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Research Article

Development and validation of machine learning-based predictive clinical decision support system for olanzapine in patients with schizophrenia

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ABSTRACT

Olanzapine is an atypical antipsychotic used to treat schizophrenia but can cause metabolic syndrome leading to severe cardiovascular events. This study aimed to develop a predictive decision tree model for clinical responses and adverse events of olanzapine, and integrate this model into the clinical decision support system (CDSS). The study consisted of three phases: (1) prospectively analyzed clinical responses and safety for hospitalized schizophrenic patients receiving olanzapine at Vietnamese National Psychiatric Hospital No.1; (2) determined the statistically significant predictors and developed predictive algorithms in machine learning (Decision Tree) to build the CDSS that incorporated warnings and predictive models for effectiveness and metabolic syndrome; and (3) conducted a longitudinal study on interventions after CDSS integration. Of 232 patients evaluated in phase 1, 76% responded positively to olanzapine, and 31% developed metabolic syndrome. 24 predictive variables were analyzed for effectiveness and 10 others were analyzed for metabolic syndrome. In phase 2, the decision tree model using Bayesian Model Averaging identified important predictive factors for effectiveness, retaining three important nodes: early response, response history, and olanzapine dose, with performance metrics of accuracy 0.89, precision 0.92, recall 0.94 and F1-score 0.93. Besides, another model using univariate regression identified important predictive factors for metabolic syndrome, retaining three important nodes: baseline waist < 89 cm, baseline triglyceride < 3.1 mmol/L, and age < 36 years with performance metrics of accuracy 0.88, precision 0.90, recall 0.69, and F1-score 0.78. Phase 3 evaluated 70 patients using CDSS, with 87% receiving “positively-responded” predictions, and 30% receiving metabolic syndrome predictions in the first week. 22 clinical pharmacist interventions led to doctors changing "clinical decisions", while 389 interventions resulted in the “monitoring plan” of doctors. Incorporating machine learning models into CDSS is valuable in helping physicians identify and make interventions to ensure effective and safe use of olanzapine in schizophrenic patients.

Keywords:
Olanzapine; Schizophrenia; Decision Tree; Machine Learning; Clinical Decision Support System

1. INTRODUCTION

Schizophrenia (SCZ) is among the top 10 illnesses globally and can lead to serious disabilities[1]. This complex, chronic mental health disorder is characterized by positive symptoms (delusions, hallucinations, disorganized speech, and behavior), negative symptoms (amotivation and social withdrawal)

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and cognitive impairment. Antipsychotic medications (APs), traditionally categorized as first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), are necessary to ameliorate symptoms and reduce relapses of SCZ[2].

Due to the burden of extrapyramidal side effects associated with FGAs, the SGAs were introduced in the 1990s and have been suggested to demonstrate greater treatment persistence[3,4]. Among them, olanzapine is one of the most common atypical drugs with several studies establishing efficacy and minimal side effects compared to other antipsychotic drugs[5,6].

However, olanzapine-treated patients still experience adverse events such as metabolic syndrome (MetS), which can lead to severe cardiovascular disorders or mortality. The prevalence of MetS among olanzapine-treated patients is 28.2%[7]. A systematic review indicated that the risk of MetS for schizophrenic patients is related to dosage, age, sex, smoking condition, concomitant drugs, race, etc[8]. However, drug selection and prescriptions for schizophrenic patients are currently based on treatment guidelines and clinical conditions without comprehensively considering other factors like serious adverse drug effects[9]. Therefore, identifying factors predicting MetS and clinical response is crucial to help doctors personalize treatment experiences and maximize patient benefits. Personalizing treatment and minimizing adverse events require integrating patient-specific influencing factors for MetS and clinical response into treatment algorithms and fostering closer collaboration between clinical pharmacists and doctors.

The intersection of rapid advancements in information technology, particularly the ability to harness big data and integrate cutting-edge artificial intelligence (AI) into clinical decision support systems (CDSS), offers a transformative approach to healthcare delivery. This presents a significant opportunity to equip physicians with powerful tools for predictive and personalized treatment planning. Recently, the clinical decision support system has been applied in many hospitals in Vietnam to improve drug safety and effectiveness. Moreover, machine learning (ML) – a subfield of Artificial Intelligence, has shown good accuracy in predicting treatment outcomes in patients with psychiatric disorders[10,11]. ML is defined as a computational strategy that employs algorithms to automatically determine methods and parameters learning from complex data, leveraging the power of large-scale, multidimensional databases and advanced biological data sources to develop prediction models[12]. Therefore, non-knowledge-based CDSS incorporating ML has the potential to develop accurate and generalizable safety and effectiveness predictions for schizophrenic patients.

To the best of our knowledge, there is a paucity of predictive models that incorporate ML for treatment outcomes and adverse events in schizophrenic patients. Therefore, this research project aimed to integrate ML into CDSS to improve the quality of olanzapine treatment for schizophrenic patients. Besides integrating ML, the benefits of CDSS lie in its ability to utilize consecutive patient data and treatment responses over a certain time period instead of data from a single visit to predict final treatment responses. Moreover, the CDSS could support physicians in alerting real-time drug interactions and overdoses, suggesting doses for patients with renal impairments, and storing demographics and medical history information. These capabilities help physicians make decisions on antipsychotic drug selection during treatment courses.

2. MATERIALS AND METHODS

This section describes data sources, data processing, model construction, evaluation, and analysis of interventions after CDSS integration with machine learning.

2.1. Data source for model development and validation.

Clinical data on inpatients during olanzapine treatment was prospectively collected from medical records at Vietnamese National Psychiatric Hospital No.1. from December 2015 to June 2019.

Patients with these criteria were included: **(1)** diagnosed and treated for schizophrenia according to ICD-10 (ICD code: F20) with olanzapine use, **(2)** accessible Brief Psychiatric Rating Scale (BPRS) score, and **(3)** metabolic syndrome determined according to NCEP ATP III criteria at the beginning and during the treatment.

We excluded patients who had one of the following criteria: **(1)** epilepsy or structural brain lesions (brain injury, brain tumors); **(2)** substance-induced mental disorders; or **(3)** history of olanzapine uses in the 4 weeks leading up to hospital admission.

The team, including physicians, clinical pharmacists, and researchers, worked together to evaluate the BPRS score before treatment and NCEP ATP III at the beginning and during the treatment.

Demographic characteristics, diagnoses, medical history, biochemical blood results, and olanzapine dosage were obtained for all patients receiving olanzapine treatment.

Conventions of research:

Clinical response: Our study defined "clinical response" in schizophrenic patients as a ≥ 40% reduction in BPRS score from baseline, aligning with previous studies on olanzapine efficacy and schizophrenia treatment using the BPRS[12,13,14,15]. The percentage reduction was calculated using a standard formula[16]:

$$\%\ \text{BPRS score reduction} = \frac{\text{pre treatment} - \text{post treatment score}}{\text{pre treatment score} - 18} * 100\%$$

Early response: patients having ≥ 20% BPRS reduction after 2 weeks of olanzapine were defined as "having early response to olanzapine"[14].

High olanzapine dose: According to the Royal College of Psychiatrists' Consensus Guidelines (2008), high antipsychotics dose is defined as a total daily dose that exceeds the upper limit of the recommended dose in the British National Formulary (BNF)[17,18]. The BNF recommends olanzapine at 5-20 mg/day for the treatment of schizophrenia[18]. Therefore, by this definition, a high dose is considered to be more than 20 mg/day.

Metabolic Syndrome Diagnosis: Based on The Modification of The US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[19], MetS is diagnosed when patients fulfill at least three of the following criteria: waist size of at least 90 cm for males and at least 80 cm for females; triglycerides of at least 1.7 mmol/L (150 mg/dL); HDL cholesterol level of < 1 mmol/L (< 40 mg/dL) for males and < 1.3 mmol/L (50 mg/dL) for females; blood pressure of more than 130 mmHg systolic or 85 mmHg diastolic; and fasting glucose of more than ≥ 5.6 mmol/L (100 mg/dL).

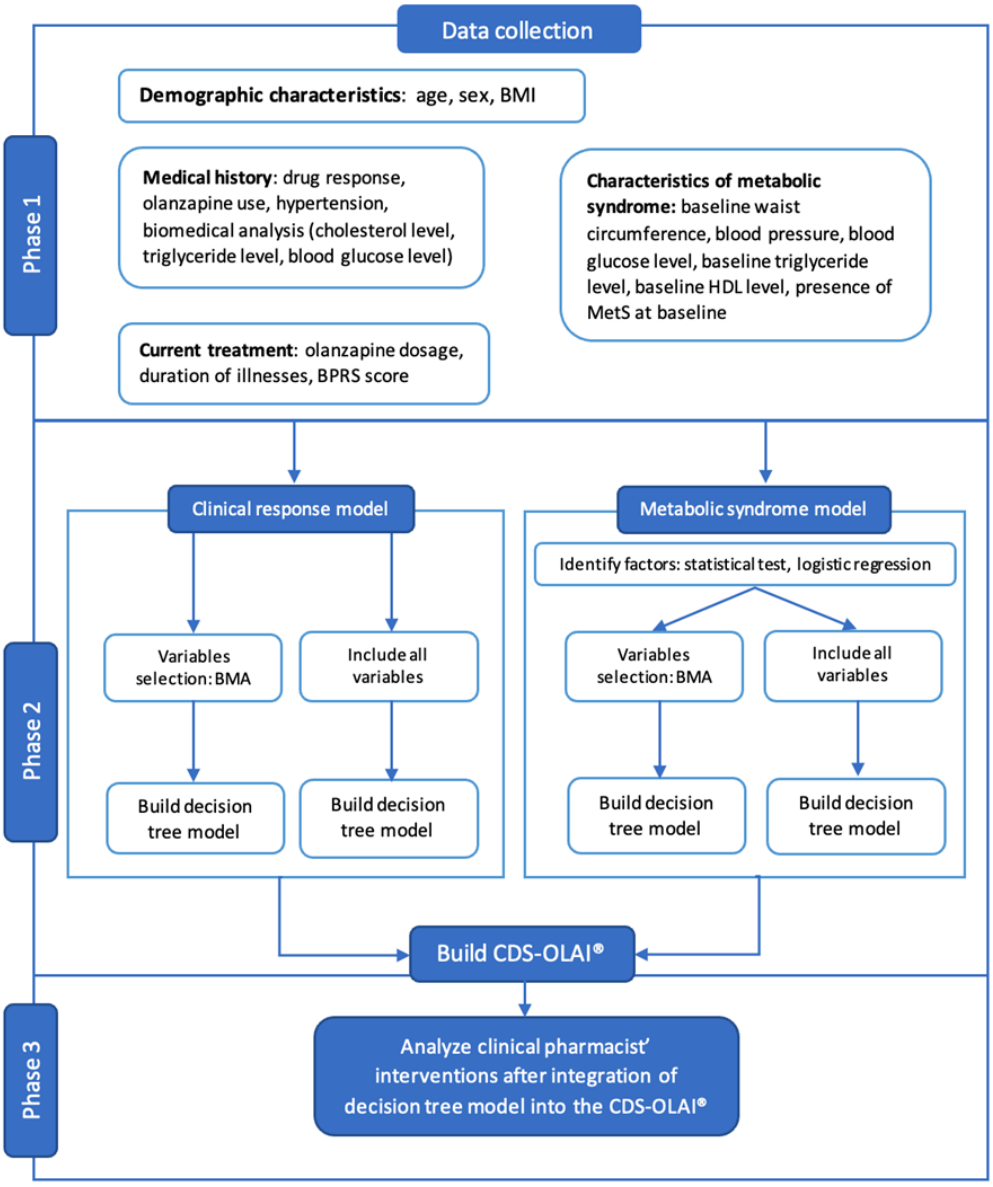


Figure 1. Research flow
BMI: Body mass index; BPRS score: Brief Psychiatric Rating Scale score; MetS: metabolic syndrome;
BMA: Bayesian model averaging; CDS-OLAI®: The CDSS software at Vietnamese National Psychiatric Hospital No.1

2.2. Data processing and model construction

After auditing and validating data in Excel, we used R to statistically describe variables: mean ± SD for normally or approximately normally distributed variables and median (min-max) for non-normally distributed variables. A 95% confidence interval was determined, and a p-value of less than 0.05 was considered statistically significant. Package BMA was used for the Bayesian Model Averaging method.

For the clinical response prediction model, we employed a decision tree model to visually depict factors affecting the treatment response outcome (a minimum 40% reduction in BPRS score from baseline was considered a positive response).

For the metabolic syndrome model, variables were selected by statistical tests and the logistic regression model. Then, a decision tree model was developed to describe the predictive factors for MetS visually.

In the decision tree model for clinical response prediction, the dependent variable was labeled 1 if the patient had a positive response (≥ 40% reduction in BPRS score) and 0 if they did not respond positively.

For the MetS model, the dependent variable was labeled 1 if the patient had MetS and 0 if they did not have MetS during.

The Gini impurity criterion was used to split the nodes in the decision tree.

The process to determine important nodes:

In a decision tree model, each node represents a feature or attribute in the dataset, and the tree structure partitions the data based on these features. The algorithm selects the best feature and threshold at each node to maximize the homogeneity of the resulting subsets. This process continues recursively, with each split aiming to reduce impurity or increase information gain. Nodes that result in significant impurity reduction are considered more important. The importance of a node can be determined by its contribution to the overall reduction in impurity or increase in information gain across the entire tree.

Clinical response prediction model construction:

Decision tree models were constructed in two methods: first, by performing variable selection before incorporating it into model analysis using Bayesian Model Averaging (BMA) method for variable selection analysis, and second, by including all variables in the analysis.

Metabolic syndrome prediction model construction:

Screening factors was performed before entering the model through **(1)** using statistical tests to identify statistically significant factors (t-test for normally distributed variables, the Kruskal-Wallis test for non-normally distributed variables. For categorical variables, use Pearson's chi-square test when the sample size is more than 5 in all groups, and Fisher's exact test when the sample size of at least one group is fewer than 5), then use **(2)** logistic regression to determine the odds ratio of developing MetS for each influencing factor before using **(3)** variable selection (with or without BMA) to build the final models.

Then, the decision tree model was constructed in two methods: **(1)** all of the above factors were included in the model analysis; **(2)** variable selection was selected again using the Bayesian Model Averaging (BMA) model, and only the variables suggested by BMA were included in the decision tree model analysis.

In **method 1**, if there were two influencing factors with the same measurement index but different variable forms (continuous and binary), then additional analysis was performed: only retaining the continuous form variable **(method 3)** or only retaining the binary form variable **(method 4).** The binary variable for each index was based on clinical practice standards and the NCEP ATP III standards for Asians[19].

2.3. Model evaluation and optimization

The performance of the decision tree model was evaluated using 10-fold cross-validation. The data were divided into 10 folds, and the model was trained and evaluated on 9 folds at a time, with the remaining fold used for testing. This process was repeated 10 times, and the average performance of the model across all folds was calculated.

2.4. Model metrics

The metrics used to compare ML models included accuracy, recall, precision, and F1-score:

Accuracy: calculated as the number of correct predictions divided by the total number of predictions.

Recall: calculated as the number of true positives divided by the total number of actual positives.

Precision: calculated as the number of true positives divided by the number of predicted positives.

F1-score: The F1-score is a harmonic mean of precision and recall. The F1-score was calculated as:

$$\frac{2}{\mathrm{F1}} = \frac{1}{\mathrm{precision}} + \frac{1}{\mathrm{recall}}$$

2.5. Analysis of interventions after integrating CDSS with machine learning

A longitudinal study of interventions was conducted after the CDSS integration. Interventions were made on patients with the following criteria: **(1)** diagnosed and treated for schizophrenia according to ICD-10 (ICD code: F20) with olanzapine use, **(2)** accessible Brief Psychiatric Rating Scale (BPRS) score, **(3)** metabolic syndrome determined according to NCEP ATP III criteria at the beginning and during the treatment, and **(4)** treatment duration was more than one week. Patients who had one of these criteria were excluded: **(1)** epilepsy or structural brain lesions (brain injury, brain tumors); **(2)** substance-induced mental disorders; and **(3)** history of olanzapine uses in the 4 weeks leading up to hospital admission.

The following features were described: **(1)** CDSS capabilities: clinical response prediction and metabolic syndrome prediction; **(2)** clinical pharmacist interventions: interventions that led to doctors making clinical decisions; interventions that led to monitoring plans by doctors. Clinical decisions made by physicians included: **(1)** dose reduction of olanzapine; **(2)** dose reduction of other antipsychotic drugs; **(3)** addition of concomitant medications. Monitoring plans made by physicians included: **(1)** BPRS monitoring every 2 weeks, **(2)** MetS monitoring through biochemical blood tests, blood pressure, waist circumference; dietary and physical activity.

Table 1. Patient characteristics

	Features	n	Results[1]
	Demographic data		
	Age *(years)*, *mean ± SD*	232	39.0 ± 11.0
	Sex (male)		190 (81.9)
	Body mass index (BMI) *(kg/m^2)*, *mean ± SD*		21.1 ± 2.8
	Past medical history		
	Past response to antipsychotic medications	232	127 (54.7)
	Past use of olanzapine		90 (38.8)
	Past cholesterol level ≥ 6.2 *(mmol/L)* and/or triglyceride level ≥ 1.7 *(mmol/L)*		18 (7.8)
	Past blood glucose level ≥ 7 *(mmol/L)*		38 (16.4)
	Past hypertension with blood pressure ≥ 140/90 *(mmHg)*		8 (3.4)
	Current treatment		
	Duration of illness *(years)*, *median (min-max)*	232	10 (1 - 40)
	Baseline BPRS score *(scores)*, *mean ± SD*		51.1 ± 6.8
	Baseline olanzapine dose *(mg/day)*, *median (min-max)*		20 (5 - 30)
	Maintenance olanzapine dose *(mg/day)*, *median (min-max)*		20 (10 - 30)
	High olanzapine dose (> 20 mg/day)		72 (31.0)
	Characteristics of metabolic syndrome		
	Baseline waist circumference *(cm)*, *median (min-max)*	216	79.5 ± 8.3
	Systolic blood pressure *(mmHg)*, *mean ± SD*	232	116.6 ± 8.0
	Diastolic blood pressure *(mmHg)*, *mean ± SD*	232	74.5 ± 6.3
	Baseline blood glucose level *(mmol/L)*, *mean ± SD*	230	5.84 ± 1.99
	Baseline triglyceride level *(mmol/L)*, *median (min-max)*	213	1.60 (0.30 – 10.4)
	Baseline HDL level *(mmol/L)*, *mean ± SD*	168	1.18 ± 0.29
	Presence of metabolic syndrome	232	44 (19.0)
	Treatment outcomes		
	Reductions in BPRS score *(scores)*, mean ± SD	232	-16.2 ± 6.9
	Patients who responded to olanzapine	232	177 (76.3)
	Patients who developed metabolic syndrome	202	63 (31.2)

[1] Numbers represent number (%) unless otherwise indicated

3. RESULTS AND DISCUSSION

3.1. Patient characteristics

Patient characteristics (demographic data, past medical history, current treatment, MetS characteristics, and treatment outcomes) were displayed in **Table 1**.

A total of 232 patients were included in the study, with a mean baseline BPRS score of 51.1 ± 6.8. The mean baseline blood glucose level was 5.84 mmol/L, which was higher than 5.6 mmol/L – NCEP ATP III's criteria for MetS.

Patients were mostly prescribed 20 mg/day of olanzapine, which was the maximum recommended dose. Regarding the high olanzapine dose, 72 patients (31%) received a regimen of 25 mg/day or higher.

The treatment response rate observed in the entire study sample was 76.3%. Of 232 patients, sufficient information on MetS was obtained for 202 patients, of which 63 (31.2%) developed metabolic syndrome.

3.2. Determination of statistically significant predictors and development of decision tree model to build the clinical decision support system (CDSS)

Clinical Response

We constructed two decision tree models for clinical response prediction: one using Bayesian Model Averaging (BMA) analysis for variable selection, which helps identify the most relevant factors for prediction and another including all variables.

In the BMA method, 24 predictive variables for effectiveness were analyzed using BMA, which suggested 5 models with the highest posterior probability (Figure S1). The variables used in these models were: history of medication response, early response at 2 weeks, olanzapine dosage, baseline MetS status and phase of schizophrenia, which were subsequently integrated into the decision tree model analysis (Figure S1 and S2). After evaluating and optimizing the model using 10-fold cross-validated resampling technique and pruning, we obtained the final decision tree model (Figure 2, model 1A), retaining three important nodes: early response, response history, and olanzapine dose, with the performance metrics of accuracy 0.89, precision 0.92, recall 0.94 and F1-score 0.93.

In the second method, all variables for effectiveness were included in the analysis without variable selection. We constructed another decision tree model **(Figure 2, model 1B),** which comprised of 4 nodes: early response, baseline BMI, treatment with haloperidol before olanzapine use, and treatment with valproate before olanzapine use; with performance metrics of accuracy 0.78, precision 0.86, recall 0.86 and F1-score 0.86.

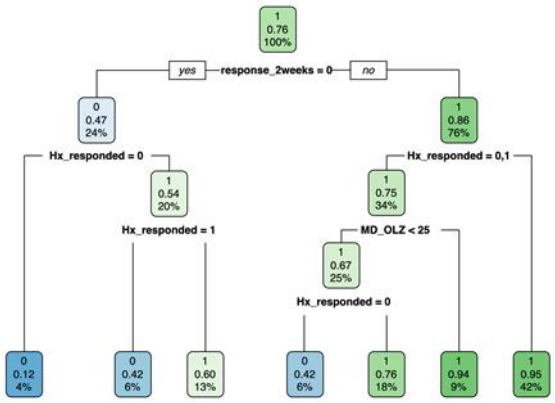
To sum up, the decision tree model developed using BMA **(model 1A)** with three important nodes: early response, response history, and olanzapine dose showed superior performance across all metrics, with high interpretability and was used to predict the effectiveness in real clinical scenarios. When accurate information on past drug response is lacking but data on concomitant medication are available, the model without variable selection may be used to predict response.

Metabolic syndrome

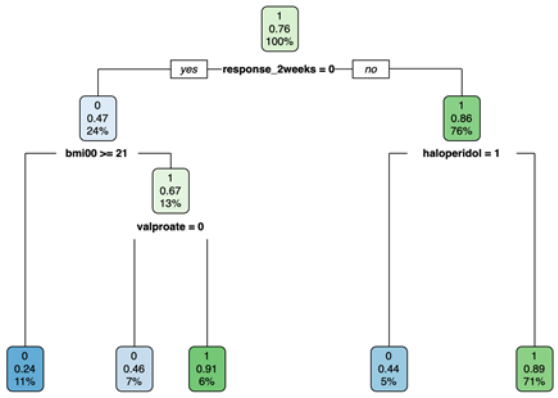
We built the prediction model in three steps: **(1)** identifying statistically significant factors, **(2)** determining the odds ratio using logistic regression, and **(3)** building decision tree models with or without variable selection (using BMA).

Firstly, statistical tests identified 14 significant factors that differentiated patients with MetS (n=63) from those without (n=139) during the 16-week treatment period **(Table S1)**. We then included these variables in a logistic regression analysis to confirm the odds ratio of each influencing factor **(Table S2)**. These variables included 8 continuous variables, including age, BMI, duration of illness, baseline waist circumference, baseline drug glucose, triglycerides, cholesterol, and HDL level; and 6 binary variables: history of elevated cholesterol and/or triglycerides levels, overweight at baseline, high baseline waist circumference, high baseline triglycerides level, low baseline HDL level, and presence of MetS at the start of the study. We then incorporated these variables into decision tree models using four methods **(Table S3)**: **method 1**: without further variable selection; **method 2**: variable selection using BMA; **method 3**: without further variable selection, using continuous form variables; and **method 4**: without further variable selection, using binary form variables.

The first three methods yielded the same decision tree model **(Figure 3, model 2A),** retaining three important nodes: baseline waist < 89 cm, baseline triglyceride < 3.1 mmol/L, and age < 36 years with performance metrics of accuracy 0.88; precision 0.90; recall 0.69; and F1-score 0.78. The model obtained in method 4 **(Figure 3, model 2B)** consisting of 5 nodes could be used when baseline MetS information is available. However, its performance metrics were all below 0.8 and lower than the above model, with accuracy 0.71, precision 0.54, recall 0.54, and F1-score 0.58. In conclusion, model 2A with three nodes: baseline waist < 89 cm, baseline triglyceride < 3.1 mmol/L, and age < 36 years demonstrated superior performance compared to model 2B in predicting Mets.



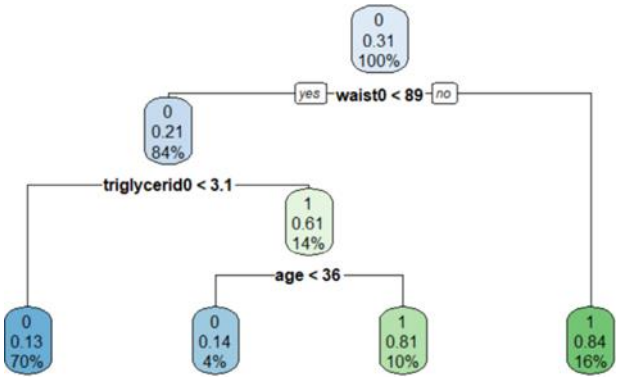
1A. Decision tree model using BMA variable selection



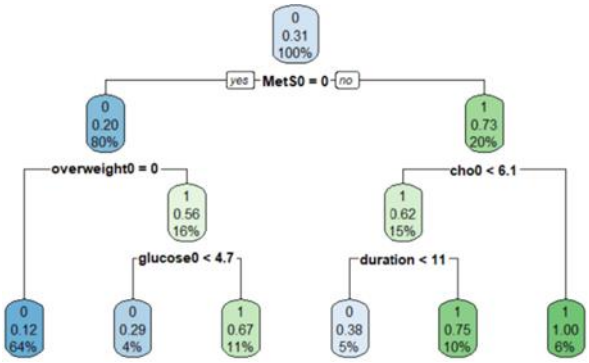
1B. Decision tree model without variable selection

Model	Accuracy	Recall	Precision	F1-score	False positive	False negative
1A	**0.8913**	**0.9429**	**0.9167**	**0.9296**	27.3%	5.7%
1B	0.7826	0.8571	0.8571	0.8571	45.5%	14.2%

Figure 2. The optimal decision tree model in predicting clinical response and performance metrics
Response_2weeks: early response at 2 weeks (0/1:reduction of ≥ 20% BPRS scores); Hx_responded: history of drug response to antipsychotic medications (0: responded poorly, 1: past response unknown; 2: positively responded); MD_OLZ: maintenance dose of olanzapine (mg); Bmi00: baseline BMI; haloperidol=1: patient used haloperidol; valproat=0: patient did not use valproat; Yes/No: critera met/ did not met



2A. Decision tree model in **method 1,2,3**



2B. Decision tree model in **method 4**

Model	Accuracy	Recall	Precision	F1-score	False positive	False negative
2A	**0.878**	0.692	**0.900**	0.783	3.6%	30.8%
2B	0.707	0.538	0.538	0.583	21.4%	46.1%

Figure 3. The optimal decision tree model in predicting metabolic syndrome and performance metrics
waist0: baseline waist circumference (cm); triglycerid0: baseline triglycerides level (mmol/l); MetS0: baseline MetS status; overweight0: overweight at baseline (1: yes, 0: no); cho0, glucose0: baseline cholesterol and glucose level (mmol/L), duration: duration of illness (years); 0: patient did not have MetS; 1: patient had MetS; Yes/No: critera met/did not met

Integration of decision tree model into CDSS

We compiled and integrated the information required for the effectiveness and safety of olanzapine use in patients with schizophrenia into the CDSS software at Vietnamese National Psychiatric Hospital No.1 (CDS-OLAI®) along with the developed decisiontree model. The CDSS comprises 7 functional modules, including:

1- Management of patients' information
2- Management of medication use
3- Management of clinical progress
4- Management of clinical laboratory tests
5- Monitor of schizophrenia clinical symptoms progress
6- Prediction for clinical response and MetS
7- Physician clinical decision

In the module 'Response prediction' and 'MetS

prediction', all variables required for the prediction models, derived from the information that was updated and stored in the CDSS, were displayed again to allow users (physicians or pharmacists) to review the information before clicking the prediction button. The model's output consists of a binary classification for both clinical response ("Response" or "Non-response"), MetS status ("MetS" or "Non-MetS). Additionally, the model provides the corresponding percentage predicted for each category.

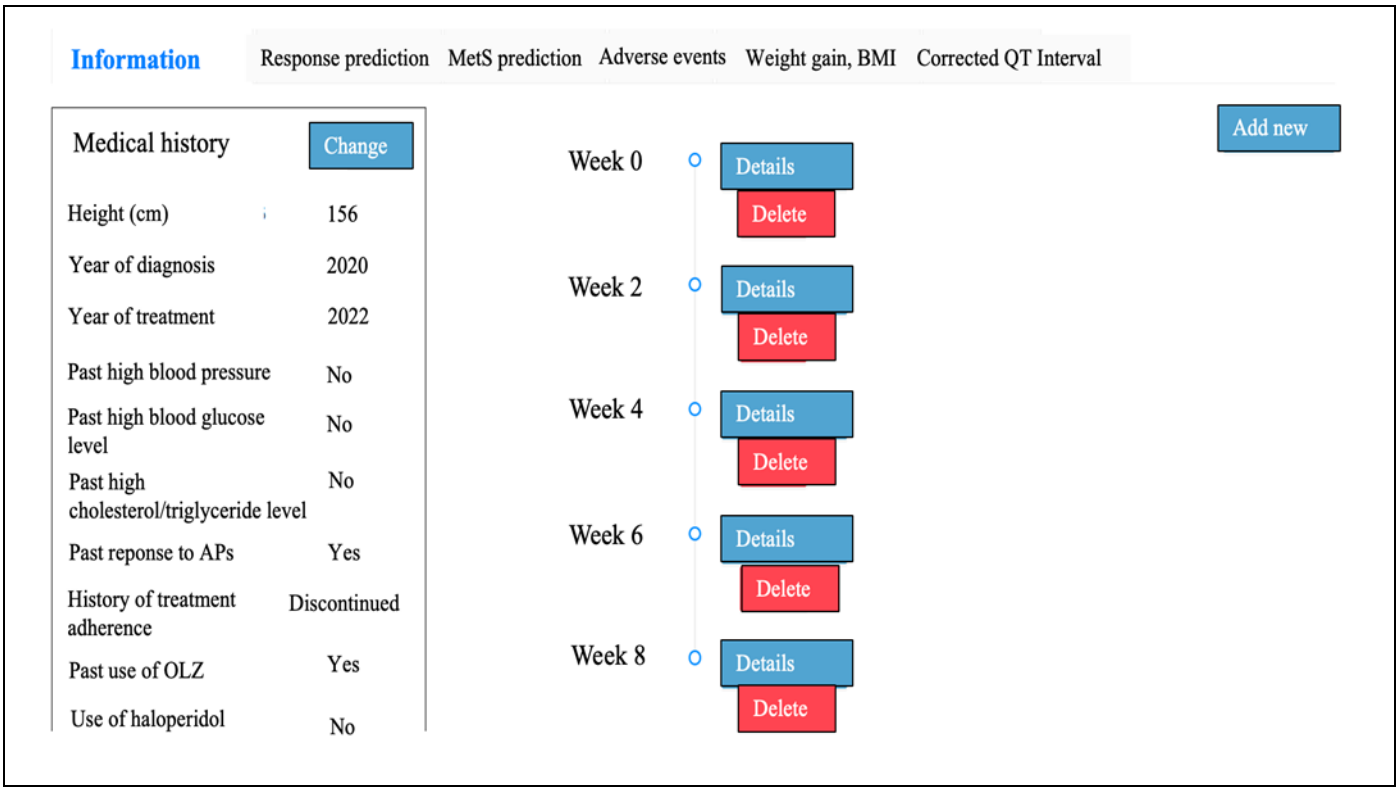


Figure 4. The interface of CDS-OLAI® after integrating Decision Tree model to support clinical predictions.

3.3. Analysis of interventions after integrating CDSS with machine learning

We enrolled 70 patients who met the inclusion and exclusion criteria for the longitudinal study, aiming to analyze interventions following the integration of the decision tree model into the CDSS.

At the start of the treatment, the predicted rate for "positive response" was 87.1% (on the second day), providing a reference point to assist the physician in maintaining the medication. However, by the second week, when patients had shown initial improvement in BPRS scores, doctors and clinical pharmacists were able to reassess the patient's response, with the "positive response" prediction rate dropping to 82.1%. Similarly, in the subsequent weeks, doctors, clinical pharmacists and the medical team could continue to predict the effectiveness of olanzapine.

Within the first 3 days, after clinical laboratory test results became available and updated to the software, doctors were notified of the presence of MetS. Additionally, doctors and pharmacists predicted the rate of patients who were prone to develop MetS. The rate of positive prediction in this group was 30.3%.

Clinical pharmacists or researchers discussed with doctors based on the prediction results or notifications from the CDS-OLAI® software. Based on the information exchanged, doctors considered the benefits/risks for each patient to perform interventions in one of the two forms: **(1)** making clinical decisions related to changes in medication use; and **(2)** planning patient monitoring with pharmacists or nurses. These interventions were performed and stored directly in the software for evaluation, synthesis, and monitoring for subsequent interventions. The results of clinical pharmacists' interventions were summarized in **Table 3**.

The total number of clinical pharmacist interventions that led to doctors making clinical decisions was 22, while 389 interventions resulted in patient monitoring plans by doctors.

Table 2. Predictions for clinical response and metabolic syndrome on CDSS

CDSS function		W0 n=70	W2 n=67	W4 n=59	W8 n=34
Prediction for clinical response, n (%)	*Yes*	61 (87.1)	55 (82.1)	46 (78.0)	28 (82.3)
	No	9 (12.9)	12 (17.9)	13 (22.0)	6 (17.7)
Prediction for metabolic syndrome, n (%)	*Yes*	17 (30.3)	16 (28.6)	15 (28.8)	15 (51.7)
	No	39 (69.7)	40 (71.4)	37 (71.2)	14 (48.3)

Table 3. Interventions after the intergration of CDSS with machine learning

Time points	Interventions			
	Clinical decision		Monitoring plan	
	Interventions	Interventions/patient	Interventions	Interventions/patient
W0 (n=70)	6	0.09	125	1.8
W2 (n=67)	5	0.08	90	1.3
W4 (n=59)	7	0.12	102	1.7
W8 (n=34)	4	0.12	72	2.1
Total	**22**	**0.3**	**389**	**5.6**

4. DISCUSSION

Decision tree models for clinical response prediction

Previous studies mainly focused on the relationship between the reduction of BPRS scores and influencing factors instead of clinical response. Our study aimed to target the clinical response of olanzapine for schizophrenic patients (the minimal reduction of 40% of BPRS scores) in the decision tree model. Therefore, to fully exploit the underlying associations between influencing factors and clinical response, we used BMA variable selection directly on the dataset of our studied population **(Figure 2, model 1A)**. Another decision model **(Figure 2, model 1B)** used variables without BMA selection was built simultaneously to compare with model 1A. Finally, we extracted three important nodes in model 1A: early response, response history, and olanzapine dose. Meanwhile, in the absence of prior variable selection, the decision tree **(model 1B)** retained four nodes: early response, baseline BMI, treatment with haloperidol before olanzapine use, and treatment with valproate before olanzapine use. Model 1A is preferred due to better performance metrics.

In a concurrent study conducted by our research team on factors associated with BPRS score reduction in the same population, we employed multivariate linear regression and identified four statistically significant factors: baseline BPRS scores, response history, gender, high olanzapine dose (dose > 20 mg)[20]. This finding was consistent with our decision tree model 1A in two factors: response history and high olanzapine dose. High dose as a predictor had also been demonstrated in the previous study of Kinon et al., which demonstrated better response at higher doses for patients with higher baseline PANSS[21]. Regarding using response history as a predictive factor, while no study has directly evaluated its relationship with clinical response, the selection of therapy based on past drug response has been mentioned in many treatment guidelines for SCZ[22, 23]. Our findings indicated that among patients with early response to olanzapine and a history of previous response, the probability of achieving clinical response was relatively high (0.95 with a maintenance dose of > 25mg and 0.94 with a dose of ≤ 25mg). This may be because our patients were prescribed medications based on previous drug responses. In our study, most hospital admissions were due to non-adherence to outpatient treatment. Thus, restarting medication, particularly for those with a history of response to antipsychotic therapy, likely led to clinical improvements. The factor "early response" at week two appeared as the first splitting variable in both models (our results suggested that early responders have a 0.86 probability of achieving clinical response). This result aligned with the study of Agid et al., which demonstrated that early antipsychotic response predicted improvement in global functioning score for up to 6 months[24]. Another randomized, double-blind study showed that compared with early non-responders, risperidone early responders showed a significantly greater reduction in PANSS total score at the study endpoint[25].

Compared with model 1B, model 1A had better performance with recall, precision, and F1-score, all above 90% and accuracy being 89.1%. Furthermore, the false positive and false negative rate of model 1A were lower than those of model 1B. Therefore, the first model showed superiority in performance across all metrics, high interpretability, and could predict response effectively in clinical practice. However, in cases where

accurate information about drug response history is lacking and information about concomitant medications is available, the second model can be used as an alternative to predict response.

Although our study was mainly conducted on patients prescribed olanzapine monotherapy, some patients were also prescribed other antipsychotics. In the BMA analysis, variables related to antipsychotics were not statistically significant; only haloperidol and valproate were included in model 1B (this model had lower predictive indicators than the selected model). Therefore, future studies should focus more on the effects of antipsychotic polypharmacy in schizophrenic patients.

Decision tree models for metabolic syndrome prediction

As olanzapine-treated patients have a higher risk of MetS than other antipsychotics (except for clozapine), finding the correlation between influencing factors and MetS is necessary to ensure the safety of patients[26]. We performed a statistical comparison to identify factors significantly associated with MetS, followed by a logistic regression analysis. Selected factors were then used to develop a decision tree model with or without BMA variable selection. The developed prediction model 2A **(Figure 3, model 2A)** retained three important nodes: baseline waist < 89 cm, baseline triglyceride < 3.1 mmol/L, and age < 36. Model 2A had high stability with an accuracy of 0.878 and a precision of 0.9; however, the F1-score was only 0.783, and the recall was 0.692. This model had better prediction ability compared to model 2B **(Figure 3, model 2B)** with all model metrics below 0.8.

The strength of this approach lies in its ability to focus on clinically relevant variables within the Vietnamese patient population studied through statistical comparison before building the decision tree model, thereby avoiding the statistical fallacy. Particularly, among the three factors in model 2A, the waist circumference cutoff point (< 89 cm) is quite similar to the waist circumference criterion in the 5 criteria of MetS according to the NCEP ATP III standard[19]. Similarly, our finding that age < 36 is a significant factor affecting MetS occurrence aligns with previous research on MetS in schizophrenic patients[7,8,27]. However, the model's triglyceride cutoff point is < 3.1 mmol/L, which is higher than the NCEP ATP III proposed criterion (≥ 1.7 mmol/L)[19]. This may be due to the relatively short follow-up time (from 4 weeks or more, most of which are from 4 to 8 weeks), so the results may not fully reflect the group of patients with triglyceride levels from 1.7 to less than 3.1 mmol/L. The model also suggested that baseline waist circumference is the most important factor, highlighting its potential for predicting MetS in olanzapine-treated patients.

With the high true positive rate (TPR = 0.692) and the very low false positive rate (FPR = 0.04), model 2A demonstrated high sensitivity in predicting MetS and a good specificity in avoiding false alarms. However, doctors should pay attention to patients with negative predictions to give proper treatment because of the moderate false negative rate (FNR = 0.308) of the model. To address this limitation, physicians agreed to monitor patients with a non-predicted risk of MetS every 3 months, including measuring waist circumference, blood pressure, blood glucose and triglyceride levels, and HDL levels if possible.

Interventions suggested by CDSS incorporated with the decision tree models

After integrating CDSS with machine learning-based predictive models, the software was trained on data collected from over 200 schizophrenia patients. Therefore, when presented with new patient data, the model can predict response or non-response on day 2 based on prior learning from past data and the input information (such as patient characteristics, medical history, etc.).

For the clinical response prediction, 100% of physicians agreed to continue medication and monitor safety for the “positive response” prediction. With a predicted "non-response," 100% of physicians agreed to re-evaluate the clinical situation, including the patient's history of response, while also agreeing to follow-up response using the BPRS scale.

Our MetS prediction model focuses on identifying patients at risk before diagnosis. The predicted prevalence of MetS increased steadily over the study period, ranging from 28.6% at week 0 to 51.7% by week 8. This could be due to the long-term effects of olanzapine treatment on factors like triglyceride levels and waist circumference.

Physicians used the CDSS predictions to inform treatment decisions and monitoring plans. For patients with positive predictions for both clinical response and MetS, physicians often reduced the antipsychotic medication dosage. The specific drug targeted for dose reduction (olanzapine or others) depended on individual clinical experience. Besides, patients with “negative response” prediction didn’t receive dose increase decision from physicians due to two reasons. Firstly, many patients in the longitudinal study used a high olanzapine dose. Therefore, when receiving negative response predictions, physicians tended to implement monitoring plans instead of dose increases to avoid adverse events for patients. Secondly, suppose patients have “negative response” predictions in the first two weeks. In that case, physicians will not increase olanzapine because it can take four to six weeks for olanzapine to show its full effects. Patients predicted to

develop MetS received additional medications to manage blood pressure, cholesterol, and blood glucose levels. These medications included diabetes drugs (e.g., metformin), hypertension medications, and artichoke-based supplements for cholesterol reduction. Notably, the current CDSS lacked a drug suggestion feature; therefore, medication choices were based solely on physician expertise. Future studies are planned to analyze prescription behavior to inform the development of this function alongside the existing prediction features.

The CDSS predictions led to two primary monitoring plans: BPRS monitoring and MetS monitoring. BPRS monitoring allows for early prediction of treatment response, which is advantageous compared to the qualitative methods currently used for diagnosis at hospitals (often unsuitable for week 0 or week 2 assessments). The decision tree predictive model and quantitative BPRS scoring facilitated easier evaluation of clinical progression in the early treatment phase, potentially enabling earlier medication adjustments for schizophrenic patients. The MetS monitoring within the CDSS assisted physicians by streamlining laboratory data storage and retrieval. This enabled routine monitoring of diagnostic parameters for MetS, encompassing a comprehensive patient follow-up strategy that considers three key dimensions: clinical progression, dietary, and physical activity. The lower number of interventions observed in weeks 2 and 8 can be attributed to two factors. First, biochemical blood tests were conducted only once a month, limiting opportunities for new interventions in week 2. Second, half of the patients were discharged by week 8.

Limitations

The current study has several limitations that should be addressed in future research. Firstly, treatment duration was not incorporated in the model analysis, although all patients were monitored from admission to discharge. Secondly, the CDSS only covered olanzapine therapy, whereas SCZ treatment typically involves other medications. Lastly, the study only included the decision tree model due to its intuitive nature and high interpretability.

To address these limitations, future research needs to incorporate features of other antipsychotic drugs into the CDSS and other ML models for comparison with enhanced visual results.

5. CONCLUSION

This study examined the characteristics of Vietnamese patients with schizophrenia who received olanzapine and investigated relevant factors affecting clinical response and metabolic syndrome. An optimal decision tree model was developed to predict these outcomes, using several variable selections, and its performance metrics demonstrated relatively high accuracy and F1-score. The decision tree model, characterized by its intuitive nature and high interpretability, was integrated into the CDSS at the hospital and resulted in interventions pertaining to clinical decisions or vigilant monitoring by physicians. Overall, this study offers a valuable tool for physicians to identify and ensure the effectiveness and safety of olanzapine use in schizophrenic patients. Further research focusing on other machine learning models and other antipsychotic drugs is necessary to improve the safety and effectiveness of schizophrenic patients.

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Authors contribution

All authors contributed to the idea and design, data collection, data analysis and interpretation, article writing or critical revision for significant intellectual content, and the final approval of the published version.

Conflict of interest

The authors declare that they have no conflict of interest.

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REFERENCES

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet. 1997;349(9063):1436-42.
2. Haddad PM, Correll CU. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. Ther Adv Psychopharmacol. 2018;8(11):303–18.
3. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. Br Med Bull. 2015;114(1):169-79.

4. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013;16(6):1205-18.
5. Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: Combined results of the North American and international trials. J Clin Psychiatry. 2001;62(10):757–71.
6. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60(6):553–64.
7. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophr Bull. 2013;39(2):306-18.
8. Sneller MH, de Boer N, Everaars S, Schuurmans M, Guloksuz S, Cahn W, et al. Clinical, biochemical and genetic variables associated with metabolic syndrome in patients with schizophrenia spectrum disorders using second-generation antipsychotics: A systematic review. Front Psychiatry. 2021;12:625935.
9. Correll CU, Martin A, Patel C, Benson C, Goulding R, Kern-Sliwa, et al. Systematic literature review of schizophrenia clinical practice guidelines on acute and maintenance management with antipsychotics. Schizophrenia (Heidelb). 2022;8(1):5.
10. Sajjadian M, Lam RW, Milev R, Rotzinger S, Frey BN, Soares, et al. Machine learning in the prediction of depression treatment outcomes: a systematic review and meta-analysis. Psychol Med. 2021;51(16):2742-51.
11. Pigoni A, Delvecchio G, Madonna D, Bressi C, Soares J, Brambilla P. Can machine learning help us in dealing with treatment resistant depression? a review. J Affect Disord. 2019;259:21-26.
12. Bobes J, Gibert J, Ciudad A, Alvarez E, Cañas F, Carrasco JL, et al. Safety and effectiveness of olanzapine versus conventional antipsychotics in the acute treatment of first-episode schizophrenic inpatients. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(3):473-81.
13. Chan CYW, Abdin E, Seow E, Subramaniam M, Liu J, Peh CX, et al. Clinical effectiveness and speed of response of electroconvulsive therapy in treatment-resistant schizophrenia. Psychiatry Clin Neurosci. 2019;73(7):416-22.
14. Sanger TM, Lieberman JA, Tohen M, Grundy S, Beasley C Jr, Tollefson GD. Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry. 1999;156(1):79-87.
15. Xu M, Li S, Xing Q, Gao R, Feng G, Lin Z, et al. Genetic variants in the BDNF gene and therapeutic response to risperidone in schizophrenic patients: a pharmacogenetic study. Eur J Hum Genet. 2010;18(6):707-12.
16. Alvarez E, Ciudad A, Olivares JM, Bousoño M, Gómez JC. A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. J Clin Psychopharmacol. 2006;26(3):238-49.
17. Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. Royal College of Psychiatrists, London. 2014:4-40.
18. Association British Medical, Committee Joint Formulary, et al. Psychoses and schizophrenia, BNF 76 (British National Formulary September 2018 - March 2019), Pharmaceutical Press. 2019:394-95.
19. Heng D, Ma S, Lee JJ, Tai BC, Mak KH, Hughes K, et al. Modification of the NCEP ATP III definitions of the metabolic syndrome for use in Asians identifies individuals at risk of ischemic heart disease. Atherosclerosis. 2006;186(2):367-73.
20. Kieu MA, Nguyen TTT, Nguyen HC, Nguyen TH. Analyzing clinical effectiveness of olanzapine in schizophrenic patients using a decision tree model. J. Pharm. Res-DI. 2022;13(2):24-31.
21. Kinon BJ, Volavka J, Stauffer V, Edwards SE, Liu-Seifert H, Chen L, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin Psychopharmacol. 2008;28(4):392–400.
22. Scottish Intercollegiate Guidelines Network (SIGN). Management of schizophrenia. Edinburgh: SIGN; 2013. (SIGN publication no. 131), https://www.sign.ac.uk/assets/sign131.pdf. Accessed 03 May 2024.
23. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The american psychiatric association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry. 2020;177(9):868–72.
24. Agid O, Siu CO, Pappadopulos E, Vanderburg D, Remington G. Early prediction of clinical and functional outcome in schizophrenia. Eur Neuropsychopharmacol. 2013;23(8):842–51.
25. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Zhou W, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology. 2010;35(2):581–90.
26. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry. 2015;14(3):339-47.
27. Grover S, Aggarwal M, Dutt A, Chakrabarti S, Avasthi A, Kulhara P, et al. Prevalence of metabolic syndrome in patients with schizophrenia in India. Psychiatry Res. 2012;200(2-3):1035-37.