

Correlation Between Efficacy of Treatment with Anti-psychotics and Adherence in Schizophrenic Patients: A Cross-sectional Study in Saudi Arabia

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ABSTRACT

Background: Schizophrenic patients' adherence to medication regimens can determine clinical outcome success. This study focuses on medication adherence and its correlation with the efficacy of anti-psychotics. The study's goal is to (1) assess the efficacy of anti-psychotics and adherence using the Self-evaluation of Negative Symptoms (SNS) tool and Medication Adherence Rating Scale (MARS), and (2) examine the demographic and clinical factors that could impact both outcomes (SNS and MARS). **Materials and Methods:** Between November 2021 and February 2022, a cross-sectional study was carried out. Only 45 of 100 schizophrenia patients screened were included in the sample. MARS and SNS self-assessment questionnaires that took approximately 15 min to complete were administered to patients in a scheduled clinic interview. Other patients' demographic, physical, and clinical information was gathered from their electronic medical records via a Redcap designed data collection sheet. **Results:** Almost 53.3% of the current schizophrenic patients had perceived mild negative symptoms (scored 1 to <20 out of 40 on SNS). Surprisingly, 64.4% were either poor adherent ($n=13$ scored 5 to 6) or non-adherent ($n=16$ scored <5). There was a notable negative correlation between the total MARS score and both total SNS ($r = -0.325, p=0.03$) and social withdrawal scores ($r = -0.436, p=0.003$). Non-adherence was significantly associated with lower education levels ($p=0.028$) and unemployment ($p=0.008$), whereas SNS total score and anhedonia were both markedly associated with different marital status ($p=0.046$, and $p=0.016$, respectively). **Conclusion:** According to the study, medication schizophrenia nonadherence correlates negatively with the efficacy of anti-psychotics as perceived by patients, which reflects patient quality and perception of life. These findings strongly emphasize the importance of developing adherence interventions to enhance compliance with anti-psychotic regimens and improve patients' perceived self-evaluation of negative symptoms.

Keywords: Schizophrenic patients, Anti-psychotics, Saudi Arabia, Medication regimen, Medication Adherence Rating Scale.

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INTRODUCTION

As a complex and severe chronic mental disorder, Schizophrenia causes elevated grades of disability and high levels of dependence and mortality.¹ The World Health Organization (WHO) estimates that globally 20 million people have schizophrenia disorder.¹ The Global Burden of Disease study reported that 1.1% are burdened with schizophrenia, and this number continues to grow.² Schizophrenia affects all age groups and has a life

expectancy of 20 years.³ It presents both positive and negative symptoms, including disorganized speech, distorted thoughts, and hallucinations. Many of the symptoms of schizophrenia are challenging to treat and manage. Therefore, a multidimensional approach that involves various clinical outcomes (e.g., relapse, medication adherence, co-morbidities, patient perception, insight, subjective experience, cognition, Quality of Life [QOL], autonomy, functional capacity) should be considered for the effective management and treatment of the disorder.⁴

This study's main focus is adherence—the determinate factor for assessing clinical outcomes, efficacy, and safety. WHO define adherence as “the extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health-care



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provider.⁷⁵ There are a couple of studies,^{6,7} that support the claim that it is essential to assess adherence to avoid hospitalization and relapse as non-adherence has been found to contribute to increased substance abuse, addiction, suicidal attempts, smoking, economical burdens, and healthcare expenditure.⁸ Adherence to anti-psychotic drugs is often attributed to positive attitudes toward medication, social alliance, insight, manageable adverse effects, and efficacy.⁸ Substance abuse and other psychiatric symptoms, such as depression and anxiety, often accompany schizophrenia and can greatly influence and make the management of the disease through anti-psychotic drug therapy more complicated.⁹

García *et al.*⁸ carried out a systematic review containing 38 studies with evidence that encompasses varying types of research (e.g., meta-analyses, systematic reviews, randomized clinical trials, observational studies, and clinical trials) demonstrating the factors and aspects that contribute to poor adherence to anti-psychotic medication in patients having schizophrenia, or schizophrenia accompanied by bipolar disorder. It was concluded that adherence can be influenced by many factors which are patient-, drug-, and health system-related, among other social factors. Hostility and substance abuse were consistent with schizophrenic patients who have poor adherence.^{8,10} Older schizophrenic patients were shown to be more compliant with their anti-psychotic drugs than younger patients, which could be attributed to their level of awareness.^{8,11} Anti-psychotic adverse effects such as neuroleptic dysphoria, secondary extrapyramidal symptoms, weight gain, and sexual dysfunction were associated with poor adherence.^{8,12} In addition, it was found that adherence/discontinuation rates were not defined according to a certain subclass of anti-psychotics (either first-generation anti-psychotics [FGA] or second-generation anti-psychotics [SGA]). Garcia *et al.*⁸ and Larco *et al.*¹³ concluded that evidence of non-adherence and whether the type of treatment is FGA or SGA is inconclusive. Recent studies have shown that good adherence and further good response were attributed to social relationships and alliances. According to one study, 80% of adherent schizophrenia patients received higher family involvement and care.^{8,14}

Assessing adherence to anti-psychotic drugs posed a challenging problem that affected current related studies, especially since the assessment tools are quite variable in terms of validity and accuracy.^{7,8,16-19} In Stentzel *et al.*,¹⁷ a German prospective controlled randomized study that involved 127 schizophrenic patients, the Medication Adherence Report Scale, German version (MARS-D) was used to measure non-adherence. According to the study, forgetting to take medication was the leading contributing factor to non-adherence. Whereas patients who were employed, older, had greater levels of global functioning (a measure of how well patients are doing overall), had social support, and took conventional anti-psychotics showed good adherence.

Whereas, in Nagai *et al.*'s study,¹⁸ which involved a cross-sectional examination of 148 Japanese patients with schizophrenia, the

Drug Attitude Inventory-10 (DAI-10)⁷ was employed as a proxy to evaluate adherence. The findings demonstrated that those who had been ill for a longer period and had higher scores of insights into illness provided higher DAI-10 scores, which reflect a favorable attitude toward anti-psychotics.

Studies focusing on adherence remain limited in Saudi Arabia. Therefore, further investigation needs to be done to detect the prevalence of poor adherence to anti-psychotics and the factors associated with it. Further research in this field can help patients reach their desired outcomes from anti-psychotic therapy. The purpose of this study is to assess (1) to evaluate the efficacy of anti-psychotics in schizophrenic patients using an Arabic version of the validated self-evaluation of negative symptoms (SNS) tool,²⁰ (2) to evaluate patients' adherence by implementing the Medication Adherence Rating Scale (MARS) self-assessment questionnaire,¹⁹ and (3) to initially explore the associated factors that influence adherence in Saudi schizophrenic patients, which could aid in future recommendations for the development of various clinical pharmacist-adherence interventions.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional study was performed. The study screened a sample size of 100 schizophrenic patients (outpatient/ inpatient); however, only 45 were included as participants. They were recruited from November 2020 to February 2021 from the Security Forces Hospital in Saudi Arabia based on the inclusion/exclusion criteria of the study (Figure 1). The following were the inclusion criteria: (1) age ≥ 18 years and ≤ 65 years, (2) used anti-psychotic medication for a minimum of 4–6 weeks, (3) complies with the DSM-5 diagnostic criteria for schizophrenia, (4) has schizophrenia accompanied with psychiatric disorder, like bipolar disorder, substance abuse, and depression (5) attained an education level of elementary/ primary school or above, (6) no hearing or visual disability, (7) independent ability to perform the self-test Scale. The following were the exclusion criteria: (1) age < 18 years and > 65 years, (2) less than 4–6 weeks of using anti-psychotic medication, (3) does not comply with the DSM-5 diagnostic criteria for schizophrenia and/ or accompanied mental illness as dementia, and mental disorders caused by psychoactive substances, (4) patient refused to integrate in the study. The Defined Daily Dose (DDD) and Chlorpromazine-equivalent Daily Dose (CPZE) of typical and atypical anti-psychotics were estimated in accordance with established standards.^{21,22} Patients were informed of the research purpose and objectives before they provided consent to participate. Interviews were conducted either on-site or by telephone using either paper or an electronic format of the study tools depending on patients' preference. Patient demographic and clinical data were obtained using the Medical Record Number (MRN) viewer system.

Measures

The study aims to evaluate the efficacy of treatment using anti-psychotics, its correlation to adherence, and the factors influencing adherence. The study applied both qualitative and quantitative self-reported questionnaires—Self-evaluation of Negative Symptoms (SNS) and Medication Adherence Rating Scale (MARS), respectively. Both tools addressed the research questions and are available in a validated Arabic version.

Medication Adherence Rating Scale (MARS)

MARS is a valid and reliable tool that has been utilized for estimating compliance in schizophrenia patients. Due to the ease of assessment by patients themselves, MARS is an appropriate and useful method for the quantitative assessment of schizophrenia patients' adherence to their medication. The scale's Cronbach's α coefficient was reported to be 0.8.²³ The scale was compiled and introduced by Thompson *et al.*¹⁹ using the Drug Attitude Inventory (DAI),¹⁵ and Medication Adherence Questionnaire (MAQ).¹⁶ The scale measures 10 items: (1) Do you ever forget to take your medicine? (2) Are you careless at times about taking your medicine? (3) When you feel better, do you sometimes stop taking your medicine? (4) If you sometimes feel worse when you take your medicine, do you stop taking it? (5) I take my medication when I am sick. (6) It is unnatural for my mind and body to be controlled by medication. (7) My thoughts are clearer on medication. (8) By staying on medication, I can prevent getting sick. (9) I feel weird, like a “zombie,” on medication. (10)

Medication makes me feel tired and sluggish. The scale requires a yes/ no response, which is scored as yes=0 and no=1 for all items except 7 and 8, which are scored as yes=1 and no=0. Higher total scores indicate high compliance with the medication regimen. MARS scores are categorized as 10: complete adherence; 9–7: some kind of adherence; 5–6 poor adherence; <5: non-adherence.

Self-Evaluation of Negative Symptoms (SNS)

SNS is an innovative validated tool used to measure psychometric properties. It is an accurate reflection of the harmful symptoms of schizophrenia, as discussed by Dollfus *et al.*²⁰ According to them²⁰ SNS correlates with the Clinical Assessment Interview for Negative Symptoms (CAINS) (by $r = 0.599$), supporting its strong validity. It evaluates and covers five negative dimensions (diminished emotional range, social withdrawal, avolition, alogia, and anhedonia). Social relationships with family and friends and patient desire/ propensity are evaluated by social withdrawal to initiate new relationships (example item 1: I prefer to be alone in my corner). Reduced emotional range assesses the patient's perception of happy or sad experiences (example item 6: There are many happy or sad things in life, but I don't feel concerned by them). Avolition assesses consistency in patients' daily activity with respect to motivation, desire, and energy, as well as difficulty in achieving goals (example item 13: I find it difficult to meet the objectives I set myself). Anhedonia evaluates patient pleasure as perceived from his/ her surroundings and anticipatory pleasure (example item 19: When I imagine doing one thing or another, I don't feel any particular pleasure from the idea of it). Alogia assesses the patient's perception of his/her own fluency or poverty in speech and interaction (example item 9: I don't have as much to talk about as most people). SNS includes 20 items and requires 3 responses: “strongly agree” scoring 2, “somewhat agree” scoring 1, or “strongly disagree” scoring 0. The overall SNS score can be subclassified into 3 severity levels: ranging from 0 (no negative symptoms) and 1 to <20 (patient experiences mild negative symptoms), and from 20 to 40, which reflects moderate to severe negative symptoms a schizophrenic patient frequently experiences. Good internal consistency was indicated by its Cronbach's coefficient ($\alpha = 0.867$).²¹

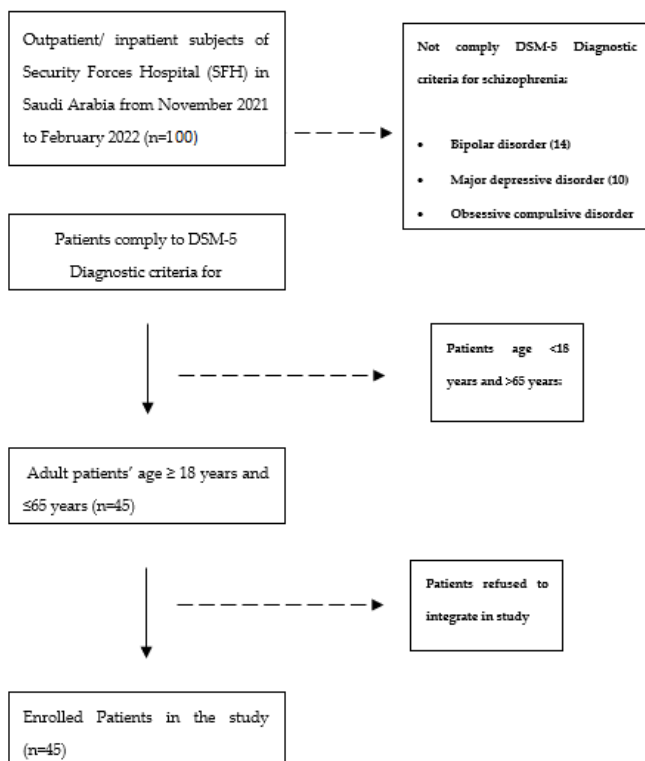


Figure 1: Cross-sectional study diagram.

Statistical Analysis

Version 28.0.1.1 of SPSS software was used to conduct the statistical analysis. All study variables were subjected to descriptive statistics calculations. The Kolmogorov-Smirnov test was used to confirm that the variables within each group were normal. Following that, a parametric test was run when the variable had a normal distribution, and a nonparametric test was run when the variable did not support the normal hypothesis. Analysis of Variance (ANOVA) was used to compare three means or more, [i.e. to examine mean score differences in patients' responses with respect to their characteristics (Categorical variables)]. While the student's *t*-test was used to differentiate two means. The

Mann-Whitney test, the Spearman test, and the Kruskal-Wallis test were the non-parametric tests that were used to compare several groups, two groups, and determine the correlation between two continuous variables, respectively. In order to remove as many potential confounding factors as possible, multivariable linear regressions were used to investigate the relationship between the total SNS or MARS score as dependent variables and continuous or categorical study variables that demonstrated $p < 0.1$ in the bivariate analysis as independent variables. Statistical significance was set at a value of $p \leq 0.05$.

RESULTS

Participants

Table 1 summarizes the characteristics of the sample. This study comprised 45 people with schizophrenia in total, of which 55.6% were men ($n=25$), 64.4% were single, 51.1% had a high school diploma, and 55% were unemployed. The patients mean age was 33.98 ± 7.43 years.

All data are presented as numbers (%) unless otherwise indicated.

As shown in Figure 2, the most used anti-psychotic drugs for monotherapy were Paliperidone ($n=6$, 13%), Risperidone ($n=5$, 11.1%), Aripiprazole ($n=3$, 6.7%), and Clozapine ($n=1$, 2.2%). While the most frequently prescribed combination therapy was Aripiprazole-Risperidone ($n=5$, 11%), as it surprisingly takes overall preference compared with other combinations. Almost 60% of schizophrenia patients in the current sample employed combination therapy (Figure 2).

Patients received a mean total equivalent dose of chlorpromazine of 2372.77 ± 3778.61 mg. Chlorpromazine equivalent dosage was 26.66 ± 149.84 mg for typical anti-psychotics and 2446.11 ± 3785.70 mg for atypical anti-psychotics.

Measures

SNS Observed Scores

The overall SNS score (out of 40) had a mean of 15 ± 12.364 and was normally distributed. Figure 3 displays the distribution and frequency of schizophrenic patients in this study according to three SNS severity categories, which were based on their self-evaluation: 7 (15.6%) patients had a score of 0 (no negative symptoms); 24 (53.3%) had a score ranging from 1 to <20 (mild negative symptoms); and 14 (31.1%) had a score ranging from 20 to 40 (moderate to severe negative symptoms). The median scores on SNS subdomains were 2 (range: 0–8) for social withdrawal, and 3 (range: 0–8) for all the remaining 4 subscales including diminished emotional range, avolition, anhedonia, and alogia.

MARS Observed Scores

In this population, the median score was 5 (range 0–8), and the mean score for the medication adherence scale was $5.1 \pm$

Table 1: Demographic and clinical characteristics of schizophrenic patients (n=45).

Variables	Number of patients (%)
Age (years), mean (SD)	33.98 (7.43)
Age of schizophrenia onset (year), mean (SD)	27.13 (6.33)
Year of schizophrenia diagnosis, mean (SD)	6.87 (5.19)
Sex	
Female	20 (44.4%)
Male	25 (55.6%)
Marital status	
Single	29 (64.4%)
Married	13 (28.3%)
Divorced	3 (6.7%)
Education level	
Elementary/ primary school	2 (4.3%)
High school	23 (51.1%)
College	20 (44.5%)
Employment status	
Employed (Full time)	13 (28.9%)
Unemployed	25 (55.6%)
Retired	6 (13.3%)
Student	1 (2.2%)
Family history of schizophrenia	3 (6.7%)
History of attempted suicide	2 (4.4%)
Anti-psychotics usage	
1	15 (33.3%)
2	25 (55.6%)
> 3	5 (11.1%)
Self-assessment questionnaires	
MARS, mean (SD)	
Total score	5.11 (2.17)
SNS, mean (SD)	
Total score	14.62 (12.36)
Social withdrawal	2.47 (2.8)
Diminished emotional range	3.07(2.64)
Avolition	2.93 (2.8)
Anhedonia	3.11 (2.89)
Alogia	3.04 (3.06)

2.17. Figure 4 depicts the histogram of MARS scores, which clearly demonstrates that the distribution is skewed to the right (positively skewed). According to patient-reported MARS total scores, only 16 (35.6%) patients were somehow adherent (scored 7 to 9), whereas the majority 64.4% were either poor adherent ($n=13$ scored 5 to 6) or non-adherent ($n=16$ scored <5). None of the patients in this study reported a level of complete adherence (score 10).

Figure 5 shows the responses of the participants for the self-assessed MARS scale. Almost all of the participants (93.3%) said they do not take their medication when they are sick. Patients who do not stop taking medication when they feel better and when they feel worse account for 86.7% and 76.1%, respectively.

Demographic and clinical factors associated with SNS

Bivariate analysis of SNS total score

Table 2 provides a summary of the bivariate analyses of continuous variables connected to the overall SNS score. The

anhedonia domain showed a positive correlation with the number of concomitant medications used ($r = 0.379$), while social withdrawal and avolition were positively correlated with a higher total daily dose of chlorpromazine-equivalent ($r = 0.301$ and $r = 0.294$, respectively). This indicates that patients receiving higher doses will reflect more negative perceptions of their psychiatric conditions. However, the DDD for typical and atypical anti-psychotics did not show any statistically significant correlation with either SNS total or subdomain scores (Table 2).

The SNS total and subdomain scores are shown in Table 3 by various categorical patient characteristics. The initial univariate analysis failed to uncover any factors that could significantly affect the overall patient SNS score ($p \geq 0.05$), except for married patients, which showed a significantly lower SNS score (7.69) compared to patients who were single or divorced ($p=0.046$). Marriage significantly improves patients' responses to anhedonia, according to subsequent univariate research conducted within SNS subdomains ($p=0.016$). Nevertheless, none of the SNS subdomains significantly affected how patients responded,

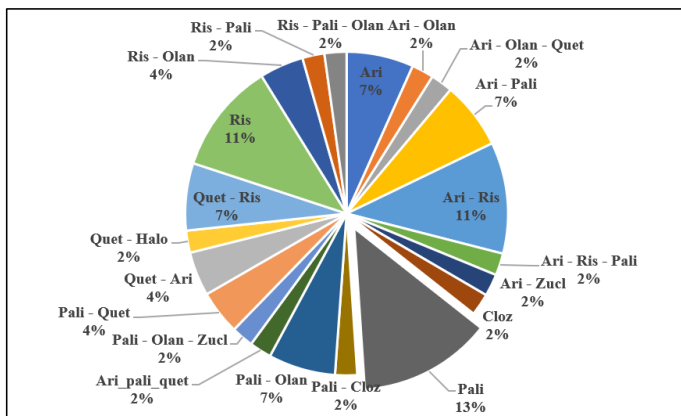


Figure 2: Pattern of most used anti-psychotics either as a monotherapy or a combined therapy (more than one).

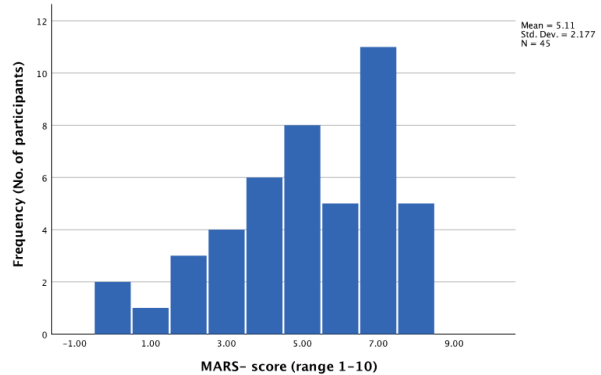


Figure 4: Histogram of MARS score (MARS score of 10: complete adherence; 9-7: some kind of adherence; 5-6 poor adherence; <5: non-adherence).

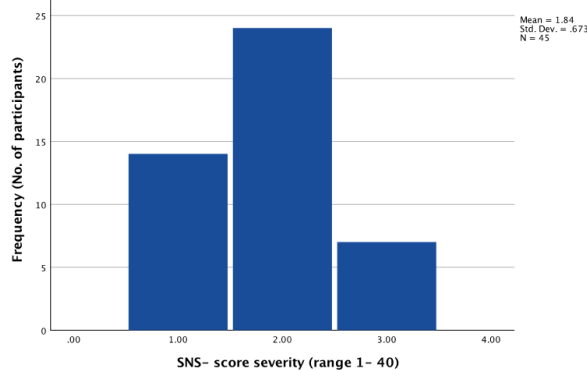


Figure 3: Histogram of SNS score severity; Total score of SNS is a sum of 20 items, ranging from 0 (no negative symptoms score=3) and 1 to <20 (patient experience mild negative symptoms score=4) and from 20 to 40 (moderate to severe negative symptoms score=1).

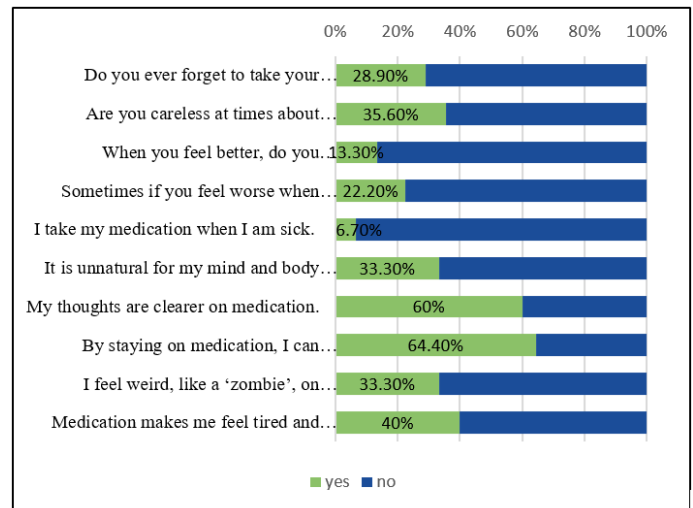


Figure 5: Bar chart of relative frequencies of medication adherence rating scale (MARS) distribution among the participants.

regardless of their gender, marital status, level of education, employment status, or concurrent medication use ($p \geq 0.05$).

Demographic and clinical factors associated with the MARS scale

Bivariate analysis (MARS total score)

In Table 4, a summary of the bivariate analysis of continuous variables related to the overall MARS score is provided. The overall MARS score did not significantly correlate with any of the specified continuous variables, as revealed by the obtained weak r -Spearman correlation coefficient values.

The ANOVA test and *post hoc* Tukey test were used to examine patients' categorical variables and the results are shown in Table 3. Interestingly, the state of having a college education and full-time employment reported significantly higher levels of mean adherence as compared to having a lower level of education (p -value=0.028) and unemployment (p -value=0.008). There were

no other apparent relationships between adherence and other patient demographics or clinical characteristics in this sample ($p \geq 0.05$).

Multivariable analysis (SNS total score)

Table 5 displays the outcomes of a forward linear regression. The results show that, using the overall SNS negative score as the dependent variable, and there was no significant relationship between the total SNS negative score and any of the continuous or categorical variables introduced in the model.

Correlation analysis of adherence in schizophrenia patients

Table 6 displays the correlation analysis of medication adherence level with SNS total and subdomain scores of schizophrenia patients. Interestingly, a notable negative correlation was seen between the total MARS score and both total SNS ($r = -0.325$, $P=0.03$) and social withdrawal scores ($r = -0.436$, $P = 0.003$). This indicates that patients who reported more total severe negative

Table 2: Bivariate analysis of continuous variables related to the self-evaluation of negative symptoms scale total and subdomain scores.

Variables	r-Spearman's correlation coefficient–Sig. (2-tailed)					
	SNS total score	Social withdrawal	Diminished emotional range	Avolition	Anhedonia	Alogia
Age (year)	r = 0.068	r = 0.085	r = 0.142	r = 0.047	r = 0.015	r = 0.063
Age of schizophrenia onset (year)	r = 0.006	r = -0.088	r = 0.005	r = 0.086	r = 0.028	r = 0.069
Year of schizophrenia diagnosis	r = 0.29	r = 0.187	r = 0.097	r = -0.091	r = -0.050	r = -0.064
No. of anti-psychotics	r = -0.005	r = 0.081	r = -0.049	r = -0.010	r = -0.033	r = 0.001
No. of concomitant medications	r = -0.336	r = -0.0246	r = -0.222	r = -0.315	r = 0.379‡	r = -0.270
Duration of anti-psychotics therapy	r = -0.186	r = -0.062	r = -0.252	r = -0.137	r = -0.210	r = -0.207
CPZE						
Chlorpromazine total equivalent daily dose	r = 0.208	r = 0.301‡	r = 0.112	r = 0.294‡	r = 0.079	r = 0.164
Chlorpromazine equivalent daily dose for atypical anti-psychotics	r = 0.126	r = 0.221	r = 0.048	r = 0.207	r = 0.000	r = 0.81
Chlorpromazine equivalent daily dose for typical anti-psychotics	r = -0.014	r = -0.034	r = 0.044	r = 0.006	r = -0.001	r = 0.030
DDD						
Defined daily dose total	r = 0.171	r = 0.252	r = 0.102	r = 0.127	r = 0.099	r = 0.077
Defined daily dose for atypical anti-psychotics	r = 0.195	r = 0.275	r = 0.113	r = 0.152	r = 0.127	r = 0.091
Defined daily dose for typical anti-psychotics	r = -0.034	r = -0.53	r = 0.032	r = -0.013	r = -0.020	r = 0.013

Significant and non-significant results are listed in the table. ‡ $p < 0.05$. § $p < 0.01$.

symptoms—specifically social withdrawal symptoms—were less likely to be adherent to their anti-psychotic medications. In addition, patients' scores on other SNS subdomains (including diminished emotional range, avolition, and anhedonia) were negatively associated with their adherence level, although, the r-Spearman correlation coefficients did not reach the statistical significance level ($P>0.05$). However, a small trend for positive association was found between adherence and alogia ($r = 0.2$), which implies the patient's perception of how much to converse with other people and the effort needed by the patient to engage in conversation. However, this result did not reach a significant correlation level as well ($P>0.05$).

DISCUSSION

Schizophrenia is a mental disability often characterized by psychosis, which is the inability to distinguish ideas and thoughts from reality, and can be accompanied by other psychological symptoms.¹ Nonadherence is still a significant obstacle to good health in schizophrenia and other psychiatric diseases.²⁴ In Saudi Arabia, it is regarded as one of the major medical issues among psychiatry patients.²⁵

In the present study we investigated patient adherence to anti-psychotic therapy and its efficacy from the point of view of the patient based on their own experiences. We found that adherence level is mostly rated as poor by 64.4% of the sample. Most patients reported having either mild or no negative symptoms. According

Table 3: Bivariate analysis of categorical factors related to SNS total, SNS subdomain, and total MARS score.

Variables	One-way ANOVA test, (mean)						
	SNS total score	Social withdrawal	Diminished emotional range	Avolition	Anhedonia	Alogia	MARS total score
Sex							
Male ($n=25$)	14.52	2.52	2.92	3.08	2.88	3.12	5.56
Female ($n=20$)	14.75	2.4	3.25	2.75	3.4	2.95	4.55
p	0.951	0.888	0.682	0.7	0.555	0.856	0.123
Marital status							
Single ($n=29$)	17.79	2.93	3.69	3.48	3.93	3.76	5.1
Married (13)	7.69	1.46	1.92	1.69	1.23	1.38	5.69
Divorced ($n=3$)	14	2.33	2	3	3.33	3.33	2.67
p	0.046‡	0.296	0.101	0.162	0.016‡	0.063	0.093
Education level							
Elementary/ primary school ($n=2$)	28	5	7	5.5	4.5	6	3
High school ($n=23$)	16.7	3.09	3.22	3.13	3.74	3.52	4.52
College ($n=20$)	10.9	1.5	2.5	2.45	2.2	2.2	6
p	0.088	0.073	0.63	0.311	0.193	0.139	0.028‡
Employment status							
Employed (Full time, $n=13$)	15.38	2.31	3.31	3.23	3.15	3.38	6.38
Unemployed ($n=25$)	17.2	3.12	3.48	3.44	3.48	3.68	4.2
Retired ($n=6$)	3.5	0.5	1.33	0.67	0.83	0.17	6.33
Student ($n=1$)	7	0	0	0	7	0	4
p	0.9	0.161	0.2	0.112	0.11	0.5‡	0.008‡

‡Statistically significant result.

to Barkhof *et al.*²⁶ and Cramer and Rosenheck,²⁷ schizophrenic patients have an incidence of non-adherence to anti-psychotic medication that varies from 20% to 89%, which agrees with similar findings in other studies. For example, Mukattash *et al.* in their cross-sectional study,²⁸ observed that 64.2% of their sample's psychiatric patients showed non-adherence, suggesting

its prevalence. Other studies reported even higher percentages of non-adherence. In Alsalem,²⁵ a study that assessed psychotropic medication non-adherence in 342 psychiatric patients, found that 74% were non-adherent. This outcome is in line with Nirojini *et al.*²⁹ which showed that 76% of psychiatry patients were non-adherent.

Table 4: Bivariate Study of continuous factors linked to the overall score on the self-evaluation of medication adherence scale.

r-Spearman's correlation coefficient-Sig. (2-tailed)	
Variables	MARS total score
Age (year)	r = -0.115
Age of schizophrenia onset (year)	r = 0.040
Year of schizophrenia diagnosis	r = -0.202
No. of anti-psychotics	r = -0.016
No. of concomitant medications	r = -0.280
Duration of anti-psychotics therapy	r = 0.010
CPZE	
Chlorpromazine total equivalent daily dose	r = -0.095
Chlorpromazine equivalent daily dose for atypical anti-psychotics	r = -0.135
Chlorpromazine equivalent daily dose for typical anti-psychotics	r = 0.206
DDD	
Defined daily dose total	r = -0.069
Defined daily dose for atypical anti-psychotics total	r = -0.088
Defined daily dose for typical anti-psychotics total	r = 0.204

The reasons behind non-adherent in this study's findings did not match with those reported in other studies. Alsalem²⁵ and Tesfay *et al.*³⁰ reported that 71.6% and 78.2% of patients, respectively, forget to take medications. In Alsalem's,²⁵ study, 58.1% of patients are careless about timing their medications, and 59.1% feel tired and sluggish after taking them. In Tesfay *et al.*,³⁰ 35.6% of patients stopped psychotropic medications when they felt better. Interestingly, our findings display lower percentages; 20% of schizophrenia patients forget to take their medications, 35% were careless about when to take them, and 33.3% felt tired and sluggish when taking them (Figure 5).

The current analyses show that adherence was closely linked with higher levels in patients with a college education and full-time employment. These results are consistent with Stentzel *et al.*,¹⁷ who conducted a randomized clinical study where good adherence was found more in patients who were employed ($p < 0.0001$). Similar results were observed in Alsalem's study,²⁵ where significance was found between adherence and patients with higher educational levels ($P < 0.05$). Furthermore, in agreement to a study by Liu-Seifert *et al.*,³¹ another factor contributing to nonadherence in patients could be their lack of disease insight and knowledge about their illness.

Consistent with our findings, no serious correlation was found between either gender or age with medication adherence in Alsalem's study.²⁵ Nevertheless, there are inconsistencies between the current study findings and those of Hajj *et al.*³² with regard to the analyses of negative symptoms, as older age patients and

Table 5: Multivariable analysis; linear regression using the overall score on the scale for self-evaluation of negative symptoms as the dependent variable.

Variable	Unstandardized coefficients		Standardized coefficients	p-value	95% CI	
	B	Standard error			Lower bound	Upper bound
Age (year)	0.266	0.398	0.143	0.511	-0.562	1.095
Sex	-1.687	5.729	-0.065	0.771	-13.601	10.226
Educational level	-1.216	3.511	-0.9	0.733	-8.517	6.086
Family history of schizophrenia	4.433	10.437	0.104	0.675	-17.272	26.138
No. of anti-psychotics	1.154	5.503	0.048	0.836	-10.29	12.598
No. of concomitant medications	-7.919	5.503	0.048	0.065	-16.381	0.543
Chlorpromazine total equivalent daily dose	0.001	0.001	0.22	0.355	-0.001	0.003
Defined daily dose total	-3.08E-06	0	-0.019	0.93	0	0

The table lists significant and insignificant findings. * $p < 0.05$. \$ $p < 0.01$.

Table 6: Medication adherence level correlation analysis with SNS total and subdomain scores of schizophrenia patients.

Variables	r-Spearman's correlation coefficient (2-tailed <i>p</i> value)	
	r	p
SNS		
Total score	-0.325‡	0.03
Social withdrawal	-0.436§	0.003
Diminished emotional range	-0.0229	0.131
Avolition	-0.272	0.7
Anhedonia	-0.249	0.1
Alogia	0.251	0.097

Statistically significant result ‡*p* < 0.05. §*p* < 0.01

female gender were considerably connected with higher scores of SNS (*p*<0.001).

Being married interestingly scored significantly less for negative symptoms as compared to being single and divorced (*p*=0.046), and was also found to be positively correlated with the anhedonia domain. Li *et al.*³³ showed a similar outcome, which was attributed to the probability of better psychological adjustment and improved patient physical health in married patients. On the contrary, Hajj *et al.*³² showed that married patients were more likely to have negative symptoms than single or divorced patients (*p*<0.017).

Anhedonia and a low number of anti-psychotic medications taken at once were significantly correlated. Similarly, Alsalem's study²⁵ demonstrated that with more drugs, 24% of patients developed non-adherence.

Contrarily, regarding dose measures, social withdrawal and avolition were positively correlated with a higher total daily dose of chlorpromazine-equivalent. This indicates that patients receiving higher doses reflect more negative perceptions of their psychiatric conditions. However, the DDD for typical and atypical anti-psychotics had not shown any statistically significant correlation with either SNS total or subdomain scores. These findings are somehow inconsistent with results obtained in a previous Lebanese study,³² where the total SNS score was significantly correlated with the total daily dose of chlorpromazine-equivalent and a higher daily dose of chlorpromazine-equivalent for typical anti-psychotics, while it was negatively related to a higher chlorpromazine-equivalent daily dose for atypical anti-psychotics. This contradiction could perhaps be explained by the difference in the mean of the total equivalent dose of chlorpromazine among patients in Hajj, *et al.*³⁰ (1150.91 ± 973.70 mg), which is mainly composed of typical anti-psychotics (1010.57 ± 973.63 mg), more than the newer

atypical group (163.57 ± 305.97 mg). Interestingly, though our study subjects were receiving a higher mean of total equivalent dose of chlorpromazine (2372.77 ± 3778.61 mg) than the patients in Hajj *et al.*,³⁰ it was found to be more composed of equivalent total daily dose of atypical anti-psychotic (2446.11 ± 3785.70 mg) than typical drugs (26.66 ± 149.84 mg), which is known to be more tolerable in terms of side effects.

Our study showed that the MARS score is negatively correlated with total SNS and social withdrawal scores (*p*=0.03, *p*=0.003, respectively). This presents a reasonable explanation that non-adherence to anti-psychotics could be most influenced by having more negative and social withdrawal symptoms, which can negatively impact the patient perceptions and QOL. Similarly, Ogunnubi *et al.*³⁴ found that QOL significantly decreased with poor anti-psychotic therapy adherence in schizophrenia patients.

CONCLUSION

The study found that medication nonadherence correlates negatively with the efficacy of anti-psychotics as perceived by schizophrenia patients. This reflects patient QOL and perception of life. The study strongly emphasizes the importance of developing clinical pharmacist-adherence interventions that could influence patients' measured response to medication regimens.

To the best of our knowledge, in Saudi Arabia, this is the first study that employed two validated Arabic versions of self-assessment scales (SNS³⁵ and MARS³⁶) to investigate patient adherence, and examine associated demographic and clinical factors that influence both measures' scales. We found it interesting that patients in this sample frequently admitted to not adhering to their anti-psychotic therapy, which is very unusual for schizophrenia patients. This finding warrants further investigation and deep analyses in the future to address the phenomena that were encountered in the current sample. We deem this study an early step in the development of pharmaceutical care research and quality standards in schizophrenia. As such, it moves the clinical pharmacy field forward. At the very least, it should promote more research in anti-psychotics effectiveness and also provoke apprehension about the quality of pharmaceutical care plans presently provided to patients with schizophrenia in Saudi Arabia.

This study has a number of limitations. First, given the number of study variables and the time frame for data collection, the sample size was small. However, the variability of patients' fixed variables (demographics, educational level, multiple anti-psychotics use, and chlorpromazine total equivalent daily dose) might improve the generalizability of our results and limit the potential of bias arising from the small sample studies.³⁷ Second, the design employed was primarily cross-sectional. We focused on point-in-time treatment strategies and did not attempt to investigate any changes in treatment adherence over time. For example, we asked patients if they were adherent and correlated that parameter

with their self-evaluated effectiveness measure based on their current mono- or combination anti-psychotic therapy. This analysis does not capture the estimate of prior adherence to anti-psychotic monotherapy therapy among 60% of our patients who currently receiving multiple anti-psychotics which will subsequently resolved after considerable suffering, nor does it reflect future estimate of failure to adhere among the remaining 40% of our subjects who are currently on monotherapy and might need further escalation in number of anti-psychotics. However, the employment of chlorpromazine-equivalent daily dose as a covariate in our multiple logistic regression analyses could resolve all these confoundings.³⁷ Third, social desirability by patients might have influenced their responses to measures as the methodology employed for completing both tools (SNS and MARS) was one-to-one interviews. Finally, some of the non-significant correlation findings could be due to small frequencies in categorical variables, which may account for some of the negative results due to decreased statistical power. Therefore, larger-scale, multicenter studies are warranted to validate the current findings in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Institutional Review Board Statement

The study was approved by the Institution Review Board (IRB) committee of the Security Forces Hospital in Saudi Arabia (Research number: 21-537-50). All procedures were performed in accordance with the national and ethical standards of the said committee.

Informed Consent Statement

All enrolled patients showed the capacity to understand and complete the questionnaire and provide written and verbal informed consent.

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