THE COMPARATIVE EFFECTIVENESS OF FOUR CATEGORIES OF ANTIPSSYCHOTIC TREATMENT REGIMENS AGAINST THE THREE MAJOR SYMPTOMS DOMAINS IN SCHIZOPHRENIA SPECTRUM DISORDER

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ABSTRACT

Aims: This study focused on the responsiveness of older and newer generations of oral and injectable long-acting APDs to positive, negative, and psychopathological symptoms. To study these four APD classes' effects on managing schizophrenia's three dimensions, patient adherence was also considered.

Methods: Between January 2021 and January 2023, the Princess Aisha Bint Al Hussein (Marka Military Medical Centre) Medical Centre diagnosed adults and aged psychiatric patients with schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and psychotic disorders not otherwise specified). The Positive and Negative Syndrome Scale (PANSS) assessed baseline severity and therapeutic effectiveness. This method uses multiple linear regression modeling and chi-square tests show other variables. This study used SPSS 25 with 5% significance.

Results: A multiple linear regression analysis was conducted to predict responsiveness percentage in three psychosymptomatic domains based on patients' antipsychotic class and adherence patterns. The results showed a significant model in the positive and psychopathological domains, while not in the negative domain. The independent variables, antipsychotic class I-IV and patients' adherence pattern, were significant predictors for the positive and psychopathological domains. The study suggests that these factors can help improve patient outcomes and reduce the need for medication.

Conclusion: The study found significant differences in clinical outcome dimensions across APD classes, including positive symptoms and psychopathological symptoms, indicating the main roles of first-generation APDs.

Keywords: Schizophrenia Spectrum Disorder; Oral and long-acting anti-psychotics; Psychiatric patients; Positive, negative, and psychopathology criteria.

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INTRODUCTION

Schizophrenia causes psychosis and daily difficulties. This top-20 global illness affects individuals, families, and societies. The global prevalence of schizophrenia in 2022 was 0.32 percent. Despite its low prevalence, schizophrenia causes significant morbidity due to its chronicity, episodic nature, persistent symptoms, comorbidities, and suicide risk. These factors contribute to schizophrenia's higher mortality and morbidity rates. Schizophrenia patients may struggle with unexpected psychiatric hospital and emergency room admissions. This causes pharmacoeconomic and clinical issues. Schizophrenia and other psychoses cripple many people due to their long-term effects and poor prognosis.[1-3]

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METHODS

This study only included adults (18 or older) with schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or another psychotic illness. The patients were divided into four age groups: 50–60, 60–70, 70–80, and over 80. To learn more about Jordanian schizophrenia patients, we studied at Princess Aisha Bint Al Hussein (Marka Military Medical Centre) Medical Centre from January 2021 to January 2023. In particular, we wanted to assess how well oral and injectable antipsychotic medications (APs) manage psychological, positive, and negative symptoms, expectations, and worries. At our psychiatric hospital, APs were distributed in four groups. They were then tested on how well they managed three-dimensional schizophrenia. How well patients followed their treatment plan was also considered.

DSM-type diagnostic systems are used to diagnose mental illnesses. The subjects' initial average rating scale scores were assessed using the Positive and Negative Syndrome Scale (PANSS). By tracking rates that dropped by at least 20% from the starting points in all three types of symptoms (positive, negative, and psychopathological) and adding up the PANSS scores, we found a clinically significant response. The BARS is a brief, four-item questionnaire that assesses medication adherence. Easy and cheap to give. It quickly and accurately assesses a patient's treatment compliance. A clinician manages the four-part tool. A detailed visual analogue rating scale and three questions determine how much of the patient's monthly prescription they take (0% to 100%). The three questions assess the patient's knowledge of their prescription routine, including how often to take their medication, whether they miss doses, and whether they take less than the recommended amount. Each half of the patients' adherence scales (BRAS) was 25% farther apart.

The 1987 psychopharmacologic therapy study Positive and Negative Syndrome Scale (PANSS) by Stan Kay et al. measured schizophrenia symptoms' severity. The PANSS rating scale helps clinicians identify, classify, and track schizophrenia symptoms. It has been studied for its effects on quality of life, functioning, schizophrenia progression, and treatment. The PANSS is reliable when tested repeatedly and between raters. Researchers will track percentage reductions in positive symptoms (P1–7), negative symptoms (N1–7), and psychopathologies (G1–16). This will show how bad the four oral and LA-APD types were at the start of the study and how well the treatment worked. The study will also assess patient APD compliance.

Based on APDs, we divided eligible patients into four groups. Older APDs like Haloperidol, Risperidone, and Amisulpride are Class I. Class II includes older IAPs like Fluphenazine LA, Flupentixol LA, Haloperidol LA, and Zuclopenthixol LA. Quetiapine, olanzapine, aripiprazole, and paliperidone are new Class III oral antipsychotics. Class IV includes Class III APDs and IAPs from recent generations, like Paliperidone LA and Risperdal consta. A Chi-square analysis showed how the tested variables were distributed across these four APD classes. The variables tested were gender, age, all positive, negative, and psychopathological symptoms domains before treatment, adventure after APD, and response rates. Between APD classes, the entire PANSS was compared.

To determine the significance and actual association between the tested APDs' classes (Class I-IV) against each of the investigated psychosymptomatic domain; positive, negative, and psychopathological domains, we conducted an individual multiple linear regression analysis to abstract the association coefficients, multiple correlation coefficient ®, coefficient of determination (R^2), measure of variance accounted for the number of independent variables (adjusted R^2), effectiveness of the independent for prediction dependent variables (F-ratio), and the F-ratio associated significance. We adopted APDs Class I as reference and accordingly we recode other APDs II-IV into different dummy variables.

RESULTS

This study looked at 303 people who had been diagnosed with schizophrenia spectrum disorder. We put all of the eligible patients into four APD classes based on how the APDs were made and whether IAPs were present or not. Class I is made up of only older APDs, like haloperidol tablets, risperidone tablets, and amisulpride tablets. Some examples of APDs in Class II are Fluphenazine LA, Flupentixol LA, Haloperidol LA, and Zuclopenthixol LA. These drugs are older orals with somewhat older IAPs. Modern oral antipsychotic drugs (APDs), such as quetiapine, olanzapine, aripiprazole, and paliperidone, are in Class III. The Class IV group includes Class III APDs as well as newer IAPs like Paliperidone LA and Risperdal consta. About 23.76% of the patients, or 72, were put in the APDs' Class I category. There were 91 patients in APD's Class II, which is about 30.03% of the total. In the same way, 51 patients, or 16.83%, were put into APDs' Class III. Finally, 89 patients with Class IV APDs were included, which is about 29.37% of the total.

In all four APD classes, the distribution of gender did not matter. The total for men and women was about the same: 140 (46.2%) for men and 163 (53.8%) for women, p-value = 0.528. In this study, women were slightly more likely than men to use older oral APDs without or with older IAPs [39 (54.2%) vs. 33 (45.8%) or 54 (59.3%) vs. 37 (40.7%), respectively]. Men were less likely than women to pick oral newer APDs but more likely to pick their congeners of newer IAPs [27 (52.9%) vs. 24 (47.1%) and 43 (48.3%) vs. 46 (51.7%), respectively]. The early elderly (60–70 years) age group had the highest percentage of people with schizophrenia spectrum disorder (57 (18.8%), then the pre-elderly (50–60 years) age group [196 (64.7%)]. Regarding the older age groups of 70–80 years and >=80 years, they had smaller percentages [42 (13.9%) and 8 (2.6%), respectively]. This could be because their families didn't know about these syndromes that affect older patients.

Most of the patients who were tested had positive symptoms in the domain that was scored between 28 and 34 points. Following this were 21 to 27 points, 14 to 20 points, 35 to 41 points, and finally 7 to 13 points. Most of the patients had a score between 28 and 34 points for their negative symptoms. The next most common scores were between 21 and 27 points, 35 to 41 points, 14 to 20 points, 42 to 49 points, and finally between 7 and 13 points. When it came to psychopathological symptoms, most of the patients who were studied got scores between 64 and 79 points. The next most common scores were 48 to 63 points, then 80 to 95 points, and finally 32 to 47 points.

A responsiveness of at least -20% from baseline was used in this study, as in others. Positively symptomatic patients responded 79.2% (240 out of 303 patients) to the 4 APD classes studied (Class I–IV), compared to 20.8% (63 out of 303 patients) who responded below 20%. Most patients who responded received APDs Class II (older oral and injectable), then Class I, then Class IV, and finally Class III [84 (92.3%), 63 (87.5%), 60 (67.4%), and 33 (64.7%), in that order]. In the tested APD classes (Class I–IV), psychopathological responsiveness rates were significant but lower than positive symptoms responsiveness rates. There, 34.3% (104 patients out of 303 patients) were responsive and 65.7% (199 patients out of 303 patients) were unresponsive. APD Class IV patients responded best, followed by Class III patients. The residual responsiveness rate was similar for APD Classes I and II. [66 (74.2%), 34 (66.7%), 2 (2.8%), and 2 (2.2%), respectively]. We found no significant response to negative symptoms in our APD classes compared to positive and psychopathological symptoms. Overall responsiveness was 40.6% (123 patients out of 303), while negative symptoms domain unresponsiveness was 59.4% (180 patients). APD classes I–IV had similar responsiveness rates: 25 (34.7%), 41 (45.1%), 22 (43.1%), and 35 (39.3%).A multiple linear regression analysis was run to predict responsiveness percentage, as determined by % Δ for each of the 3 investigated psychosymptomatic domain from baseline, according to patients adopted antipsychotic class while considering their adherence patterns as a significant interacting independent variable. This resulted in a significant model in both %Δ positive domain and %Δ psychopathological domain [$F(4, 298) = 19.763$, $p < 0.01$, $R^2 = 0.210$] and [$F(4, 298) = 153.80$, $p < 0.01$, $R^2 = 0.674$], respectively, while in %Δ negative domain was not [$F(2, 3298) = 0.515$, $p > 0.05$, $R^2 = 0.515$]. The individual predictors were examined further and indicated that both the tested 4 independent variables; patients' adherence pattern and antipsychotic class II-IV dummy variables were significant predictors for the investigated %Δ positive domain and %Δ psychopathological domain, except for APDs Class II dummy variables when we adopted APDs Class as a reference [(t=2.588, p-value=0.010), (t=0.815, p-value=0.416), (t=3.446, p-value=0.001), and (t=4.016, p-value=0.000)] and [(t=--11.258, p-value=0.000), (t=-0.900, p-value=0.369), (t=-5.683, p-value=0.000), and (t=-7.570, p-value=0.000)], respectively. Accordingly, we demonstrated from the conducted multiple linear regression analysis that as we stepped up in the tested APDs classes [Class I to Class II to Class III to Class IV, considering the APD Class I as the reference for the other APDs Classes II-IV], we significantly revealed incrementing in the %Δ Positive Domain and decrementing in the % Δ Psychopathology Domain All statistical analyses results were fully represented in Tables 1-2.

Table I. A multiple linear regression analyses results for each of the tested psycho domains

Investigated Domains	B±SEM	Beta	t	p-value	R R2 Adjusted R2	F (df) Sig
% Δ Positive Domain						
(Constant)	-76.812±10.802		-7.111	0	0.458 0.210 0.199	F (4, 298) =19.763 0.000
% BARS	0.424±0.164	0.185	2.588	0.01		
APDs Class II	2.448±3.003	0.053	0.815	0.416		
APDs Class III	13.959±4.051	0.246	3.446	0.001		
APDs Class IV	14.776±3.680	0.317	4.016	0		
% Δ Negative Domain						
(Constant)	-14.929±9.092		-1.642	0.102	0.083 0.007 0.006	F (4, 3298) =0.515 0.724
% BARS	-0.060±0.138	-0.035	-0.432	0.666		
APDs Class II	-0.936±2.528	-0.027	-0.37	0.712		
APDs Class III	0.554±3.409	0.013	0.162	0.871		
APDs Class IV	2.981±3.097	0.085	0.962	0.337		
% Δ Psychopathology Domain						
(Constant)	49.693±4.975		9.988	0	0.821 0.674 0.669	F (4, 298) =153.80 0.000
% BARS	-0.850±0.076	-0.517	-11.258	0		
APDs Class II	-1.245±1.383	-0.0037	-0.9	0.369		
APDs Class III	-10.602±1.866	-0.261	-5.683	0		
APDs Class IV	-12.830±1.695	-0.384	-7.57	0		

· A multiple linear regression analyses were conducted for the three investigated psycho domains; positive, negative, and psychopathological, to explore the significance and actual association of each versus the tested antipsychotic drugs classes; Class I-IV, while taking into account the contribution of patients' behavioural adherence rating scale.
· We adopted APDs Class I as reference and accordingly we recode other APDs II-IV into different dummy variables.

APDs: Antipsychotic drugs. BARS: Behavioural adherence rating scale

Table 2. Analysed the distribution rates of the patients' tested variables; demographics, adherence, and responsiveness rates, among the four different classes of anti-psychotic medications.

	APD Class I (N=72, 23.76%)	APD Class II (N=91, 30.03%)	APD Class III (N=51, 16.83%)	APD Class IV (N=89, 29.37%)	Total (303)	p-value
Gender						
Female	33 (45.8%)	37 (40.7%)	24 (47.1%)	46 (51.7%)	140 (46.2%)	0.528
Male	39 (54.2%)	54 (59.3%)	27 (52.9%)	43 (48.3%)	163 (53.8%)	
Age						
50-<60	19 (26.4%)	16 (17.6%)	10 (19.6%)	12 (13.5%)	57 (18.8%)	0.265
60-<70	39 (54.2%)	61 (67.0%)	35 (68.6%)	61 (68.5%)	196 (64.7%)	
70-<80	12 (16.7%)	13 (14.3%)	6 (11.8%)	11 (12.4%)	42 (13.9%)	
>=80	2 (2.8%)	1 (1.1%)	0 (0.0%)	5 (5.6%)	8 (2.6%)	
BARS						
25%-<50%	72 (100.0%)	0 (0.0%)	51 (100.0%)	0 (0.0%)	123 (40.6%)	0
50%-<75%	0 (0.0%)	45 (49.5%)	0 (0.0%)	58 (65.2%)	103 (34.0%)	
>=75%	0 (0.0%)	46 (50.5%)	0 (0.0%)	31 (34.8%)	77 (25.4%)	
% Δ Positive Domain						
Un-Responsiveness	9 (12.5%)	7 (7.7%)	18 (35.3%)	29 (32.6%)	63 (20.8%)	0
Responsiveness	63 (87.5%)	84 (92.3%)	33 (64.7%)	60 (67.4%)	240 (79.2%)	
% Δ Negative Domain						
Un-Responsiveness	47 (65.3%)	50 (54.9%)	29 (56.9%)	54 (60.7%)	180 (59.4%)	0.577
Responsiveness	25 (34.7%)	41 (45.1%)	22 (43.1%)	35 (39.3%)	123 (40.6%)	
% Δ Psychopathology Domain						
Un-Responsiveness	70 (97.2%)	89 (97.8%)	17 (33.3%)	23 (25.8%)	199 (65.7%)	0
Responsiveness	2 (2.8%)	2 (2.2%)	34 (66.7%)	66 (74.2%)	104 (34.3%)	

A Chi Square test was conducted and the results were expressed as rates with their counts. A p-value of 0.05 was adopted.

Class I is made up of only older APDs, like Haloperidol tablets, Risperidone tablets, and Amisulpride tablets. Some examples of APDs in Class II are Fluphenazine LA, Flupentixol LA, Haloperidol LA, and Zuclopenthixol LA. These drugs are older oral with somewhat older IAPs. Modern oral antipsychotic drugs (APDs), such as Quetiapine, Olanzapine, Aripiprazole, and Paliperidone, are in Class III. The Class IV group includes Class III APDs as well as newer IAPs like Paliperidone LA and Risperdal consta. Responsiveness limit was determined in this study at reduction percentage at least 20% from baseline.

BRAS: Behavioural Adherence Rating Scale.

APDs: Anti-psychotic drugs.

DISCUSSION

A serious mental illness, schizophrenia, improves and worsens. Maintenance treatment is crucial, and the question of whether intramuscular long-acting (depot) antipsychotics can prevent medication discontinuation is unanswered.[20-21] This study assigned schizophrenia spectrum disorder patients to one of four APD classes: Class I had only older APDs, Class II had both older oral and IAPs, Class III had only newer APDs, and Class IV had a mix of newer oral and IAPs. Schizophrenia patients' drug nonadherence hinders symptom control, and stopping treatment can cause relapse and hospitalisation.[22] Most patients in this study adhered 25%–50% [123, or 40.6%]. Both older ("Class I") and newer ("Class III") APDs caused these non-follow-through rates [72 (100% of those surveyed) and 51 (100% of those surveyed), respectively]. The patients' BRAS levels rose above 50% after adding IAPs to their oral APDs. For instance, 49.5% (45 patients) and 50.5% (46 patients) had BRAS levels of 50%-75% and ≥75%, respectively, after adding older IAPs to older oral APDs, while 65.2% (58 patients) and 34.8% (31) had BRAS levels of 50%-75% and ≥75%, respectively, after adding newer IAPs.

taking them. Our study found more males than females in APD Classes I and III [39 (54.2%) vs. 33 (45.8%) and 27 (52.9%) vs. 24 (47.1%)]. In the negative symptoms domain, which scored 28–34 points, APD Classes I and III had higher rates [36 (50.0%) and 22 (43.1%), respectively, than Classes II and IV [37 (40.7%) and 38 (42.7%)]. Even after APD interventions, negative symptoms domains were higher in APD Classes I and III than Classes II and IV [17 (23.6%) and 9 (17.6%) vs. 20 (22.0%) and 15 (16.9%)].

Long-acting injectable antipsychotics (LA-IAPs) have become more popular in recent decades, helping to solve this problem. First-generation LA-IAPs used in this study were Fluphenazine LA, Flupentixol LA, Haloperidol LA, and Zuclopenthixol LA. These drugs cause drowsiness, salivation, sexual issues, and extrapyramidal effects, so only aggressive or nonresponding patients receive them. Second-generation LA-IAPs reduce extrapyramidal effects, sedation, and sexual dysfunction. They also improve life quality, social functioning, and patient resilience by controlling negative, cognitive, and affective symptoms. This is why doctors are considering injectable therapy early in illness. This study used 2nd-generation LA-IAPs Paliperidone LA and Risperdal consta. I

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In this study, 23.76%, or 72 patients, had Class I APDs. There were 91 Class II APD patients, or 30.03%. Similarly, 51 patients (16.83%) were classified as APD Class III. Class IV APDs comprised 29.37% of the total, with 89 patients.[23-25]

Neurocognition and the improvement in cognitive functioning by some molecules have garnered attention, so more molecules with a smaller negative effect on cognitive symptoms are used. Second-generation LA-IAPs have more regular patient-mental health service contacts and fewer therapy discontinuations than first-generation ones. Second-generation LA-IAPs are more expensive and can have dangerous metabolic side effects for people with diabetes, obesity, or metabolic syndrome, making them harder to use. Second-generation antipsychotics now treat mood, anxiety, obsessive-compulsive, and somatic mental disorders in addition to psychosis

Better biochemical profile, bioavailability, lower risk of accidental overdose, more stable blood concentration, and no peak effect are all advantages of injectable formulations over oral ones. Several studies have found that injectable therapy has higher therapeutic adherence than oral therapy, but few have found significant differences in emergency room access, psychiatric ward admissions, voluntary or compulsory nature, and hospitalisation length..[26-28]

The main goal of this study was to examine common APD responsiveness rates practically. Oral APDs alone and with LA-IAPs were examined in older and younger generations. We then compared the two groups using a validated symptomatic score (PANSS) for the three main schizophrenia spectrum disorder symptoms. We examine the major effects of these APD classes on symptom domains while considering strong patients' adherence. The validated Behavioural Rating Adherence Scale (BRAS) was used to assess patient adherence to treatment plans. A validation study compared BARS to electronic monitoring in 61 adult schizophrenia patients. BARS had 73% sensitivity and 71% specificity. However, it has major issues. Memory biases, ignorance,

and the desire to fit in can cast doubt on self-reported drug adherence metrics.

Long-acting injectable antipsychotics (LAIs) reduced hospitalisations more than oral antipsychotics in a meta-analysis of 25 mirror-image studies of 5940 schizophrenia patients from 28 countries. Finnish and Swedish cohort studies show that LAIs improve schizophrenia patients' compliance, clinical outcomes, and quality of life. However, 50% medication non-adherence increases recurrence, hospitalisation, healthcare resource consumption, costs, and patient quality of life. Three studies found LAI risperidone to improve Positive and Negative Syndrome Scale (PANSS) scores and be well tolerated. In India, retrospective studies examined adolescents with severe mental disorders who received first-generation LAI for reasons like failed or partial oral antipsychotic response, severe, aggressive behaviour, and oral AP non-adherence. Most patients received LAI fluphenazine (60.5%), accompanied by flupentixol (34.2%) and zuclopenthixol (18.4%). LAI risperidone had the most cases, followed by LAI paliperidone. Most studies and case reports showed clinical improvement in the short and medium term (up to 12 months) with good tolerability. Children and adolescents tolerate LAIAs well, with side effects ranging from 0 to 45%..[29-32]

Our study found that first-generation oral APDs without (Class I) or with (Class II) first-generation LA-IAPs showed the highest %Δ improvement in positive symptoms (-49.46%±20.85% and -47.09%±18.95%, respectively). Second-generation oral APDs without (APDs' Class III) or with (APDs' Class IV) LA-IAPs followed [-30.16%18.38% and -29.24%18.57%]. Negative symptoms domain scores for APD Classes I-IV were similar: -18.77%±19.56%, -19.69%±16.39%, -18.97%±16.63%, and -16.55%±11.39%. Psychopathological symptoms showed the greatest improvement in second-generation oral APDs with or without second-generation LA-IAPs (APDs' Class III and IV) [-26.41%±13.89% and -28.85%±14.06%, respectively]. First-generation oral APDs without (APDs' Class I) or with (APDs' Class II) first-generation LA-IAPs followed [-5.09%5.92% and -6.18%5.90%]. These findings support previous research that negative symptoms affect APD adherence more. This study found that long-acting and injectable APDs, ot patients' desire to take their medications, increased

adherence in Classes II and IV. Our study supports previous research on the main roles of first-generation APDs in positive symptoms and second-generation APDs in psychopathological symptoms.

For oral antipsychotic non-adherent severe schizophrenia patients, LA-IAPs may help. Monitoring for non-adherence and treating with LA-IAPs are options for patients with poor insight. If side effects persist after improvement, switching to LA-IAP formulations may improve tolerability. LA-IAPs may help patients with recent or first psychosis, and comorbid substance use should be considered when starting an antipsychotic medication (APD). LA-IAPs should be discussed with patients and carers during therapeutic plan development. The study's small sample size and inability to track relapse, remission, side effects, and maintenance length are flaws.

CONCLUSION

As shown in the tests of between-subjects effects table, both the positive scale and the psychological scale in the APDs Classes I–IV are significant, while the negative scale is insignificant. Our study agrees with other research that has been done on the main roles of first-generation APDs in the positive symptoms area and second-generation APDs in the psychopathological symptoms area.

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