Artificial neural network prediction of clozapine response with combined pharmacogenetic and clinical data

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ABSTRACT

Although one third to one half of refractory schizophrenic patients responds to clozapine, however, there are few evidences currently that could predict clozapine response before the use of the medication. The present study aimed to train and validate artificial neural networks (ANN), using clinical and pharmacogenetic data, to predict clozapine response in schizophrenic patients. Five pharmacogenetic variables and five clinical variables were collated from 93 schizophrenic patients taking clozapine, including 26 responders. ANN analysis was carried out by training the network with data from 75% of cases and subsequently testing with data from 25% of unseen cases to determine the optimal ANN architecture. Then the leave-one-out method was used to examine the generalization of the models. The optimal ANN architecture was found to be a standard feed-forward, fully-connected, back-propagation multilayer perceptron. The overall accuracy rate of ANN was 83.3%, which is higher than that of logistic regression (LR) (70.8%). By using the area under the receiver operating characteristics curve as a measure of performance, the ANN outperformed the LR (0.821 ± 0.054 versus 0.579 ± 0.068; $p < 0.001$). The ANN with only genetic variables outperformed the ANN with only clinical variables (0.805 ± 0.056 versus 0.647 ± 0.066; $p = 0.046$). The gene polymorphisms should play an important role in the prediction. Further validation of ANN analysis is likely to provide decision support for predicting individual response.

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1. Introduction

Clozapine was the first atypical antipsychotic drug (also named second-generation antipychotics, SGA). Although more and more SGAs have been released into the market, clozapine is still regarded as the most effective antipsychotic for treating refractory schizophrenia [1,2]. A Cochrane review of comparative randomized trials concluded that clozapine is more effective than conventional antipsychotics for all patients with schizophrenia, and that the comparative advantage of clozapine is greater in patients whose condition is classified as treatment-resistant [3]. Clozapine has clinical response rates of 30–50% in treatment-refractory schizophrenia patients and it produces substantially fewer extrapyramidal side effects compared with conventional antipsychotic agents. As a result, it is often used for schizophrenic patients who respond poorly to conventional agents or are unable to tolerate side effects, such as extrapyramidal side effects. Despite such benefits, several adverse effects are often complained of, including sialorrhea, orthostasis, sedation, anticholinergic effects, weight gain, urinary incontinence and so on [4,5]. Moreover, the use of this antipsychotic carries significant morbidity from seizure and serious blood disorders such as potentially fatal agranulocytosis, the need for continual blood monitoring, and consequent high costs [6,7].

At present, there is little evidence to predict the clozapine response of an individual patient. Trial and error still remains the best option to find out which patient will benefit from clozapine. This has major implications both for successful treatment regimens and for the prevention of serious side effects. If we can predict the response to clozapine, we can make a better decision regarding the use of clozapine and reduce the number of unnecessary trials with ineffective medications. The pre-treatment identification of non-responders and the development of special treatment options is also an important task, for both efficacy and safety. In recent years, clinical and genetic studies have investigated this problem, but many of these studies have had inconsistent results that await unequivocal confirmation [8–22]. Although genetic variation may have a significant effect on clozapine response [23], there is no single factor that can predict it. It has been postulated that there are contributions from the combinations of mutations in neurotransmitter-receptor-related genes.

Multiple logistic regression (LR) is a widely used statistical modeling technique in which the probability of a dichotomous outcome event is assumed to be related to a set of explanatory variables in a sigmoid relationship. LR is a generalization of linear regression. The response (dependent) variable is the natural logarithm of the odds ratio representing the ratio between the probability that an event will occur and the probability that it will not occur (e.g., probability of being a responder or not) [24]. Arranz et al. [9] used LR analysis to predict clozapine response with combinations of 19 genetic polymorphisms. They found the combination of five polymorphisms in the serotonergic system (5-HT_{2A} 102 T/C and His452Tyr, 5-HT_{2C} −330-GT/−244-CT and Cys23Ser, 5-HTTLPR) and one in the histaminergic system (H2-1018-G/A) can successfully predict the response to clozapine in 76.8% of patients. The combination had a sensitivity of 95.89%, and a specificity of 38.3%. Therefore, predicting clinical outcome before treatment is possible by combining pertinent information from key genes [9].

While LR is a very powerful modeling tool for prediction, it assumes that the response variable (the log odds) is linear in the coefficients of the predictor variables [25]. However, the relationship between genetic polymorphisms and the log odds of clozapine response may be non-linear and complicated. In addition, the predictive models have to be tested with unseen data. The artificial neural network (ANN) is a form of artificial intelligence that employs non-linear mathematical models to mimic the human brain's own problem-solving process. Just as humans apply knowledge gained from past experience to new problems, a neural network takes previously solved examples to build a system of "neurons" that makes new decisions, classifications, and forecasts. The classification rules are not written into algorithms, but rather are learned by the network from examples. An ANN comprises layers of neurons.

The input layer is formed by neurons that may receive a single clinical or genetic feature for a specified problem. The hidden layer of neurons receives the data from the input layer, and is connected to the output layer, with multiple connections between neurons among the layers by weights. The hidden layers process the information and feed the response to an output layer. The output layer forms the outputs of the network. The input–output relationship is controlled by a transfer function in the hidden layer of neurons, thus allowing the network response to be non-linear. During the supervised training stage, a dataset is presented to the ANN with the correct outputs available. The ANN is trained by first randomly initializing the connection weights between the neurons and then running the data through the network and comparing the output with the known responses. The process repeats and the network alters the weights between connections so that the errors in the outputs are reduced to negligible values. The ANN can then be used for prediction. Unlike logistic regression, which fits the data to a descriptive function, in ANN the input data is transformed on each layer, changing its dimensional space to define the rule to get to the decision region. Thus the two approaches are inherently different, raising the question of whether one approach has a better predictive performance than the other.

To our knowledge, there do not appear to be any published papers to date regarding the prediction of clozapine response by means of ANNs. To investigate this problem, we applied ANNs and LR to the analysis of both clinical and pharmacogenetic data from schizophrenic patients taking clozapine in an attempt to achieve accurate predictions of clozapine response for unseen individual patients. A comparison of the performance between the models was made. Second, we compared the performance of ANN analysis with genetic variables and that with clinical variables.

2. Methods

2.1. *Study population*

Our sample consisted of 93 inpatients in Yuli Veterans Hospital in Taiwan. Some of the participants were included in our

previous studies on clozapine-induced body weight gain and urinary incontinence [5,26,27]. Our previous studies obtained clinical efficacy, clinical status, and genetic polymorphisms. The data from these studies were merged with the following inclusion criteria: (1) inpatients who met the DSM-IV diagnostic criteria for schizophrenia; (2) took clozapine for at least 3 months; and (3) were aged 20–60 years. Patients with comorbidity of organic mental disorders and major medical illnesses were excluded from the study. The study was approved by the Institutional Review Board of Yuli Veterans Hospital, Taiwan and all participants gave written informed consent to participate.

2.2. *Data preparation*

The clinical predictor variables, i.e., input variables, included gender, age, height, baseline body weight, and baseline body mass index. The variables of genetic polymorphisms included 5-HT_{2A} 102 T > C, adrenergic α_{1A} Arg347Cys, adrenergic α_{2A} −1291 C > G, and adrenergic β3 Trp64Arg, and G-protein β3 825 C > T. Previous pharmacological treatments and side effects of our refractory schizophrenic patients were complex and not included in our previous studies. Therefore, previous pharmacological treatments and side effects were not included as the input variables. The coding of the input variables is shown in Table 1. Each genetic polymorphism input was converted into a set of three numeric values, with one value set to indicate the type of polymorphism. For example, the variable 5-HT_{2A} 102 T > C has data types of (CC, CT, TT); CC can be represented as (1, 0, 0), CT as (0, 1, 0) and TT as (0, 0, 1). All the other inputs were scaled between 0 and 1. The laboratory methods for the genotyping of all genetic polymorphisms were the same as those shown in a published paper [27]. Each categorical input was computed for a measure of Shannon entropy, considered as an information source [28]. The output value was the dichotomous response to clozapine which was recoded from an evaluation of the Clinical Global Impression Scale (CGI)-improvement score. Patients who received a score of 1 (very much improved) and 2 (much improved) were considered to have a significant clinical response to clozapine treatment. The other patients were considered not to have a significant response. The CGI-improvement score was evaluated by senior research psychiatrists blind to genetic data. Both the ANN and LR analyses were tested using the same set of clinical and genetic features.

2.3. *Artificial neural network analysis*

We constructed feed-forward networks consisting of three layers – an input layer, a hidden layer, and an output layer. Several architectures of ANN were examined including multilayer perceptrons, radial-basis-function, and linear function networks. The ANN was designed to give a categorical value of 1 for the output node when the patient was a clozapine responder and 0 when the patient was a clozapine non-responder. The training technique was set to back-propagation and conjugate gradient descent algorithms, which adjust the internal parameters of the network over the repeated training cycles to reduce the overall error. One iteration consists of a single presentation of each set of inputs for all cases followed by automatic adjustments of the weight connections to minimize the total error for all patients whose data were used in the training. The estimation of error was based on the sum-squared error or entropy function [29].

Several types of ANN analysis were performed. The first aimed to find the optimal ANN architecture. The dataset was randomly divided into two separate groups: 69 patients (around 3/4) as the training set and 24 (around 1/4) as the testing set. Twenty-six responders (28.0%) were distributed to the two sets proportionally. Because no well-established theoretical method exists for designing an ideal ANN [30], and the optimal number of hidden nodes and iterations are unknown, the best designs are typically determined through trial and error [31]. To find an optimal network, different ANN architectures with 5–25 hidden neurons were constructed and trained with the training test. A learning algorithm can over fit an ANN to the training examples and thereby decrease the generalization accuracy. For this reason, the number of iterations and hidden neurons were limited. Then all models were tested with the testing set to determine their predictive accuracy of clozapine response. The network with the highest classification accuracy was kept.

Using the optimal architecture, we performed the other ANN analyses by leave-one-out cross-validation. The second ANN analysis was performed with all variables as inputs (designated as ANN_A). A third ANN analysis with five variables of genetic polymorphisms was constructed to determine the performance of the ANN with only genetic data (ANN_G). Similarly, a fourth ANN model was developed with five clinical variables to determine the performance of the ANN with only clinical data (ANN_C). The performance of the last three models was tested by leave-one-out cross-validation.

2.4. *Logistic regression*

Multiple logistic regression was first trained using the same training dataset of 69 patients as the first ANN analysis with maximum likelihood estimation. Although logistic regression does not involve training, we used a “training set” to refer to that portion of the database used to derive the regression equations [24]. The model was then applied to predict the clozapine response in the testing set of 24 patients. To enable the comparison of LR models with the ANN analyses, other LR analyses were performed by leave-one-out cross-validation with the same methods as the second to fourth ANN analyses (designated as LR_A, LR_G, and LR_C respectively). Block entry of variables was used for all LR analyses. Categorical covariates were contrasted with reference to the last category.

2.5. *Performance of models*

Although there are several ways of evaluating the performance of an ANN, the area under the receiver operating characteristic curve (AUC) provides the best measure of the global accuracy of the model. The performance of LR and ANN on a per patient basis was plotted as receiver operating characteristic (ROC) curves. The area under the curve (with 95% CI) [32] was used as a quantitative measure of the ability of the predictor models to distinguish between responders and non-responders. The performance and accuracy of the ANN model was com-

Table 1 – Coding and values of features for artificial neural network inputs and logistic regression variables

Inputs (variables)	Coding	Mean (±S.D.) or frequency	Shannon entropy [28]
Gender	Female: 0; male: 1	0.527	0.998
Age (years)		38.4 ± 7.9	–
Height (m)		1.63 ± 0.098	–
Baseline body weight (kg)		62.1 ± 13.4	–
Body mass index (kg/m^2)		23.2 ± 4.5	–
5-HT$_{2A}$ 102 T > C	CC: (0, 1)	0.204	0.730
	CT: (0, 1)	0.366	0.947
	TT: (0, 1)	0.430	0.986
Adrenergic α_{1A} Arg347Cys	CC: (0, 1)	0.849	0.611
	CT: (0, 1)	0.129	0.524
	TT: (0, 1)	0.022	0.150
Adrenergic α_{2A} −1291C > G	CC: (0, 1)	0.344	0.929
	CG: (0, 1)	0.473	0.998
	GG: (0, 1)	0.183	0.686
Adrenergic β3 Trp64Arg	AA: (0, 1)	0.054	0.302
	AT: (0, 1)	0.215	0.751
	TT: (0, 1)	0.731	0.840
G-protein β3 825 C > T	CC: (0, 1)	0.237	0.789
	CT: (0, 1)	0.559	0.990
	TT: (0, 1)	0.204	0.730

pared with the logistic regression model [33]. Other measures of performance (sensitivity and specificity, positive and negative predictive values) were computed for the first ANN and LR analyses.

2.6. *Generalization of the models*

The aim of a predictive model is to generalize their algorithms to the general population and to evaluate the performance of the algorithms with a set of cases not used during construction of the model. For generalization of the model, the leave-one-out method was used to test the performance of the LR and ANN models in predicting clozapine response [34,35]. With this method, all patients except one were used to develop the LR or ANN models. The model was then tested with the patient's data that was left out to predict the probability of clozapine response. The process was repeated so that data from every patient were included once as a test case. With the leave-one-out method, the performance of the ANN is established in a population that has not actually been used for training. The results of the test sets were combined to get an overall estimate of predictive accuracy and finally checked at different thresholds [36]. The AUC was used to evaluate the performance of each model to eliminate the need for a threshold value.

2.7. *Statistical analysis*

Mean values (±standard deviation [S.D.]) were used to describe continuous variables, and frequencies were calculated for categorical variables. Univariate analyses were conducted using chi-square testing for categorical data and Student's *t*-testing for continuous data between responders and non-responders. The probabilities predicted for AUC were compared with a two-tailed approach between (1) ANN_A and LR_A, (2) ANN_G and ANN_C, and (3) LR_G and LR_C [33]. The ANNs were run by STATISTICA Neural Networks (Statistica-Neural-Networks TM-6.0, StatSoft, Hamburg, Germany). The statistical software used for LR was SPSS for Windows (Rel. 11.5.0. 2002. Chicago: SPSS Inc.). The AUCs were estimated and compared with MedCalc for Windows, version 8.1 (MedCalc Software, Mariakerke, Belgium).

3. Results

Of the 93 patients, 49 (52.7%) were men. Mean age was 38.4 ± 7.9 years; mean baseline body weight, 62.1 ± 13.4 kg; mean baseline BMI, 23.2 ± 4.5 kg/m^2; mean duration of clozapine use, 14.0 ± 6.2 months; and mean clozapine dose, 388.2 ± 141.1 mg/day. Of the participants, 26 were responders (28.0%) and 67 were not.

From the results of the first ANN analysis, we found that the standard feed-forward, fully-connected, back-propagation neural network with 25 hidden nodes provided the optimal network architecture (Fig. 1). In this model, the hyperbolic and logistic functions were used as an activation function in the hidden and output layers respectively. The classification threshold for predicted values was optimally set to 0.774. Entropy function was used to estimate the error.

The first LR analysis showed that none of the independent variables had a statistically significant influence on clozapine response. The overall accuracy, sensitivity, specificity positive predictive value, and negative predictive value of the ANN and LR models are shown in Table 2. The overall accuracy rate of ANN was 83.3%, which is higher than that of LR (70.8%).

The AUCs for ANN_A, ANN_G, ANN_C, LR_A, LR_G, and LR_C were 0.821, 0.805, 0.647, 0.579, 0.516, and 0.604 respectively (Table 3). By using the AUC as a measure of performance, ANN_A outperformed LR_A significantly (0.821 ± 0.054 versus 0.579 ± 0.068; $p < 0.001$, see Fig. 2). The ANN_G per-

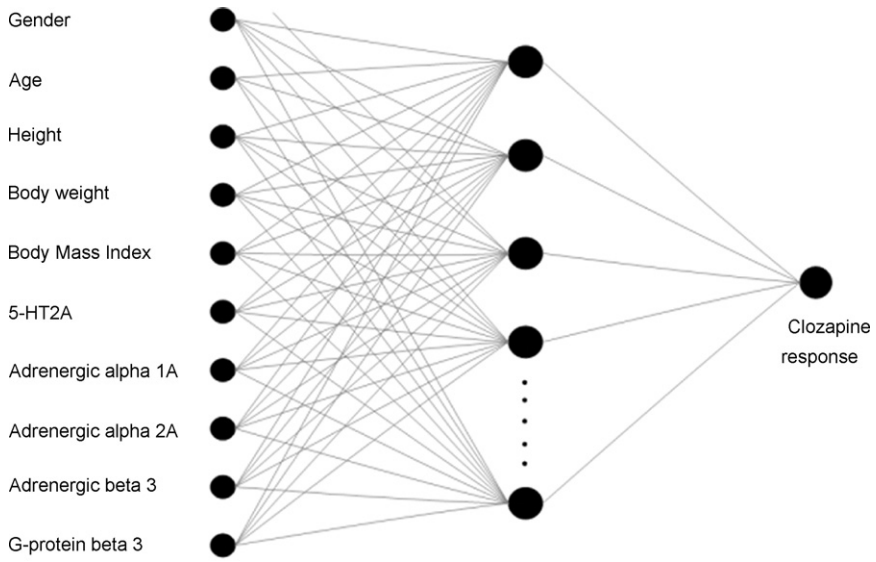

Fig. 1 – The optimal network architecture of the artificial neural network: a multi-layer perceptron. The input neurons included five clinical variables and five genetic variables. All the hidden neurons (25 in the final version) had the same hyperbolic transfer function. The output neuron had logistic transfer function.

Table 2 – Predictive accuracy of ANN and LR

	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ANN	83.3	100	76.5	63.6	100
LR	70.8	28.6	88.2	50.0	75.0

ANN, artificial neural network; LR, logistic regression.

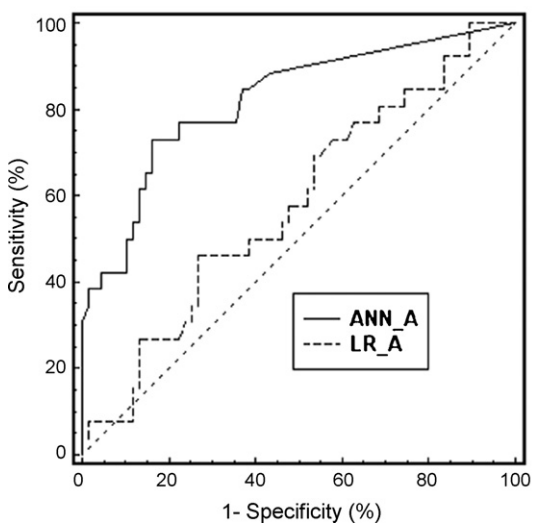

Fig. 2 – Comparison of ROC curves between ANN_A and LR_A. Solid line indicates artificial neural network analysis with all variables (ANN_A); dotted line indicates logistic regression analysis with all variables (LR_A). The area under the ROC curves for ANN_A and LR_A are 0.821 and 0.579, respectively ($p < 0.001$).

formed significantly better than ANN_C (0.805 ± 0.056 versus 0.647 ± 0.066; $p = 0.046$, see Fig. 3). However, no statistically significant difference was found between the performances of LR_G and LR_C (0.516 ± 0.067 versus 0.604 ± 0.067; $p = 0.33$, see Fig. 4). The superiority of models with genetic data over those with clinical data was only found in ANN analysis, but not in LR analysis. Therefore, to make a confident prediction of clozapine response with ANN, genetic polymorphisms needed to be included, which resulted in an ANN with an AUC of 0.805 ± 0.056; this value was not statistically differ-

Table 3 – The area under the receiver operating characteristic curves of different ANN and LR models

	AUC	S.E.	95% CI
ANN_A	0.821	0.054	0.728–0.893
ANN_G	0.805	0.056	0.710–0.880
ANN_C	0.647	0.066	0.541–0.743
LR_A	0.579	0.068	0.472–0.680
LR_G	0.516	0.067	0.410–0.621
LR_C	0.604	0.067	0.497–0.704

ANN, artificial neural network; LR, logistic regression; AUC, the area under the receiver operating characteristic curve; S.E., standard error; ANN_A, ANN model with all inputs; ANN_G, ANN model with only genetic inputs; ANN_C, ANN model with only clinical inputs; LR_A, LR model with all inputs; LR_G, LR model with only genetic inputs; LR_C, LR model with only clinical inputs.

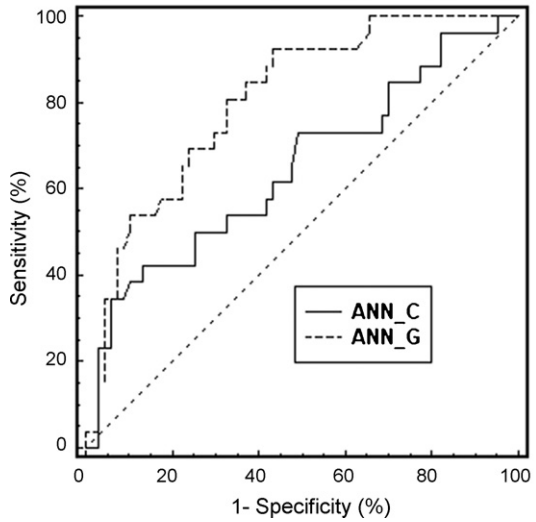

Fig. 3 – Comparison of ROC curves between ANN_C and ANN_G. Solid line indicates artificial neural network analysis with clinical variables (ANN_C); dotted line indicates artificial neural network analysis with genetic variables (ANN_G). The areas under the ROC curve for ANN_C and ANN_G are 0.647 and 0.805, respectively ($p = 0.046$).

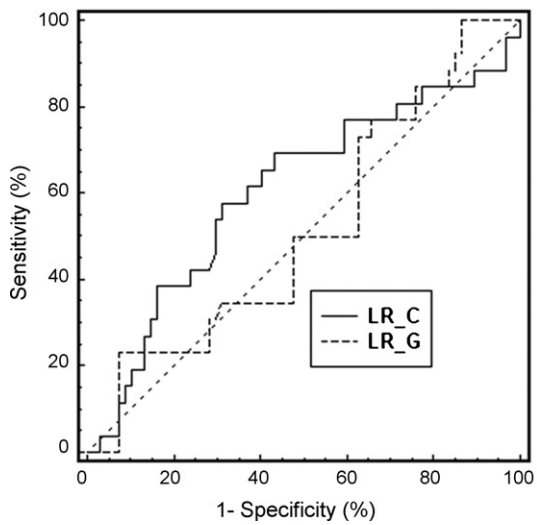

Fig. 4 – Comparison of ROC curves between LR_C and LR_G. Solid line indicates logistic regression analysis with clinical variables (LR_C); dotted line indicates logistic regression analysis with genetic variables (LR_G). The areas under the ROC curve for LR_C and LR_G are 0.604 and 0.516, respectively ($p = 0.33$).

ent from that of the all-inputs ANN (ANN_A, 0.821 ± 0.054, $p = 0.787$)

4. Discussion

When is the right time to use clozapine? In the 2nd version of the Texas Medication Algorithm Project (TMAP) for pharmacological treatment of schizophrenia, clozapine was placed at the stage 5, i.e., clozapine was suggested for use after the failure of four different first- and second-generation antipsychotics [37]. Schizophrenic patients may suffer greatly for a long time before clozapine can be prescribed, according to the algorithm. The Texas Implementation of Medication Algorithms (TIMA) has revised the TMAP antipsychotic algorithm and clozapine was placed at stage 3. However, once a patient has failed or only partially responded to adequate trials of two SGAs, the branch point in the algorithm after stage 2 indicates that the trial of a third atypical or traditional antipsychotic is also a reasonable treatment alternative to clozapine. In the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders, clozapine is suggested to be confidently introduced at the earliest opportunity if evidence of treatment-resistant schizophrenia is present [38]. Treatment-refractory schizophrenia is defined as the failure of full remission of positive symptoms or the lack of satisfactory clinical improvement despite sequential use of recommended doses of two or more antipsychotic medications for 6–8 weeks. Therefore, the dilemma of deciding to use clozapine after 2, 3, or more adequate trials of different antipsychotics still exists for clinicians. If we could predict the response to clozapine, it would assist us to make a better decision and reduce the number of unnecessary trials. More patients would benefit from clozapine treatment earlier if a positive response could be predicted.

Traditional statistical techniques are particularly suited to the analysis of data with a low dimensional complexity and linear separation. Advances in computer processing speed and neural network theory have facilitated the application of neural networks to the non-linear analysis of complex data in the prediction of outcome in the psychopharmacological domain. For example, ANN was used to forecast antidepressant treatment response for patients receiving sertraline treatment [39,40]. Furthermore, multiple gene polymorphisms have been included in the neural network analysis of fluvoxamine response with a sensitivity of 77.5% and a specificity of 51.2% [41]. In our study, we demonstrated that ANN is also useful to predict antipsychotic response. Although clozapine response could also be predicted with LR in Arranz et al.'s study, the specificity was as low as 38.3% and the LR model has never been examined with unseen data. Our first ANN analysis was performed by training the networks with the training set and testing their performance with the testing set. To allow direct comparison, the LR model was constructed from the training set and its performance assessed in the case of the testing set. It is evident from Table 2 that the overall accuracy, sensitivity, positive predictive value, and negative predictive value were considerably higher for ANN. All clozapine responders and 76.5% of non-responders were successfully predicted by the ANN model. This implied clinically that no patient, who might respond to clozapine, would be missed for the use of clozapine by the prediction of the ANN model, and three-fourth of non-responders would avoid the unnecessary trial of clozapine. The LR model could predict only 28.6% of responders, although it could predict 88.2% of non-responders successfully. Because the LR model had a low accuracy in predicting responders, it could be rendered useless clinically.

Previous research has indicated that the leave-one-out method may effectively address the problem of processing small datasets, due to its capability of processing almost all of the available data for training the classifier. Overall, this method produced the highest accuracy estimates for the classification problems of genomic data compared with cross-validation and bootstrap techniques [42]. Because the dataset in our study was relatively small, it was important to perform a leave-one-out test for the whole available dataset to gain a better estimate for the generalization power of the analysis than is obtained using only a separate test set. Using the leave-one-out method, the AUC of the ANN model was significantly higher than that of the LR model. The result is probably related to the better description of non-linear relationships between variables in the ANN analysis compared with the LR analysis. Thus, the ANN analysis seems to provide a superior method for the prediction of clozapine response.

The performance of the ANNs was also assessed by using only genetic or clinical inputs. Our results demonstrated that the neural network trained with genetic variables had a better prediction for clozapine response than the neural network trained with clinical variables. This finding highlights the importance of genetic polymorphisms of receptors or related molecules to the clozapine response. In our study, only five genetic polymorphisms for serotonin receptor, adrenergic receptor, and G-protein were included and the resultant AUC was high. Clozapine possesses relatively high affinity for the serotonin 5-HT2 receptor subtypes, where this greater 5-HT2 versus D2 antagonism ratio has been proposed as the correlate of atypicality of the novel compound [43]. However, clozapine is also a potent antagonist of 5-HT6, D4, histamine H1, muscarinic M1 and adrenergic 1- and 2-receptor subtypes, and the relative proportions of its high affinity at these multitarget sites may also contribute to its unique therapeutic efficacy [44]. Previous studies have broadly focused on investigating genes within dopamine and serotonin pathways, given the proposed roles of these systems in the etiology of schizophrenia and their contribution to mediating antipsychotic drug efficacy. More recently, genes of potential importance, including those involved in α-adrenergic, histamine and muscarinic pathways, and those encoding the drug-metabolizing cytochrome P450 enzyme (CYP), have also been examined. Although LR analysis with genetic variables resulted in lower prediction accuracy, and univariate analysis of each genetic polymorphism showed no significant difference for clozapine response, ANN still had significantly higher predictive accuracy, implying that the relationship among the genetic polymorphisms may be complex and non-linear.

In regard to the clinical variables, we included only age, gender, height, baseline body weight, and body mass index. In prior studies, high levels of symptoms [18,45], a lesser degree of negative symptoms [22], lower severity of illness [22], and a paranoid subtype of schizophrenia [12,45] have been reported to predict good response to clozapine. Although the results of these studies have been inconsistent or contradictory, further studies should include these clinical variables that may elevate the predictive accuracy of ANN. The results of these studies may confirm that the predictive accuracy of ANN with genetic variables is higher than that with clinical variables.

To the best of our knowledge, this is the first study using ANN to predict antipsychotic response. We found that a neural network analysis is potentially more successful than traditional statistical techniques in predicting clozapine response for individual patients. This finding implies that the prediction of clozapine response may involve a complicated non-linear relationship. ANN could therefore assist in the decision to use clozapine for individual patients. However, there are some limitations to this study. First, our sample size was still limited. More training and testing cases are needed in the future for better generalizability. In addition, other genetic variants or clinical variables that may affect clozapine's response were not included in our study. Future studies should test the value of adding more related clinical features and genetic polymorphisms as inputs for network training with a larger dataset of patients to confirm the findings of this preliminary study. Nevertheless, our preliminary findings are encouraging. Since pharmacogenetic or genomic data are becoming more available and, at the same time, more difficult for direct human interpretation, ANN can better interpret the final result, no matter how many genetic inputs are used. Another useful feature of ANN analysis is that it is possible to continuously refine the capability of the network by retraining and testing when new data become available [46].

In conclusion, we developed an artificial neural network that yielded a higher level of correct prediction for clozapine response than did the multiple logistic regression method. Information related to genetic polymorphisms may have played an important role in our high predictive accuracy. Further research could bring us one step closer to "personalized medicine" in the use of clozapine with schizophrenic patients.

Conflict of interest statement

None declared.

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