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Original Research

Effect of LAI Antipsychotics on Relapse Frequency and Adverse Drug Events of Schizophrenia Patients

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Abstracts

Introduction: Non-adherence to oral antipsychotic medication is common in schizophrenia patients, and it is very likely to lead to recurrence. Whereas the frequency of recurrence in schizophrenia is associated with poorer long-term outcomes and disease progression. The use of long-acting injectable (LAI) antipsychotics has become a favorable approach in the management of schizophrenia, especially to reduce relapse rates and minimize treatment-related side effects. The aim of this study was to evaluate the effect of using LAI antipsychotics, specifically fluphenazine decanoate, on the relapse rate of schizophrenia patients as well as to assess the potential associated side effects. **Methods:** This study was a quantitative analytical study design with a retrospective cohort approach involving 1102 schizophrenia patients in RSJ Prof. Dr. Soerojo Magelang who received LAI therapy (fluphenazine decanoate) in various administration frequencies and time intervals. Data on relapse frequency and adverse drug events were obtained from medical records and adverse drug events yellow forms. The bivariate test used was a Wilcoxon signed rank test. **Results:** The results showed that 77.86% of respondents received LAI with an administration interval ≥ 180 days, and 92% received LAI with low administration frequency (1–5 times). There was a significant decrease between the frequency of relapse in schizophrenia patients and the incidence of drug side effects before and after the administration of antipsychotic LAI. **Conclusions:** In this study, it was found that the use of antipsychotic LAI (fluphenazine decanoate) can significantly reduce the frequency of relapse and the incidence of adverse drug events in schizophrenia patients.

Keywords: Long-Acting Injectable Antipsychotic, Schizophrenia, Relapse, Adverse Events, Fluphenazine Decanoate.

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INTRODUCTION

Mental disorders rank as the fifth most disabling disease globally, at 14.4% [1]. Among these mental disorders, schizophrenia is one of the disorders that most affects the quality of life of individuals. Schizophrenia is chronic and is considered a life-shortening disorder, with life expectancy 15-20 years shorter than the average population [2]. In addition, schizophrenia is one of the most prevalent mental disorders, affecting an estimated 23.6 million people worldwide in 2019 [3].

Schizophrenia is a complex condition with a multiple combination of symptoms that can be categorized into negative, positive, and cognitive symptoms [4]. Among adults, schizophrenia affects 1 in 222 people, or 0.45%. The most common age of onset of schizophrenia is during late adolescence and the twenties, but in males it often occurs earlier than in females [5]. The prevalence of relapse among individuals with schizophrenia ranges from 50 to 92% worldwide [6]. Even around 80% of schizophrenia patients experience repeated relapses [7]. Relapse is defined as when a patient who has been in remission experiences acute psychotic exacerbation again [8].

Relapse could result in major consequences, such as the risk of the patient endangering either themselves or others, deteriorating personal relationships, education, or employment status [9]. The most significant factors related to schizophrenia relapse include the frequency of psychotic episodes, non-adherence to treatment, comorbid psychiatric diseases, side effects of therapy, substance abuse, layoffs, stressful life circumstances, and psychotic stress [7].

Initiating long-acting injectable (LAI) was primarily recommended by current guidelines among patients with a history of inconsistent and inadequate compliance [10]. Furthermore, LAI is also often associated with lower relapse rates compared to oral antipsychotics [11]. This is because long-acting injectable (LAI) antipsychotics have been shown to improve continuity of therapy and strengthen adherence due to their longer pharmacokinetic half-life and less frequent administration [12].

Fluphenazine is a typical antipsychotic used for the symptomatic management of psychosis in patients with schizophrenia. Long-acting injectable (LAI) formulation of fluphenazine decanoate is used predominantly as maintenance therapy for chronic schizophrenia along with associated psychotic disorders in patients who are unable to tolerate oral formulations or for whom adherence to medication is of concern [13]. However, due to dopaminergic antagonism, fluphenazine can cause extrapyramidal symptoms, including acute dystonic reactions, akathisia, parkinsonian features such as resting tremor and shuffling gait, tardive dyskinesia, opisthotonos, and oculogyric crises [13].

In Indonesia, the prescription of injectable long-acting antipsychotics is highly prevalent among patients with schizophrenia, especially in mental health care facilities such as mental hospitals. However, no studies have been conducted on the effects of using long-acting injectable (LAI) antipsychotics in schizophrenia patients in Indonesia. Therefore, this study aims to investigate the effect of using long-acting injectable (LAI) antipsychotics on the frequency of relapse and the incidence of adverse drug events in schizophrenia patients at RSJ Prof. Dr. Soerojo Magelang.

METHODS

The research design used in this study was a quantitative analytical study design with a retrospective cohort approach. This study was conducted at RSJ Prof. Dr. Soerojo Magelang in the period from January 2020 to December 2023. The population in this study were patients diagnosed with schizophrenia according to DSM V criteria in the age range of 19-59 years who received antipsychotic therapy LAI (fluphenazine decanoate) 25 mg injected intramuscularly with

a total of 1727 people. Exclusion criteria are patients with schizophrenia with comorbid organic mental disorders and comorbid physical diseases. The sampling technique used in this study was total sampling; based on the restriction criteria, a sample size of 1102 people was obtained.

Data collection was sourced from patients' medical records and drug side effect forms, including data on patient characteristics (age, gender, diagnosis, type of comorbid disease, and history of drug use), number of rehospitalizations, and number of adverse drug events reported. The side effect of LAI (fluphenazine decanoate) identified in this study was extrapyramidal syndrome with the main symptoms of hypersalivation, body stiffness, and oculogyric crisis. Statistical analysis in this study was performed with the Wilcoxon signed rank test using SPSS. The ethical approval for this research was obtained from Soerojo Hospital Ethical Clearance and Law Commission with reference number DP.04.03/D.XXXVI.12/10/2024.

RESULTS

The characteristics of the respondents in this study were grouped by age and gender, as listed in the following table:

Table 1. Patient criteria

Characteristics	n	%
Age		
19 - 44 years	852	77.31
45 - 59 years	250	22.69
Gender		
Man	690	62.61
Woman	412	37.39
Total	1102	100

Most of the respondents in this study belonged to the productive age range, namely 19-44 years old at 77%. The proportion of respondents aged 45-59 years was relatively smaller at 23 percent. Although the number of female respondents is quite significant, their proportion is still lower than that of men.

The administration of LAI antipsychotics in the respondents of this study was categorized based on the frequency and mean interval of administration, as listed in the following table:

Table 2. Number of antipsychotic LAI administered

Frequency of administration	n	%
1 - 5 times	1018	92.38
6 - 10 times	39	3.54
11 - 15 times	18	1.63
16 - 20 times	3	0.27
21 - 25 times	6	0.54
26 - 30 times	3	0.27
31 - 35 times	5	0.45
36 - 40 times	3	0.27
41 - 45 times	2	0.18
46 - 50 times	5	0.45
Total	1102	100

Based on the data obtained in this study, most of the 1018 (92%) respondents received the frequency of administration of antipsychotic LAI (fluphenazine decanoate) 1- 5 times, and only a few respondents received therapy more than 5 times. Even 795 (72%) of them only received fluphenazine decanoate injections once.

Table 3. Interval of antipsychotic LAI administration

Interval	n	%
≤ 30 days	73	6.62
31 - 60 days	94	8.53
61 - 90 days	26	2.36
91 - 120 days	19	1.72
121 - 150 days	16	1.45
151 - 180 days	16	1.45
> 180 days	858	77.86
Total	1102	100

The table shows that most of the 858 respondents were prescribed LAI (fluphenazine decanoate) antipsychotics at a mean interval of ≥ 180 days or ≥ 6 months, accounting for almost 77.86% of the total cases. Shorter administration intervals (≤ 30 days to 180 days) showed a relatively small number of cases, with percentages below 9% for each category.

The frequency of relapse of respondents before and after administration of antipsychotic LAI (fluphenazine decanoate) is illustrated in the following table:

Table 4. Frequency of relapse

Frequency of relapse	*Before LAI*		*After LAI*		
	n	%	n	%	
0 times	11	1	694	63	*p* value =
1 - 5 times	918	83.3	376	34	0.00
6 - 10 times	111	10	27	2.5	
11 - 15 times	43	3.9	4	0.5	z score =
16 - 20 times	11	1	1	0.1	-23,741
21 - 25 times	4	0.4	0	0	
>25 times	4	0.4	0	0	

In general, there was a tendency to decrease the frequency of relapse after the administration of antipsychotic LAI (fluphenazine decanoate) to respondents. As we can see from Table 3, there was a 50% reduction in relapse in respondents who experienced relapse 1-5 times, during the study period. At a relapse frequency of 6 to 20 times the decrease reached a quarter and a tenth of the initial number. Even at a relapse frequency of more than 20 times, it showed a 100% reduction in relapse. Based on the results of statistical tests, a Z score of -23.741 with a p-value of 0.000 or ≤ 0.05 obtained which can be interpreted as indicating that there is a significant reduction between the frequency of relapse before and after the administration of antipsychotic LAI (fluphenazine decanoate).

The incidence of adverse drug events (ESOs) experienced by respondents before and after administration of the antipsychotic LAI (fluphenazine decanoate) is illustrated in the following table:

Table 5. Incidence of drug side effects

Frequency of relapse	*Before LAI*		*After LAI*		
	n	%	n	%	
0 times	9	83.67	984	89.29	*p* value =
1 - 2 times	1	15.06	114	10.34	0.00
3 - 4 times	1	1.18	4	0.36	z score =
≥ 5 times	1	0.09	0	0	-4,574

In general, there was a tendency to decrease the incidence of adverse drug events (ESOs) after administration of LAI (fluphenazine decanoate) antipsychotics to respondents. This shows that the administration of antipsychotic LAI (fluphenazine decanoate) tends to reduce the incidence of adverse drug events (ESO) in respondents. Based on the results of the bivariate test, a Z score of -4.574 was obtained with a p-value of 0.000 or ≤ 0.05, which means that there is a significant decrease between the incidence of ESO before and after the administration of LAI antipsychotics (fluphenazine decanoate).

DISCUSSIONS

Based on the characteristics data in this study, 852, or more than three quarters of the total respondents, were aged 19-44 years or in the adult age category. This is in accordance with the results of research from Wander that most (95%) schizophrenia patients are adults (25-65 years) [14]. It is also in line with Kaplan & Sadock's findings that almost 90% of schizophrenia patients experience treatment at the age of 15-55 years [15], as well as the study of Abdulkareem, that the highest incidence of schizophrenia occurs at the age of 20-24 years for men and age 29-32 years for women [16]. In relation to the prevalence of schizophrenia based on gender, the results of this study showed that 62.61% of respondents were male. This finding confirms the results of a previous study stating that men experience schizophrenia more often than women, with a ratio of 1.4:1 [17]. It is also in line with Seeman's finding that premorbid effects are experienced earlier in life in boys than girls and also accompanied by more severe negative symptoms [18].

During the study period from January 2020 to December 2023, 92% of respondents received antipsychotic LAI therapy (fluphenazine decanoate) 1-5 times, and only 8% of respondents received therapy more than 5 times. Furthermore, it was found that most of the respondents, 77.86% of the total 1102 respondents, received antipsychotics LAI (fluphenazine decanoate) with an average interval of ≥ 180 days or ≥ 6 months. Meanwhile, LAI administration with an interval of ≤ 1 month was carried out in 6.62% of respondents, a 2-month interval in 8.53% of respondents, and a 3-month interval in 2.36% of respondents. This shows that most respondents received therapy with longer intervals. It is known that plasma levels of fluphenazine decanoate peak within 24 hours after intramuscular injection, and the half-life is about 7-10 days [19], and stable plasma drug levels are expected to be achieved after 3 months of regular dosing of 25 mg every 2 weeks [20].

This result indicates that the frequency of drug administration becomes less frequent, which aligns with the study of Shin-Tian Chien, which states that long-acting formulations are specifically designed to reduce frequency of administration and simplify dosing regimens by providing an extended period of action [21]. This finding is consistent with real-world evidence highlighting that one of the main advantages of LAI is lower frequency of administration, which enhances patient compliance [10]. Furthermore, Kane's study also supports this by noting that first-generation antipsychotic (FGA) LAIs were introduced with the primary objectives of improving adherence and reducing symptom exacerbation, minimizing relapse, and lowering rehospitalization rates [22].

This study also observed a significant reduction in relapse rates among respondents who were administered LAI antipsychotics, specifically fluphenazine decanoate. This finding is in accordance with the research by Milz Ruth et al., which demonstrated that long-acting injectable (LAI) antipsychotics were associated with lower relapse rates compared to oral antipsychotics. The reduction in relapse is mainly attributed to enhanced patient compliance and continuity of therapy [11]. Correll et al. stated that due to the longer pharmacokinetic half-life

and less frequent dosing of LAI, compliance is improved and therapeutic effects are sustained [12]. Similarly, Nanda Restiana et al. concluded that long-acting injectable antipsychotics offer several advantages over oral antipsychotics, including early identification of non-adherence, the elimination of daily medication reminders, reduced relapse frequency, and rehospitalization rates [4]. It is recognized that medication non-adherence is a major contributor to relapse and the need for readmission [23]. LAI antipsychotics were developed to address the issue of relapse due to medication non-adherence and have been proven more effective than oral antipsychotics in preventing relapse [24].

In this study, it was also found a significant decrease in the incidence of side effects associated with LAI antipsychotics, particularly extrapyramidal syndrome (EPS). These results align with previous research indicating that long-acting injectable antipsychotics have several advantages over oral antipsychotics, including more consistent bioavailability and stable plasma concentrations, which help promote the use of the lowest effective dose. This approach reduces the prevalence of adverse side effects [19]. While first-generation LAIs are known to cause extrapyramidal syndrome side effects, the incidence of these adverse effects was significantly lower in patients receiving fluphenazine decanoate compared to those taking oral neuroleptics [25].

Overall, these findings provide valuable insights into the real-world use of LAI antipsychotic therapy. The reduced relapse rate and lower adverse effects indicate the great potential of LAI antipsychotic therapy as an effective option in improving patient compliance and managing schizophrenia symptoms. However, the absence of a control group in this study limits the ability to draw definitive conclusions about the adverse effects of LAI therapy. Future studies could incorporate a control group to assess the comparative effectiveness of LAI versus oral antipsychotics. Additionally, longer-term follow-up studies are needed to assess the long-term effects of LAI therapy on patient outcomes, including other adverse effects of LAI, in addition to extrapyramidal syndrome.

CONCLUSION

From the results of the study, it was found that there was a significant decrease between the frequency of relapse before and after the administration of antipsychotic LAI (fluphenazine decanoate), and there was also a significant decrease in the incidence of drug side effects in the form of extrapyramidal syndrome after the administration of long-acting injectable (LAI) in schizophrenia.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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