

## Optimal values exploration for responsiveness rates in stable and unstable schizophrenic patients

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World Journal of Biology Pharmacy and Health Sciences, 2024, 17(02), 022–028

Publication history: Received on 29 January 2024; revised on 06 February 2024; accepted on 07 February 2024

Article DOI: <https://doi.org/10.30574/wjbphs.2024.17.2.0050>

### Abstract

**Background:** Schizophrenia leads to multifunctional disability, characterized by cognitive and social impairments, everyday skill and self-assessment difficulties, and negative symptoms. Long-term clinical stability, often achieved with antipsychotics, improves everyday functioning.

**Aim:** The goal is to determine to determine the efficacy of different antipsychotic classes (%Prob of APDs' Resp) and adherence rates, as measured by the Behavioural Adherence Rating Scale (BARS).

**Methods:** The study focuses on schizophrenia-spectrum disorders in adults and elderly psychiatric patients, using established diagnostic systems. The observational and retrospective study will be conducted at the Princess Aisha Bint Al Hussein Medical Centre from January 2021 to January 2023. The study will use positive and negative symptom domains to measure initial severity and assess ideal values for antipsychotic drugs. A Chi Square test will be used to analyze distribution rates and odds ratios. The study will use SPSS version 25 with a 5% significance level.

**Results:** The binary logistic regression model was created using patient adherence patterns evaluated using BARS. The model aimed to predict positive responsiveness ( $\Delta$  PANSS $\geq$ 20%) and negative responsiveness ( $\Delta$  PANSS $<$ 20%) using patient data. The model accurately identified 94.4% of cases, with a chi-square value of 4.412 and a p-value of 0.818. BARS testing revealed a probable range of APDs' reaction from 64.4% to 88.2%, with individuals determining this range. The study suggests that the specific range may be different depending on the Cox & Snell R<sup>2</sup> or Nagelkerke R<sup>2</sup> procedures used, but all factors should be considered. The model's accuracy is significant, and the findings suggest that individuals are responsible for determining this range.

**Conclusion:** The study reveals that psychotic individuals require 68.5% adherence for optimal responsiveness. Adding LAIAP to oral APDs enhances responsiveness.

**Keywords:** Optimal values; Clinical stability; Unstability status; Anti-psychotic drugs; Schizophrenia spectrum disorder

### 1. Introduction

Complex mental disease, or schizophrenia, is common worldwide and is predicted to impact roughly 0.32% of the population by 2022. Schizophrenia's chronic nature, characterised by both acute and lingering episodes of symptoms, results in a great deal of misery. Despite being relatively uncommon, schizophrenia results in a great deal of pain. Furthermore, individuals with schizophrenia often have additional negative impacts on their physical health and are

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more likely to attempt suicide. Reducing the frequency of admissions to psychiatric institutions and emergency departments (EDs) is one of the clinical and pharmaco-economic issues that schizophrenia offers. These admissions are indicators of a disease that is not being appropriately managed<sup>1-3</sup>.

Numerous factors, including a lack of self-awareness about one's condition, the emergence of depressive symptoms, cognitive decline, the presence of both positive and negative symptoms, social isolation, concurrent substance abuse, societal stigma, inadequate mental healthcare systems in some areas, and a limited understanding of the advantages and disadvantages of therapy, have been linked to the noncompliance with treatment protocols. The first generation of antipsychotics (APs) was introduced in the 1950s, and this resulted in a notable decrease in the incidence of hospitalisations for patients with schizophrenia diagnoses. It was also at this time that ambulatory care began. Despite this, a sizable percentage of patients showed inadequate treatment adherence. This may be the result of either limited treatment tolerance or a lack of understanding. These patients stopped receiving treatment as a result, which caused their psychotic symptoms to reappear.<sup>4-6</sup>

Developed in the 1970s and 1980s, long-acting injectable antipsychotics, or LAIs, were intended to increase treatment adherence for mental health conditions. Despite this, there were not enough thorough research carried out at the time to adequately prove the efficacy of LAIs. Research has shown that later generations of long-acting injectable antipsychotics (LAIs) are more effective than the original oral forms of antipsychotics (APs) at eliminating psychotic symptoms and lowering the risk of recurrence. When patients disregard the advice that their doctors have given them, difficult circumstances might occur for healthcare personnel. The simultaneous occurrence of a mental disease may make this situation even more difficult. Between forty and sixty percent of individuals with a diagnosis of schizophrenia are thought to not take their antipsychotic medication as prescribed, which can have detrimental effects on their general health and wellbeing.<sup>7-9</sup>

The answer to the question of whether or not LAIs should be prescribed to all patients remains uncertain. Examples of subgroups who may benefit from this approach include male patients, younger patients, and patients who do not comply with their medication. Second generation long-acting injectables (LAI) have been available more recently and may be beneficial for a range of patient subgroups. Clozapine is the recommended medicine for treating treatment-resistant schizophrenic symptoms, per all relevant clinical practice guidelines. The evidence that has been accumulated indicates that clozapine is more successful than other antipsychotic drugs in treating all symptoms associated with schizophrenia. Moreover, it may be able to successfully lower the recurrence rates in schizophrenia cases that don't improve with therapy.<sup>10-12</sup>

Patients with psychotic disorders who receive mental healthcare services in a community-based setting in rural Jordan were the subjects of the study, and the primary objective of the study was to determine the efficacy of different antipsychotic classes (%Prob of APDs' Resp) and adherence rates, as measured by the Behavioural Adherence Rating Scale (BARS).

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## 2. Material and Methods

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. Sociodemographics, baseline schizophrenia severity, responsiveness, and adherence were collected. At least 80% oral APD consumption before LA-IAPs commencement was considered compliance. Statistics were run on the entire patient population and pre-specified subgroups. Indeed, we sought to know how well oral and injectable antipsychotic drugs (APs) regulate psychological, positive, and negative sensations, expectations, and fears. DSM-type diagnostic methods are used to diagnose mental ailments.

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 evaluated repeatedly and between raters. Researchers will track percentage reductions in positive symptoms (P1–7), negative symptoms (N1–7), and psychopathologies (G1–16). This will demonstrate how terrible the four oral and LA-APD categories were at the outset of the trial and how well the treatment helped. The study will also assess patient APD compliance.

The three-question BARS assessment uses a thorough visual analogue rating scale to determine the patient's monthly prescription dose (0% to 100%). The three questions assess the patient's knowledge of their prescription habit, including how often to take their medication, whether they miss doses, and whether they take less than the authorised

amount. Each half of the patients' adherence scales (BRAS) was 25% farther apart. Other factors will be tested with a Chi-square test. This study will employ SPSS 25's 5% significance level. The study used a binary logistic regression analysis to examine the relationship between the responsiveness rate (%Prob of APDs' Resp) for the two interventional APD regimens, oral alone (Regimen I) and oral and LAIAPs (Regimen II), and patients' Behavioural Adherence Rating Scale (BARS) adherence. The analysis focused on correlation, the independent variables' contribution to the dependent variable's variability, and predicted accuracy. This study considers higher antipsychotic responsiveness (% Prob of APDs Resp) favourable and lower percentages undesirable.

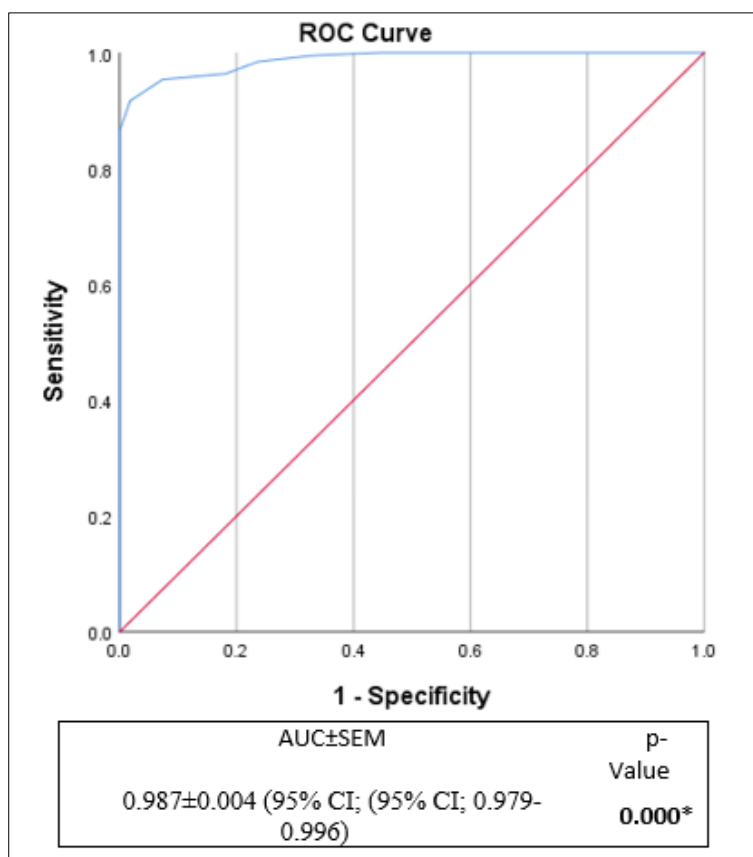
Our verified prognosticator shows that higher %Prob of APDs' Resp indicates stronger positive evidence. Higher independent variable values, which indicate patient responsiveness, are less accurate than lower percentage probabilities of APD responses because patients are less likely to continue the intervening APD regimen. This is because patients rarely follow the programme. The Receiver Operating Characteristic (ROC) test analysed AUROCs. In this study, a higher proportion of antipsychotic response (labelled 1) is positive and a smaller proportion is negative. Declining values of the independent variable support the negative state and lower the probability of an APD response. This study comprised 303 schizophrenia spectrum disorder patients. We sought the lowest adherence pattern for Jordanian psychotic patients to determine the optimal APD regimen response rate. In addition to the appropriate BARS threshold for our patient, accuracy index, sensitivity, specificity, positive and negative predictive values, etc. were examined. ROC and sensitivity data are in Tables 1–2 and Figure 1.

**Table 1** Presents the binary logistic regression model examining the relationship between patients' adherence pattern and their responsiveness to pre-selected antipsychotic interventions

Tested predictors	B±SEM	Wald	Sig.	Exp (B)	95% C.I. for EXP(B)		χ <sup>2</sup> (df) Sig	VR	%Cases
					Lower	Upper			
%Prob of APDs Resp	=e <sup>(-66.21+0.983×BRAS)</sup> / [1+ e <sup>(-66.21+0.983×BRAS)</sup> ]								
BRAS	0.983±0.156	39.597	0.000	2.671	1.967	3.628	(8) 4.412 0.818	64.4%- 88.2%	94.4%
Constant	-66.21±10.55	39.427	0.000	0.000					
The study used a binary logistic regression analysis to examine the correlation between patients' adherence and the responsiveness of different antipsychotic classes. The analysis found that a higher percentage of antipsychotic responsiveness indicates a positive condition, while a lower percentage indicates a negative condition. The results indicated that higher values support a positive state, while lower values provide more compelling evidence for a negative state.									

**Table 2** Presents the results of sensitivity tests for optimal cut-off points, sensitivity, specificity, and other sensitivity indices of the patients' Behavioural Adherence Rating Scale (BARS) in relation to the responsiveness of different antipsychotic classes (%Prob of APDs' Resp)

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI
BARS	68.50	91.7%	1.8%	89.89%	98.18%	98.88%	87.10%	5044%	94.06%	75.46%
A study of 303 individuals with schizophrenia spectrum disorder conducted sensitivity analyses to determine the efficacy of different antipsychotic classes and adherence rates. A higher percentage of antipsychotic responsiveness (%) indicates a positive state, while a lower percentage (%) indicates a negative state. Higher values indicate stronger evidence supporting the positive condition, while a lower probability of an APD response is supported by stronger evidence when the independent variable decreases.										
TPR: True positive rate or sensitivity. FPR: False positive rate. YI: Youden's index. TNR: True negative rate or specificity.							PPV: Positive predictive value. NPV: Negative predictive value. NLR: Negative likelihood ratio. PLR: Positive likelihood ratio. AI: Accuracy index.			



**Figure 1** Receiver Operating Characteristic illustration

The study used the Receiver Operating Characteristic (ROC) test to examine the correlation between patients' adherence and the effectiveness of various antipsychotic classes. A higher proportion of antipsychotic responsiveness (% Prob of APDs Resp) is considered a positive state, while a smaller proportion is a negative state. The validated predictor showed that higher values indicate more evidence in favor of the positive condition, while decreased values offer stronger evidence supporting the negative state. This study provides valuable insights into the effectiveness of antipsychotics in treating patients with APDs.

### 3. Results

A source of information that was utilised in the process of creating the binary logistic regression model was the adherence pattern of the patients, which was evaluated by BARS. The purpose of this model was to generate a forecast for the likely of positive responsiveness ( $\Delta$  PANSS $\geq$ 20%) within the supplied data, utilising the information provided by the patients. This prediction was compared to the likelihood of negative responsiveness ( $\Delta$  PANSS<20%) within the given data. It is strongly suggested that you make use of the formula  $e^{-66.21+0.983 \times \text{BRAS}}$  divided by  $[1+e^{-66.21+0.983 \times \text{BRAS}}]$  in order to ultimately accomplish the task of finishing the computation of the model.

On the other hand, the model displayed a chi-square value of 4.412 and a p-value of 0.818, which means that it accurately identified 94.4% of the cases that were investigated. This is an accomplishment of great significance. The BARS testing that was performed on the patients revealed that the probable range of APDs' reaction varied from 64.4% to 88.2%. This was discovered after the testing was completed. The results of the tests led to the discovery of this piece of information. The findings of the study have showed that individuals were responsible for determining this range. Additionally, the range was determined by individuals. However, it is possible that the specific range will be determined differently depending on whether the Cox & Snell R<sup>2</sup> or the Nagelkerke R<sup>2</sup> procedures were used. This is something that is a possibility. There is a chance that this will occur. When everything is taken into account, this is a possibility that can be taken into consideration.

A computation was carried out in order to determine the AUROC  $\pm$  standard error of the mean (SEM) value. This was done while the process of evaluating the BARS of the patients and the effectiveness of their targeted APDs was being

carried out. Following the completion of this calculation, the outcome was determined to be  $0.987 \pm 0.004$ , which was deemed to be the value. To be more specific, the confidence interval for this particular result was between 0.979 and 0.996, which is almost equivalent to the confidence interval for 95% of the findings.

It has been decided, on the basis of the findings of our research, that a minimum adherence rate of 68.5% is required in order to guarantee the most favourable reaction that is conceivable pertaining to the treatment of those who are suffering with psychosis. This criterion applies to antipsychotic drugs that are taken orally as well as those that are supplied in depot form. It does not matter how the components were formed; regardless of the kind of therapy, it is applicable to both types of medications. Under the circumstances of this particular patient, the BARS threshold demonstrated a sensitivity of 91.7%, a specificity of 89.89%, and an accuracy index of 75.465% for the course of the research that was being carried out.

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#### 4. Discussion

Although it has been demonstrated that Long-Acting Injectables (LAIs) are helpful in treating schizophrenia, their prescription in standard clinical practice is insufficient. Enhancing patient adherence to prescribed medication is the main goal of LAIs; the frequency of dose might vary from every two weeks to every three months. Implementing LAIs is still difficult, and many therapies have been abandoned because of worries about side effects or advice from medical professionals. Chinese people and particular patient cohorts—such as those who take drugs, are 65 years of age or older, or start therapy early—are more likely to experience this problem than other populations. These patients typically have bleak prognoses and little options for treatment, which reduces the number of hospital stays these people need.<sup>13-15</sup>

Schizophrenia patients who do not take their antipsychotic drugs (APDs) as prescribed are more likely to experience recurrent periods of disease, which may be a sign of worse overall prognosis. In the early stages of schizophrenia, the response rate seems to progressively decline; after every episode, regardless of the particular episode, 17% of people do not experience remission. This suggests that every recurrence entails the potential of developing treatment resistance, even for those who have previously responded successfully to treatment. In a clinical context, modifiable factors include not taking antipsychotic medication as prescribed, having comorbidities, not responding to antipsychotic treatment as soon as possible, and not seeing improvement with non-clozapine antipsychotics. The response to therapy, remission, likelihood of recurrence, and long-term symptom outcomes are all significantly impacted by non-adherence to antipsychotic medication. But with confidence and long-acting injectable antipsychotics (LAIAPs), it can be properly treated.<sup>16-18</sup>

In treating patients with front-line schizophrenia (FES), long-acting injectable antipsychotics (LAIAs) and oral antipsychotics (OAs) are similar in terms of side effects, adherence rates, and adverse events. This was found in a study comparing the long-term risk of disease relapse, healthcare use, and adverse events associated with each treatment option in an Asian population. A study involving 288 inpatients with schizophrenia discovered that during inpatient therapy, 55% of the sample experienced symptom remission. Remission was seen for "reality distortion" in 84% of cases, "disorganisation" in 85% of cases, and "negative symptoms" in 65% of cases. The influence of negative symptoms on the progression and responsiveness to treatment of schizophrenia illness was highlighted by the regression model, which accounted for 36% of the observed variation.<sup>19-21</sup>

Antipsychotic drugs have been shown in prior research to aggravate ANS dysfunction in schizophrenic patients in a dose-related manner; this finding may be connected to the frequency of side effects associated with LAIs. The LF component of ANS activity was found to be significantly influenced by the drug formulations of atypical antipsychotics, according to multiple regression analysis, which also revealed significant relationships between these drug formulations and all other components of ANS activity. The study focuses on middle-aged, chronically sick individuals with psychotic disorders who frequently reside with ageing parents who might not be able to keep an eye on their compliance with oral drug regimens. Although many individuals can benefit from treatment with LAIs, other patients are unwilling or resistant to receiving this kind of care. Only 28.1% of patients treated with an antipsychotic formulation that was accessible as a LAI were prescribed a LAI, according to a recent study, indicating that only some eligible patients actually receive it. The difficulties in sustaining such treatment were demonstrated by the fact that only 20.7% of community-dwelling patients with psychotic illnesses in Italy who were prescribed a LAI consistently continued such treatment over the six-month follow-up. The majority of patients on LAIs (17 out of 26, 65.4%) were receiving antipsychotic monotherapy, which might be a sign that they don't want to take more oral medication.<sup>22-25</sup>

The study found that the effects of LAIs were significantly greater in magnitude in non-compliant patients than compliant patients. LAIs reduced subsequent psychiatric acute care indicators by 33-39% in non-compliant patients, who were more frequently male, younger than 50 years of age, and of low socio-economic status. These patient

characteristics are consistent with those identified in most studied schizophrenia populations where non-compliance rates are usually high. Future prospective research should address the impact of LAI treatment on patients' outcomes in rural settings, particularly assessing clinical outcomes like mortality, suicide attempts, and psychotic relapses compared to patients receiving oral antipsychotics. The results lend support to previous findings in providing a rationale for switching to LAIs in patients with poor compliance to oral APs and show the effectiveness of aripiprazole LAI in compliant patients.

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## 5. Conclusion

The study reveals that psychotic individuals require 68.5% adherence for optimal responsiveness. Adding LAIAP to oral APDs enhances responsiveness.

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## Compliance with ethical standards

### *Acknowledgments*

Our appreciation goes to staff of the departments of Royal Medical Services for their enormous assistance and advice.

### *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.

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