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(RESEARCH ARTICLE)

An analysis of multiple comparisons is conducted to account for correlations among various investigated variables across four categories of antipsychotics

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Abstract

Background: First-generation antipsychotics are dopamine receptor antagonists, while second-generation atypical antipsychotics are serotonin-dopamine antagonists.

Aim: The study aims to compare the effectiveness of current anti-psychotic drugs in treating schizophrenia, focusing on their correlation with responsiveness rates in positive, negative, and psychopathological symptoms.

Methods: The study focuses on schizophrenia-spectrum disorders in adults and elderly psychiatric patients at the Princess Aisha Bint Al Hussein Medical Centre. The study will assess the initial severity of patients and evaluate the therapeutic effectiveness of four categorical-based oral and LA-APDs: older oral drugs, older oral and depot drugs, newer oral drugs, and newer oral and depot drugs. The reduction percentages in each component will be monitored, and a Chi Square test will be performed to analyze other variables. Pearson or spearman correlations will be used to explore correlation values.

Results: Upon aggregating the various symptom categories into a unified score using the Positive and Negative Scoring Scale (PANSS), this study revealed that 63.7% of patients exhibited a positive response, whereas 36.7% of patients did not respond favourably. This equated to 110 out of 303 patients responding, compared to 193 patients who did not respond. The Pearson and Spearman correlations exhibited a statistically significant positive relationship, with values of +0.581±0.038 and +0.574±0.040, respectively (χ 2=131.885, p-value=0.000).

Conclusion: Our study concluded that Psychopathological symptom therapy and patient adherence improved significantly. The efficiency of pleasant symptoms decreased significantly, whereas negative symptoms increased slightly.

Keywords: Anti-psychotic drugs; Schizophrenia spectrum disorder; Responsiveness rates; Positive and negative Symptoms

1. Introduction

Schizophrenia is a global mental disorder that impacts individuals, families, and societies. This is one of the top twenty influential factors that contribute to the global disease burden. Schizophrenia, a psychiatric disorder, can lead to psychosis and ongoing daily challenges. This worldwide pandemic, ranked within the top 20 globally, impacts individuals, families, and communities across the globe. As of the conclusion of 2022, the global prevalence of schizophrenia was 0.32 percent. Despite its relatively low prevalence compared to other mental disorders,

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schizophrenia is a debilitating condition characterised by its chronicity, intermittent and persistent symptoms, comorbidity with other medical conditions, and heightened risk of suicide. The aforementioned factors contribute to the elevated rates of morbidity and mortality commonly associated with schizophrenia1 -2.

his results in the emergence of pharmacoeconomic and clinical complexities. Many individuals afflicted with schizophrenia and other psychoses experience severe disability due to the bleak prognosis and enduring consequences of these conditions. Individuals diagnosed with schizophrenia may experience heightened challenges when confronted with unforeseen hospitalisations and emergency room visits related to their mental health concerns. It is crucial to collect data on the long-term safety of injectable antipsychotics (LAIAs) for specific individuals in this population. Individuals who use substances encounter a particularly difficult problem with not following medical advice, and it is crucial for medical professionals to determine the appropriate role that long-acting injectable antipsychotic (LAIA) treatment should have in treating their condition. The refusal of patients to avail themselves of mental health services and adhere to prescribed medication can hinder the efficacy of therapy for psychotic disorders. [3-4]

Patients should diligently adhere to the prescribed treatment regimens to optimise the efficacy of their medications and improve the quality of their interactions with their physicians. Deviation from the prescribed treatment regimen heightens the probability of symptom relapse, thereby elevating the risk of hospitalisation or attempted suicide. There has been limited research conducted on quantifying variables and providing incentives to individuals who adhere to them. Utilising technology-based therapies, engaging in family counselling, providing psychoeducation, and administering depot medication are all effective strategies for enhancing adherence. Scientists are currently engaged in the development of injectable antipsychotics that have extended-release properties, resulting in a half-life that spans from two to twelve weeks. This endeavor aims to enhance treatment adherence. The objective of developing long-acting injectable antipsychotics, also known as LAIs, was to enhance treatment adherence rates during the 1970s and 1980s. However, there has been a lack of extensive research conducted on this particular topic. [5-6]

Professionals recommend utilising long-acting injectable antipsychotics (LAIAs) to address issues pertaining to medication nonadherence. LAIAs are infrequently utilised, particularly among individuals aged 65 or older and those with substance abuse problems. Polypharmacy, the simultaneous use of multiple medications, along with pharmacokinetic changes, which are modifications in the way drugs are metabolized and eliminated from the body, can increase the likelihood of adverse effects in older individuals. Accurate and comprehensive long-term safety data are imperative for this specific population. LAIA therapy is an essential therapeutic choice for patients who do not adhere to their medication regimen. Experts and a two-year-long placebo-controlled clinical trial strongly recommend initiating treatment immediately, despite the uncertain long-term effects. There is a strong demand for antipsychotic medications that effectively alleviate psychotic symptoms and are well-tolerated during extended treatment. Individuals afflicted with psychosis can experience both immediate and enduring alleviation through the use of antipsychotic medications.[7-8]

Currently, there are no established clinical guidelines for the administration of long-acting injectable antipsychotics (LAIAs) to specific patient populations globally. Collecting long-term safety data on long-acting injectable antipsychotics (LAIAs) specifically for this population is of utmost importance. Prolonged utilisation of antipsychotic medication can modify metabolic processes and lead to the development of tardive dyskinesia. Individuals diagnosed with schizophrenia frequently encounter challenges adhering to their prescribed medication regimen due to the nature of their illness. The circumstances may arise due to various factors, including social isolation, limited understanding of their illness, and concerns regarding the adverse effects of antipsychotic medications. The initial iteration of antipsychotic medications, commonly referred to as APs, became accessible to the public in the 1950s. Conversely, Western countries derive greater advantages from research on Long-Acting Injectable Antipsychotics (LAIAPs) compared to Eastern countries. [9-10]

A research project was carried out with the purpose of addressing these knowledge gaps. The research project involved making multiple comparisons in order to take into account the correlations that exist between various variables. The purpose of the study was to examine the differences in responsiveness rates for positive, negative, and psychopathological symptoms. The study focused on four different categories of antipsychotics during its investigation. In addition to this, the research investigated the adherence patterns of individual patients with psychosis who were taking antipsychotic medications from four different groups.

2. Methods

This study only focused on persons aged 18 years or older who have received a diagnosis of a schizophrenia-spectrum disorder, including but not limited to schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional

disorder, or another kind of psychotic illness. We obtained data from our institutional electronic recording system, and any data with missing values exceeding 80% were deemed as grounds for elimination. Additionally, this study did not include individuals who had a current or previous record of substance misuse, neurological, endocrine, respiratory, or cardiovascular disorders, or those who were taking medication for other psychiatric ailments.

Prominent diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Diseases (DSM), are employed to identify mental disorders. The PANSS was utilised to examine the subjects' first mean rating scale scores. We observed a noteworthy clinical response by monitoring the rates that decreased by a minimum of 20% from the initial values in all three categories of symptoms (positive, negative, and psychopathological), while also considering the cumulative PANSS scores.

We aimed to assess the efficacy of several oral and injectable antipsychotic medicines (APs) in addressing symptoms, expectations, and concerns across three key domains: psychological, positive, and negative. At our psychiatric hospital, the administered antipsychotics were categorised into four primary classes. Subsequently, the participants underwent composite correlation testing using both Pearson and Spearman correlations. The tested variables included baseline, interventional, and percentages of changes, encompassing positive and negative psychopathological symptom domains, as well as demographic and adherence data of the patients. The entire PANSS scale was also compared among the several classes of antipsychotic drugs that were examined.

We categorised all eligible patients into four groups according to their APDs. The older generations of antipsychotic drugs, such as Haloperidol pills, Risperidone tablets, and Amisulpride tablets, all belong to Class I. Fluphenazine LA, Flupentixol LA, Haloperidol LA, and Zuclopenthixol LA, which are slightly older or more mature IAPs, belong to Class II. Quetiapine, olanzapine, aripiprazole, and paliperidone are recently developed oral antipsychotic medicines (APDs) classified as Class III. APDs classified as Class III and IAPs belonging to recent generations, such as Paliperidone LA and Risperdal consta, fall under Class IV.

The data findings of the comparison variables among the four tested anti-psychotic regimens (Regimen I-IV) were statistically analysed using the Chi-Square Test (with a significance level of p-value < 0.05). The results were expressed as numbers and percentages, representing the total altogether. The Pearson chi-square statistic (χ 2) is calculated by taking the squared difference between the observed and anticipated frequencies. The G-Test of independence, also known as the Goodness of Fit test, evaluates the agreement between observed frequencies and their predicted values by comparing the logarithm of the ratio of two likelihoods. The Mantel-Haenszel (M-H) test is used to assess linear association or linear by linear association. Chi-square, in contrast to ordinary and likelihood ratio chi-square, is an ordinal indicator of significance. The correlations, both interval by interval (Pearson, r) and ordinal by ordinal (Spearman, ρ), were represented as value± standard error of value.

3. Results

This study examined a cohort of 303 individuals who had received a diagnosis of schizophrenia spectrum illness. A total of 72 patients, accounting for 23.76% of the sample, were classified under the APDs' Class I category. APD's Class II consisted of 91 patients, accounting for approximately 30.03% of the total. Similarly, 51 patients, accounting for 16.83% of the total, were categorised into APDs' Class III. Ultimately, a total of 89 patients with Class IV APDs were included, accounting for approximately 29.37% of the entire sample. The gender distribution had no impact across the four APD classes. The aggregate count of individuals, comprising both men and women, was approximately equal: 140 (46.2%) for men and 163 (53.8%) for women, with a p-value of 0.934. The study found that both the Pearson and Spearman correlations were not statistically significant, with values of -0.008±0.058 and -0.007±0.058, respectively (χ 2=0.431).

The majority of individuals diagnosed with schizophrenia spectrum disorder were in the age category of early elderly (60-70 years), followed by individuals in the pre-elderly (50-60 years) age group [196 (64.7%)] and then the early elderly (57 (18.8%). In relation to the age groups of 70–80 years and >=80 years, they exhibited lower proportions [42 (13.9%) and 8 (2.6%), respectively]. This may be attributed to the lack of awareness among their family regarding certain illnesses that specifically impact elderly individuals. The Pearson and Spearman correlations were found to be statistically insignificant. However, unlike the gender variables, they exhibited positive directional correlations [0.072±0.061 and 0.066±0.060, χ 2=11.154, p-value=0.265].

The majority of the patients who underwent testing had positive symptoms within the range of 28 to 34 points in the scored domain. Subsequently, there were 21 to 27 points observed, which exhibited notable positive Pearson and Spearman correlations [+0.089±0.058 and +0.090±0.058, χ 2=22.114, p-value=0.036]. The majority of the patients exhibited a score ranging from 28 to 34 points for their unpleasant symptoms. The subsequent most prevalent scores

fell within the range of 21 to 27 points. However, when it comes to the baseline negative symptoms domain, the Pearson and Spearman correlations were not statistically significant (+0.014±0.057 and -0.003±0.057, χ 2=10.916, p-value=00.759).

Table 1 The correlation values and total rates of the tested variables in the comparative patients across the four investigated medications for anti-psychotic drugs

	Total (303, 100%)	**R ρ**	**χ^2 G-Test Linear-Linear**	**p-Value**
Gender				
Female	140 (46.2%)	-0.008±0.058	0.431	0.934
Male	163 (53.8%)	-0.007±0.058	0.431	0.934
Female: Male			0.021	0.884
Age (Yrs)				
50-<60	57 (18.8%)	+0.072±0.061	11.154	0.265
60-<70	196 (64.7%)	+0.066±0.060	11.953	0.216
70-<80	42 (13.9%)		1.575	0.209
>=80	8 (2.6%)			
BARS				
25%-<50%	123 (40.6%)	+0.696±0.037	188.558	0.000
50%-<75%	103 (34.0%)	+0.689±0.037	221.249	0.000
>=75%	77 (25.4%)		146.134	0.000
Positive Score 0				
7-13	1 (0.3%)	+0.089±0.058	22.114	0.036
14-20	32 (10.6%)	+0.090±0.058	23.376	0.025
21-27	114 (37.6%)		2.419	0.120
28-34	125 (41.3%)			
35-41	31 (10.2%)			
Positive Score 1				
7-13	118 (38.9%)	+0.391±0.051	85.224	0.000
14-20	95 (31.4%)	+0.417±0.051	88.561	0.000
21-27	76 (25.1%)		46.269	0.000
28-34	14 (4.6%)			
Δ Positive Score				
Un-Responsiveness	63 (20.8%)	-0.244±0.055	26.516	0.000
Responsiveness	240 (79.2%)	-0.240±0.055	27.593	0.000
			17.964	0.000
Negative Score 0				
7-13	1 (0.3%)	+0.014±0.057	10.916	0.759
14-20	23 (7.6%)	-0.003±0.057	10.760	0.769

21-27	118 (38.9%)		0.063	0.802
28-34	133 (43.9%)			
35-41	26 (8.6%)			
42-49	2 (0.7%)			
Negative Score 1				
7-13	17 (5.6%)	+0.035±0.056 +0.037±0.057	19.439 24.794 0.379	0.195 0.053 0.538
14-20	98 (32.3%)			
21-27	121 (39.9%)			
28-34	61 (20.1%)			
35-41	5 (1.7%)			
42-49	1 (0.3%)			
Δ Negative Score				
Un-Responsiveness	180 (59.4%)	+0.019±0.057 +0.022±0.057	1.976 1.987 0.111	0.577 0.575 0.739
Responsiveness	123 (40.6%)			
Data results of the comparative variables between the 4 tested anti-psychotic regimens; Regimen I-IV, were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The Pearson chi-square statistic (χ 2, Goodness of Fit (G-Test of independence, and the Mantel-Haenszel (M-H) test for linear association or linear by linear association chi-square. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value.				

The majority of the individuals examined had psychopathological symptoms, with scores ranging from 64 to 79 points. The subsequent most prevalent scores ranged from 48 to 63 points. The Pearson correlation exhibited a statistically insignificant positive correlation (+0.000±0.061, χ 2=16.472, p-value=0.058), however the Spearman correlation demonstrated a statistically significant positive correlation (+0.009±0.059, χ 2=18.622, p-value=0.029). The introduction of the four APD classes significantly altered the positive symptoms exhibited by our individuals with schizophrenia spectrum illnesses. The majority of the values fell within the range of 7 to 13 points, which is a decrease from the previous range of 28 to 34 points before to the commencement of the classes. All patients treated had a maximum score of 34 points in the positive symptom domain. The Pearson and Spearman correlations exhibited a statistically significant positive relationship, with coefficients of +0.391±0.051 and +0.417±0.051, respectively (χ 2=85.224, p-value=0.000).

Regarding negative symptoms, there was minimal variation in the score points, with the majority of treated patients maintaining scores between 21 and 27 points, followed by scores ranging from 14 to 20 points. Furthermore, the pearson and spearman correlations were also statistically non-significant, with values of +0.035±0.056 and +0.037±0.057, respectively (χ 2=19.439, p-value=0.195). Similarly, the receptiveness to positive symptom domains saw significant changes, as did the general redistribution of psychopathological symptom domains. The majority of patients received scores ranging from 48 to 63 points, as opposed to the previous range of 64 to 79 points before to the implementation of APD classes. The Pearson and Spearman correlations were both strongly negative, with values of -0.531±0.039 and -0.529±0.041, respectively. Additionally, the chi-square test yielded a value of 113.310, with a p-value of 0.000. This study employed a minimum response of -20% from the baseline, which is consistent with the approach taken by other investigations. The patients who exhibited positive symptoms demonstrated a notable responsiveness rate of 79.2% (240 out of 303 patients) to the four classes of antipsychotic drugs (Class I–IV) that were examined, in contrast to around 20.8% (63 out of 303 patients) who exhibited reactions below 20%.

The responsiveness rates for the APD classes (Class I-IV) were significant in the psychopathological domain, but lower than the responsiveness rates in the positive symptoms area. The domain had an overall response rate of 34.3%, with 104 out of 303 patients being responsive. Conversely, the unresponsiveness rate was 65.7%, with 199 out of 303 patients being unresponsive. The Pearson and Spearman correlations for the responsiveness rates across the three examined symptom domains (positive, negative, and psychopathological) were as follows: for positive symptoms, the correlation was -0.244±0.055 (χ 2=113.310, p-value=0.000); for negative symptoms, the correlation was +0.019±0.057

Table 2 The correlation values and total rates of the tested variables in the comparative patients across the four investigated medications for anti-psychotic drugs

	Total (303, 100%)	**R ρ**	**χ^2 G-Test**	**p-Value**
Pyschopathological Score 0				
32-47	6 (2.0%)	+0.000±0.061	16.472	0.058
48-63	135 (44.6%)	+0.009±0.059	18.622	0.029
64-79	154 (50.8%)		0.000	0.998
80-95	8 (2.6%)			
Pyschopathological Score 1				
16-31	11 (3.6%)	-0.531±0.039	113.310	0.000
32-47	68 (22.4%)	-0.529±0.041	128.556	0.000
48-63	160 (52.8%)		85.086	0.000
64-79	64 (21.1%)			
Δ Pyschopathological Score				
Un-Responsiveness	199 (65.7%)	+0.668±0.036	159.759	0.000
Responsiveness	104 (34.3%)	+0.661±0.035	185.614	0.000
			134.813	0.000
∑PANSS 0				
90-119	150 (49.5%)	0.041±0.057	3.671	0.721
120-149	152 (50.2%)	0.045±0.057	3.747	
150-179	1 (0.3%)		0.507	
∑PANSS 1				
60-89	109 (36.0%)	-0.344±0.053	44.107	0.000
90-119	193 (63.7%)	-0.340±0.053	44.958	0.000
120-149	1 (0.3%)		35.778	0.000
Δ∑PANSS				
Un-Responsiveness	110 (36.3%)	+0.581±0.038	131.885	0.000
Responsiveness	193 (63.7%)	+0.574±0.040	158.864	0.000
			101.979	0.000

Data results of the comparative variables between the 4 tested anti-psychotic regimens; Regimen I-IV, were statistically analyzed by Chi-Square Test (at p-value< 0.05) and expressed as Numbers (Percentage). The Pearson chi-square statistic (χ 2, Goodness of Fit (G-Test of independence, and the Mantel-Haenszel (M-H) test for linear association or linear by linear association chi-square. Both the interval by interval (Pearson, r) and the ordinal by ordinal (Spearman, ρ) correlations were expressed as value± standard error of value.

(χ 2=1.976, p-value=0.577); and for psychopathological symptoms, the correlation was +0.668±0.036 (χ 2=159.759, p-value=0.000). The APD classes we examined did not exhibit a significant response to the negative symptom domain when compared to the positive and psychopathological symptom domains. The total rate of patients who responded to the treatment was 40.6% (123 out of 303 patients), while the percentage of patients who did not respond to the treatment specifically for the negative symptoms domain was 59.4% (180 out of 303 patients).

Upon aggregating the various symptom categories into a unified score using the Positive and Negative Scoring Scale (PANSS), this study revealed that 63.7% of patients exhibited a positive response, whereas 36.7% of patients did not respond favourably. This equated to 110 out of 303 patients responding, compared to 193 patients who did not respond. The Pearson and Spearman correlations exhibited a statistically significant positive relationship, with values of +0.581±0.038 and +0.574±0.040, respectively (χ 2=131.885, p-value=0.000).

4. Discussion

This study is the first in our region to examine the relationships between four different antipsychotic treatment plans and numerous demographic, functional, and adherence factors in patients with schizophrenia. The study also examined various causes and safety outcomes, revealing a high and significant positive association between LAIAs and newer generations of APDs. The Pearson and Spearman correlation coefficients were found to be +0.696±0.037 and +0.689±0.037, respectively (χ^2=188.558, p-value=0.000). The adherence pattern in this study was evaluated using the Behavioural Adherence Rating Scale (BRAS). The Brief Adherence Rating Scale (BARS) is a concise questionnaire consisting of four items, designed to assess the level of medication adherence in patients. It is simple to provide and has a low cost. It is a rapid and precise method to assess the extent to which a patient is adhering to their treatment regimen. A clinician is responsible for overseeing the four-component tool.

A 12-week clinical trial, which included 72 individuals experiencing their first episode of schizophrenia, revealed that long-acting injectable (LAI) antipsychotic medications are not being used as much as they should be, despite their advantages in terms of convenience and treatment continuation. The study evaluated initial levels of mental illness and overall well-being by use the PANSS and WHOQOL-BREF scales. Subjects were randomly assigned to receive either oral haloperidol or long-acting injectable (LAI) haloperidol for a duration of 12 weeks. The findings indicated that both cohorts experienced a noteworthy decrease in PANSS scores and enhancement in quality of life over the 12-week duration. The LAI group exhibited superior adherence and higher quality of life compared to the oral group. A current study is being conducted on 87 patients with schizophrenia-spectrum disorders, consisting of 59 male and 28 female participants. These patients are now having therapy with the MMHU I-T and are also receiving antipsychotics. Most individuals are afflicted with schizophrenia, although additional diagnoses encompass delusional disorder, schizoaffective disorder, and various psychoses. The participants in the study are individuals who are in the middle stage of their lives, suffering from long-term illnesses. On average, they are 54.4 years old and have been dealing with their illnesses for an average of 28 years. 72.4% of the participants were treated with only one type of antipsychotic medication, whereas almost 30% received a long-acting injectable (LAI) formulation, primarily a second-generation LAI. Additionally, benzodiazepines were administered to 33% of patients and antidepressants were prescribed to almost 25% of patients as part of the treatment protocol. A comparative analysis using an independent samples t-test was performed to investigate potential disparities in age, duration of illness, total number of hospitalisations, and duration of follow-up between patients who received long-acting injectable (LAI) antipsychotic treatment and those who received oral antipsychotic treatment. The study did not find any statistically significant correlation between treatment formulation and the factors under examination, with the exception of biological sex. [11-18]

Our investigation uncovered the Pearson and Spearman correlations for the responsiveness rates in the three symptom domains (positive, negative, and psychopathological) as follows: The correlation for positive symptoms was -0.244±0.055 (χ 2=113.310, p-value=0.000). The correlation for negative symptoms was +0.019±0.057 (χ 2=1.976, p-value=0.577). The correlation for psychopathological symptoms was +0.668±0.036 (χ 2=159.759, p-value=0.000). Put simply, as the APDs' treatment plan progressed from Regimen I (older oral APDs) to Regimen II (older oral APDs with older LA-IAPs) to Regimen III (newer oral APDs) to Regimen IV (newer oral APDs and LA-IAPs), there was a significant increase in the effectiveness of the treatment for psychopathological symptoms and patient adherence. However, there was a significant decrease in the effectiveness for the positive symptoms, and only a slight increase for the negative symptoms. The study is subject to limitations, including the possibility of mis-coding mistakes, the exclusion of certain newer second-generation APDs due to their restricted availability, the observational character of the study, and potential biases resulting from the normal progression of the illness and the passage of time.

5. Conclusion

Our study concluded that Psychopathological symptom therapy and patient adherence improved significantly. The efficiency of pleasant symptoms decreased significantly, whereas negative symptoms increased slightly.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

References

[1] Citrome L, Risinger R, Cutler AJ, Du Y, Zummo J, Nasrallah HA, Silverman BL. Effect of aripiprazole lauroxil in patients with acute schizophrenia as assessed by the Positive and Negative Syndrome Scale-supportive analyses from a Phase 3 study. CNS Spectr. 2018 Aug, 23(4):284-290.

[2] Hargarter L, Cherubin P, Bergmans P, Keim S, Rancans E, Bez Y, Parellada E, Carpiniello B, Vidailhet P, Schreiner A. Intramuscular long-acting paliperidone palmitate in acute patients with schizophrenia unsuccessfully treated with oral antipsychotics. Prog Neuropsychopharmacol Biol Psychiatry. 2015 Apr 3, 58:1-7.

[3] Liu CC, Shan JC, Chiang CL, et al. Initiating long-acting injectable antipsychotics during acute admission for patients with schizophrenia—a 3-year follow-up.J Formos Med Assoc. 2015, 114(6):539-545.

[4] Huang SS, Lin CH, Loh W, Yang HY, Chan CH, Lan TH. Antipsychotic formulation and one-year rehospitalization of schizophrenia patients: a population-based cohort study. Psychiatr Serv. 2013, 64(12):1259-1262.

[5] Kim HO, Seo GH, Lee BC. Real-world effectiveness of long-acting injections for reducing recurrent hospitalizations in patients with schizophrenia. Ann Gen Psychiatry. 2020, 19:1.

[6] Shin W, Lee DH, Kim MK, Lee SH, Cho DY, Bang M. Clinical effectiveness of early treatment with paliperidone palmitate in schizophrenia: a retrospective real-world study in South Korea. Early Interv Psychiatry. 2021, 15(6): 1759-1767.

[7] Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypi- cal antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. J Clin Psychopharmacol. 2001, 21(1):8–13.

[8] Misawa F, Kishimoto T, Hagi K, Kane JM, Correll CU. Safety and tolerability of long-acting injectable versus oral antipsychotics: a meta-analysis of randomized controlled studies comparing the same antipsychotics. Schizophr Res. 2016, 176(2–3):220–230.

[9] Ostuzzi G, Bighelli I, So R, Furukawa TA, Barbui C. Does formulation matter? A systematic review and meta-analysis of oral versus long- acting antipsychotic studies. Schizophr Res. 2017, 183:10–21.

[10] Hori H, Katsuki A, Atake K, Yoshimura R. Effects of continuing oral risperidone vs. switching from risperidone to risperidone long-acting injection on cognitive function in stable schizophrenia patients: a pilot study. Front Psychiatry. 2018, 9(9):74.

[11] Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981, 213(4504): 220–222.

[12] Rompelman O, Coenen AJ, Kitney RI. Measurement of heart-rate variability: part 1-comparative study of heart-rate variability analysis methods. Med Biol Eng Comput. 1977, 15(3):233–239.

[13] Chang HA, Chang CC, Tzeng NS, Kuo TB, Lu RB, Huang SY. Cardiac autonomic dysregulation in acute schizophrenia. Acta Neuropsychiatr. 2013, 25(3):155–164.

[14] Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry. 2014, 205:135–44.

[15] Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, et al. Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. Schizophr Bull. 2018, 44:603–19.

[16] Schottle D, Clerzius G, Janetzky W, Oluboka O, Roy MA, Therrien F, et al. Real-world effectiveness of aripiprazole once-monthly REACT study: Pooled analysis of two noninterventional studies. Eur Psychiatry. 2022, 65:e42.

[17] Karlovic D, Silic A, Crnkovic D, Peitl V. Effects of aripiprazole long-acting injectable antipsychotic on hospitalization in recent-onset schizophrenia. Hum Psycho-pharmacol. 2021, 36:e2763.

[18] Kane JM, Zhao C, Johnson BR, Baker RA, Eramo A, McQuade RD, et al. Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis. J Med Econ. 2015, 18:145–54.