the most adequate treatment choice in psychotic patients with high risk of relapse and low adherence rate. On the other hand, no significant difference emerged for long-term care facilities programs. Consistently, we confirmed that these latter should be preferred in order to achieve specific treatment goals, such as improving functioning levels and occupational skills<sup>35,36</sup> or managing concomitant substance abuse<sup>54</sup>. Further studies on the specific treatment for psychotic patients, besides on psychopathological, functional and clinical outcomes beyond re-hospitalization will lead to the development of more tailored intervention strategies in such psychiatric population.

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### **Data availability statement**

The data supporting the findings of the article are not publicly available, but it can be provided by the corresponding author on reasonable request.

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**Table 1:** Comparison of socio-demographic and clinical characteristics among patients treated with oral (N=59), LAI (N=55) and oral antipsychotics administered in long-term care facilities (N=21)

	Total sample N (%)	Oral antipsychotic N (%)	LAI antipsychotic N (%)	Oral antipsychotics in long- term care facility N (%)	p	
Males	70 (52.5)	31 (54.3)	27 (38.6)	12 (17.1)	.813	
Females	65 (48.1)	28 (43.1)	28 (43.1)	9 (13.8)		
First episode	32 (23.7)	17 (53.1)	14 (43.8)	1 (3.1)	.078	
Previous episodes	103 (76.3)	42 (40.8)	41 (39.8)	20 (19.4)		
No substance or alcohol abuse	96 (71.1)	40 (41.7)	42 (43.8)	14 (14.6)	.534	
Substance or alcohol abuse	39 (28.9)	19 (48.7)	13 (23.6)	7 (17.9)		
Diagnosis	Bipolar Disorder	42 (30.4)	28 (68.3) <sup>a</sup>	12 (29.3) <sup>b</sup>	1 (2.4) <sup>b</sup>	.001
	Schizoaffective Disorder	14 (10.4)	4 (28.6) <sup>a</sup>	8 (57.1) <sup>a</sup>	2 (14.3) <sup>a</sup>	
	Schizophrenia	48 (35.6)	12 (25.0) <sup>a</sup>	25 (52.1) <sup>b</sup>	11 (22.9) <sup>b</sup>	
	Unspecified Psychosis	32 (23.7)	15 (46.9) <sup>a</sup>	10 (31.3) <sup>a</sup>	7 (21.9) <sup>a</sup>	
	mean±SD	mean±SD	mean±SD	mean±SD		
Age	42.82±13.99	42.27±14.67	42.91±12.91	44.14±16.31	.871	

a versus b p<.05

**Table 2:** Types of antipsychotics prescribed among patients treated with oral (N=59), LAI (N=55) and oral antipsychotics administered in long-term care facilities (N=21)

	Oral antipsychotic N (%)	LAI antipsychotic N (%)	Oral antipsychotics in long- term care facility N (%)
<b>Oral antipsychotics</b>			
Aripiprazole	11 (18.6)	-	3 (14.3)
Haloperidol	18 (30.5)	-	6 (28.6)
Olanzapine	11 (18.6)	-	5 (23.8)
Paliperidone	3 (5.1)	-	-
Perphenazine	2 (3.4)	-	1 (4.8)
Quetiapine	6 (10.2)	-	2 (9.5)
Risperidone	8 (13.6)	-	4 (19.0)
<b>LAI antipsychotics</b>			
Aripiprazole	-	9 (16.4)	-
Haloperidol	-	21 (38.2)	-
Paliperidone	-	21 (38.2)	-
Risperidone	-	4 (7.2)	-

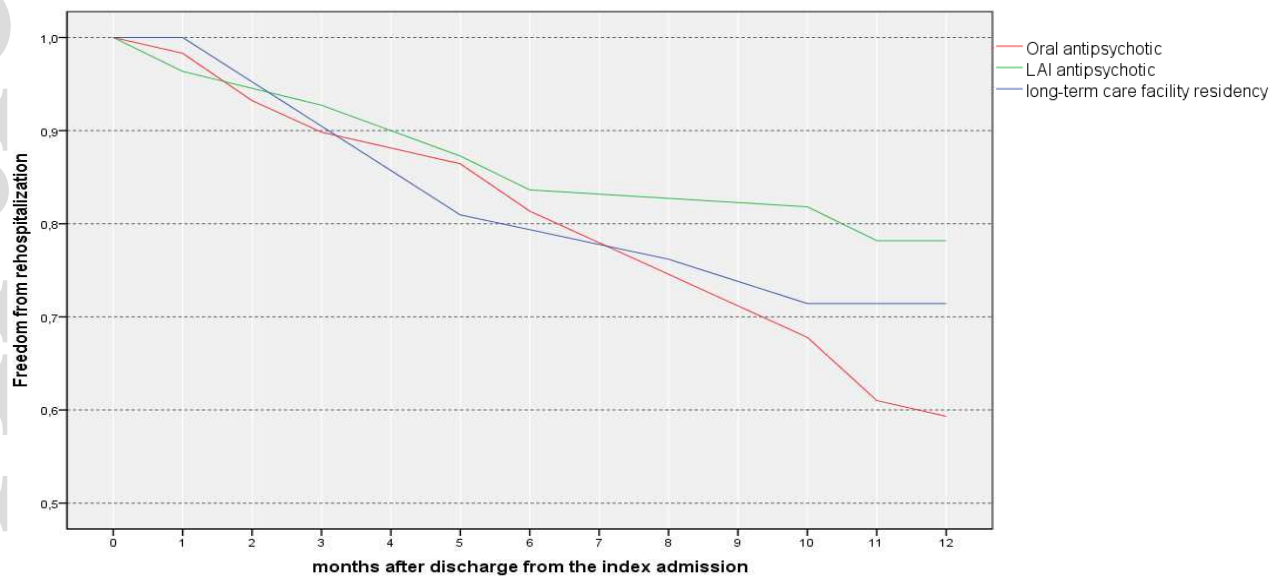
**Table 3:** Comparison of 12-month re-hospitalization rates among psychotic patients discharged with oral (N=59), LAI (N=55) or oral antipsychotics administered in a long-term care facilities (N=21).

	12 months Re-hospitalization N (%)	Mean time (months) free from re-hospitalizations (95% CI)	p*	p**	24 months Re-hospitalization N (%)	Mean time (months) free from re-hospitalizations (95% CI)	p*	p**
	24 (40.7)	9.9 (9.0 – 10.8)	-	.043	29 (49.1)	16.3 (14.1 – 18.5)	-	.019
	12 (21.8)	10.6 (9.7 – 11.4)	.043	-	15 (27.3)	19.8 (17.8 – 21.7)	.019	-
	6 (28.6)	10.1 (8.7 – 11.5)	.398	.527	8 (38.1)	18.2 (14.6 – 21.8)	.392	.378

\*with respect with oral antipsychotics

\*\* with respect with LAI antipsychotics

**Figure 1:** Comparison of 12-month re-hospitalization rates among psychotic patients discharged with oral (N=59), LAI (N=55) or oral antipsychotics administered in a long-term care facilities (N=21).



**Figure 2:** Comparison of 24-month re-hospitalization rates among psychotic patients discharged with oral (N=59), LAI (N=55) or oral antipsychotics administered in a long-term care facilities (N=21).

