

USING BAYESIAN METHODS IN THE TASK OF MODELING THE PATIENTS' PHARMACORESISTANCE DEVELOPMENT

Mariia A. Voronenko¹, Ulzhalgas M. Zhunisova², Saule S. Smailova³, Luidmila N. Lytvynenko⁴, Nataliia B. Savina⁵, Pavlo P. Mulesa⁶, Volodymyr I. Lytvynenko¹

¹Kherson National Technical University, Kherson, Ukraine, ²Astana Medical University, Astana, Kazakhstan, ³D.Serikbayev East Kazakhstan State Technical University, Ust-Kamenogorsk, Kazakhstan, ⁴Kherson City Psychoneurological Clinic, Kherson, Ukraine, ⁵National University of Water and Environmental Engineering, Rivne, Ukraine, ⁶Uzhhorod National University, Uzhhorod, Ukraine

Abstract. In this paper, we propose a methodology for using static Bayesian networks (BN) in modeling the development of pharmacoresistance in patients with a diagnosis of epilepsy. Methods for constructing the structure of a static BN, their parametric training, validation, sensitivity analysis and "What-if" scenario analysis are considered. The model was designed in collaboration with expert doctors, as well as expert pharmacologists in the selection and quantification of input and output variables.

Keywords: epileptology, pharmacoresistance, Bayesian networks, structural learning, parametric learning, sensitivity analysis, validation

ZASTOSOWANIE METOD BAYESOWSKICH DO MODELOWANIA ROZWOJU FARMAKOOPORNOŚCI U PACJENTÓW

Streszczenie. W niniejszej pracy zaproponowano metodologię wykorzystania statycznych sieci bayesowskich (BN) w modelowaniu rozwoju farmakooporności u pacjentów z rozpoznaniem padaczki. Rozważane są metody konstruowania struktury statycznej BN, jej parametrycznego treningu, walidacji, analizy wrażliwości i analizy scenariuszy "co-jeśli". Model został zaprojektowany we współpracy z ekspertami – lekarzami, a także ekspertami – farmakologami w zakresie doboru i kwantyfikacji zmiennych wejściowych i wyjściowych.

Słowa kluczowe: epileptologia, farmakooporność, sieci bayesowskie, uczenie strukturalne, uczenie parametryczne, analiza wrażliwości, walidacja

Introduction

Research in the field of expert systems focused on the development and implementation of those systems and models that are able to mimic areas of human activity that require thinking, a high level of skill and experience. One such application is medicine. The study is devoted to the creation of a system to achieve the effectiveness of drug therapy in epilepsy.

In accordance with the requirements of ILAE: "Pharmacoresistance is the inability to achieve control of the disease during therapy with two drugs in the form of monotherapy and/or combination therapy" [11].

Despite the development of the anticonvulsant drugs (PSP) number and the increase in the effectiveness of surgical treatment, the establishment of the most informative predictors and their combination as factors in the development of pharmacological resistance in a particular patient is one of the primary tasks of modern epileptology.

The work aims to develop a static Bayesian model in the problem of pharmacoresistance in patients with a diagnosis of "epilepsy".

1. Problem statement

Based on the study of the disease dynamics in patients with pharmacoresistant form of epilepsy, the following predictors of pharmacoresistance were identified:

- the presence of relatives with the diagnosis of "epilepsy",
- a history of febrile convulsions,
- the traumatic brain damage,
- the frequency of attacks more than 10 before the start of treatment,
- the lack of response to the first CAP,
- a break in treatment,
- the mental comorbidity (the patient has at least two disorders, each of which can be considered independent and diagnosed independently of each other).

The occurrence of pharmacoresistance in the future was also indicated by some electroencephalographic indicators:

- the diffuse changes on the electroencephalogram (EEG),
- a high index of epileptiform activity in the background EEG recording,

- the focal epileptiform activity,
- the polymorphism of epileptiform changes,
- the presence of several foci [6].

An important role in the development of pharmacological resistance is also played by genetic factors. They determine the development of both epilepsy itself, as well as receptor polymorphism and PSP transporter [7].

2. Review of the literature

The earliest medical decision support systems for CDS in medicine were flowcharts of problem tasks developed by doctors and coded for use by a computer [14].

While later systems are based on logistic regression models, artificial neural networks, support vector machines, and others. Although the possible use of computers in making medical decisions was mentioned 50 years ago, CDS systems have not yet been widely used and are not accepted in clinical practice [1, 13].

The potential to make them more acceptable for clinical practice has been proposed by several authors [8, 15, 16].

[15] identified four functions that are critical for CDS systems:

- (i) the system should be provided to clinicians automatically, without interfering with the workflow,
- (ii) provide decision support at the time and place of decision making,
- (iii) provide recommendation and
- (iv) should be implemented on the computer.

As the formalism is declarative in nature, any (often conditional) probabilistic statement can be computed from a given BN, where the statement may concern both individual and combinations of variables.

This allows asking questions such as "What is likely to be the result for the patient if I decide to request this test, to prescribe this treatment and so on".

Another attractive feature of the formalism is that it is closely related to causal models, which explains why some researchers refer to it as the causal probabilistic network (CPN) formalism.

In this article, BNs are discussed from the point of view of their use in making medical decisions, in particular, to simulate the development of pharmacological resistance in patients when solving the problem of choosing a treatment regimen for epilepsy.

3. Materials and methods

Bayesian network (BN) – this is a pair $\langle G, B \rangle$, in which the first component of G is a directed acyclic graph corresponding to random variables [3, 12]. A graph is written as a set of conditions of independence: each variable is independent of its parents in G . The second component of the pair, B , is a set of parameters defining the network. It contains the parameters $Q_{x^i|pa(X^i)} = P(x^i | pa(X^i))$ for each possible value of x^i from X^i and $pa(X^i)$ from $Pa(X^i)$, where $Pa(X^i)$ denotes the set of parents of the variable X^i in G . Each variable X^i in the graph G is represented as a vertex. If we consider more than one graph, then we use the notation $Pa^G(X^i)$ to identify the parents X^i in the graph G [4].

The total joint BN's probability B is calculated by the formula $P_B(X^1, \dots, X^N) = \prod_{i=1}^N P_B(X^i | Pa(X^i))$. From a mathematical point of view, BN is a model for representing probabilistic dependencies, as well as the absence of these dependencies. At the same time, the $A \rightarrow B$ relationship is causal, when event A causes B to occur, that is, when there is a mechanism whereby the value adopted by A affects the value adopted by B . BN is called causal (causal) when all its connections are causal.

The goal of parametric learning is to find the most likely θ variables that explain the data. Let $D = \{D_1, D_2, \dots, D_N\}$ be learning data, where $D_i = \{x_1[i], x_2[i], \dots, x_n[i]\}$ consists of instances of Bayesian network nodes. The learning parameter is quantified by a log-likelihood function, denoted as $L_D(\theta)$.

The sensitivity analysis of the Bayesian network allows you to set for each of the network parameters a function expressing the output probability from the point of view of the parameter being studied [2, 5, 10].

To derive the probability, we will consider the posterior marginal probability of the form $y = p(a|e)$, where a is the value of the variable A and e means available evidence. Each of the network parameters has the form $x = p(b_i | \pi)$, where b_i is the value of the variable B and π is an arbitrary combination of the values of the set of parents $\Pi = pa(B)$ of B .

Denote $p(a|e)(x)$ as a function expressing the a posteriori marginal probability $p(a|e)$ in terms of the parameter x . In the future, we will assume that in a sensitivity analysis, as the parameter $x = p(b_i | \pi)$ changes, each of the probabilities $p(b_j | \pi)$ changes accordingly. The function $y(x)$, obtained as a result of sensitivity analysis, is a quotient of two linear functions in x [9].

The sensitivity analysis in the GeNie software environment is performed using influence diagrams (Fig. 1). The influence diagram shows the most sensitive parameters for the selected state of the target node Y , sorted from the most sensitive to the least sensitive.

4. Experiments and results

Observation of patients with a diagnosis of "epilepsy" lasted one year – this is the time during which you can titrate two caps to the maximum possible therapeutic doses. 310 people were examined, the experience of the disease in each patient was at least 1 year. The average age of patients is 29 +/- 2 years. All patients underwent the following examinations:

- clinical examination,
- defined neurological and mental status,
- performed magnetic resonance imaging (MRI) of the brain,
- conducted a routine electroencephalogram (EEG) and video EEG.

A survey was conducted to establish a history.

If necessary, some patients have been adjusted drug treatment in accordance with accepted standards. The purpose of the simulation is to select curable (treatable) and resistant (resistant to treatment) from the studied group of patients. We identified the following indicators, which, in our opinion, could serve as criteria (baseline) for determining the prognosis of epilepsy in a particular patient.

Table 1. The initial data for the study

Observational data (history)		
X1	↑	An epileptic status in history
X2	↑	Presence /absence of epilepsy in relatives
X3		Febrile seizures in history
X4		Mental disorders in history
X5	↑	Cranio cerebral trauma with changes in MRI
X6	↑	More than 10 attacks before treatment
X7		The response to the drug after the first epileptic seizure
X8	↑	Transferred a stroke
X9	↑	Effective treatment for relatives with epilepsy
X10	↑	A positive result on the EEG after the first Epileptic Seizure
Laboratory tests		
Z1	↓	Diffuse changes in the EEG
Z2	↓	High index of epileptic activity
Z3	↓	Focal epileptic activity with the generator
Z4	↓	Polymorphism of epileptic changes
Z5	↓	High slow-wave EEG
Z6	↓	Many epileptic foci on the EEG
Z7	↓	Presence / absence of epilepsy on the EEG
Z8	↓	No / there are changes in MRI
Z9	↓	Genetic analysis of glycoproteins P-gp1, P-gp2, SCN1A
Z10		Total Blood Pressure Monitoring

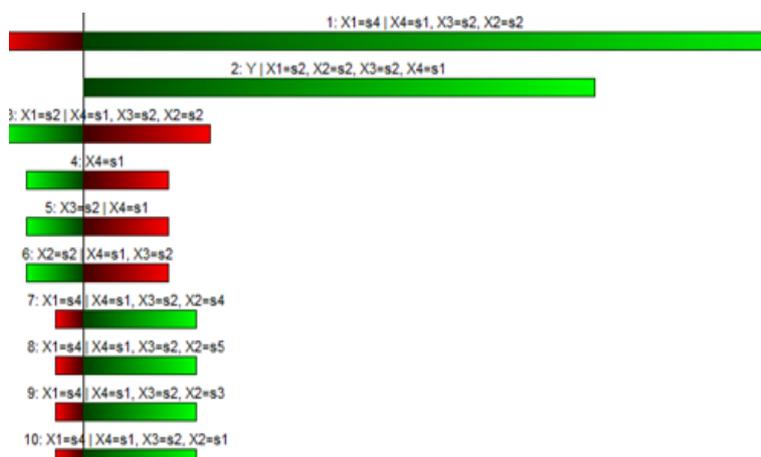


Fig. 1. The sample of influence chart

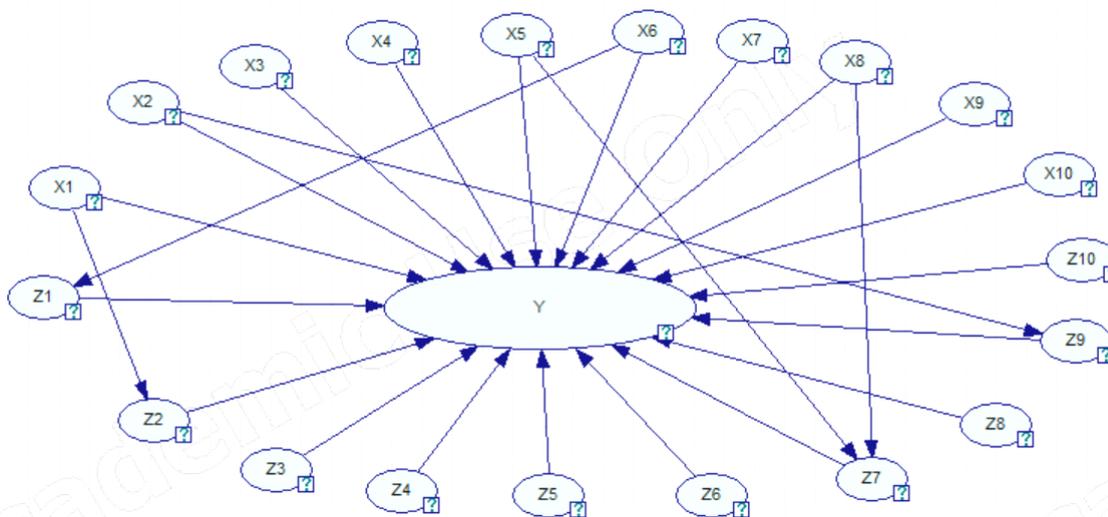


Fig. 2. Structural model of static BN in determining patient pharmacological resistance

Figure 2 shows the structural model of the static BN being developed. According to the presented model, a variety of different concepts that characterize it (both historical data and laboratory results) can be associated with pharmacological resistance. At the same time, the proposed model does not limit the rigid unidirectionality of actions but can be used both to detect causal characteristics and to predict the consequences.

The above-described properties of the model in figure 2 are illustrated by arrows showing the movement of information between the selected blocks. All indicators X and all indicators Z are directly related to Y (presence/absence), there is also a correlation of some studies with historical data: X1→Z3, X6→Z2, X5→Z8, X8→Z8, X2→Z9.

It should be noted that, due to the specifics of the work of Bayesian networks, all conclusions of this model, with respect to the information sought, are of a probabilistic nature and are presented in the form of a ranked list (according to the values of probability of fidelity of one or another conclusion).

The final decision on the confirmation of pharmacoresistant/curability and prescription of treatment to the patient is made by the doctor.

The solution to the problem of building a Bayesian network was made using the GeNIe 2.3 Academic software environment.

At the same time, we carry out parameterization, sensitivity analysis of the model and validation. The node determining the presence/absence of pharmacoresistance was taken as the target node.

Let the nodes X1-X10 represent observational data (history). Nodes Z1-Z10 – laboratory tests and the results of the analyzes. Y – the presence/absence of pharmacoresistance in a particular patient.

All nodes have two states:
state s1 – means the absence of this feature;
state s2 – means the presence of this sign in the clinical picture.

We have clinical observations of the symptoms of 310 patients, supported by the analyses performed. We took a sample of data from 16 patients and analyzed each specific clinical case. The results of the analysis are shown in table 2.

The static Bayesian network model, focused on solving the problem of determining pharmacoresistance in an individual patient, is presented in figures 3–6. Consider a clinical case 1. As can be seen from table 2 with a probability of 75% the patient is curatable, which means he will respond well to the standard scheme of drug treatment (Fig. 3).

Table 2. The results of clinical observations analysis of the patients' symptoms and laboratory studies

Clinical Case:	Clinical observations and anamnesis										Conducted research										The probability of the presence/absence of pharmacoresistance
	No	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9	
1 fig.2	0	1	0	1	0	0	1	1	1	1	1	1	1	0	1	1	0	1	1	1	Yes-25% No-75%
2	1	0	0	1	0	1	1	1	0	0	0	1	0	1	1	0	0	0	1	1	Yes-25% No-75%
3	1	1	1	0	0	1	0	1	0	0	1	0	1	0	1	0	1	0	1	0	Yes-75% No-25%
4	1	1	0	1	1	0	1	1	0	1	1	0	1	0	0	1	0	0	0	1	Yes-25% No-75%
5	0	0	0	1	0	0	0	1	1	0	0	0	1	1	0	0	1	0	1	0	Yes-25% No-75%
6 fig.3	0	1	0	1	1	1	0	0	1	1	0	0	0	0	1	0	1	1	0	0	Yes-50% No-50%
7	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	1	Yes-25% No-75%
8	1	1	0	1	0	1	1	0	1	1	1	1	0	1	0	0	1	1	0	1	Yes-25% No-75%
9 fig.4	1	1	0	0	1	0	0	0	1	0	1	1	1	0	1	0	0	1	1	1	Yes-75% No-25%

Table 2 (cont.). The results of clinical observations analysis of the patients' symptoms and laboratory studies

Clinical Case:	Clinical observations and anamnesis										Conducted research								The probability of the presence/absence of pharmacoresistance		
	0	1	0	1	0	0	1	0	1	0	1	1	0	0	1	0	0	0		0	1
10	0	1	0	1	0	0	1	0	1	0	1	1	0	0	1	0	0	0	0	1	Yes-25% No-75%
11	1	1	0	1	1	0	1	0	1	0	1	0	1	1	0	0	0	1	1	1	Yes-75% No-25%
12	0	0	0	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	Yes-75% No-25%	
13	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	0	0	0	1	Yes-25% No-75%	
14	1	1	1	0	0	1	0	1	1	1	1	0	0	0	1	1	0	0	0	Yes-75% No-25%	
15	1	0	0	0	0	0	1	1	0	0	1	1	0	0	1	0	1	1	0	Yes-25% No-75%	
16	0	0	0	1	0	0	0	0	1	1	0	1	1	0	1	0	1	0	0	Yes-25% No-75%	

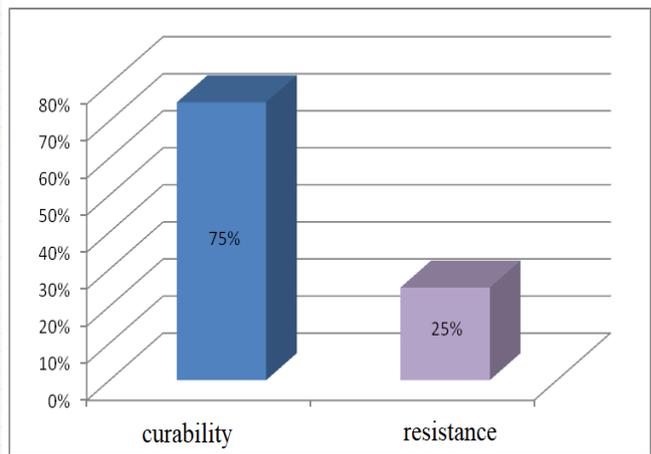
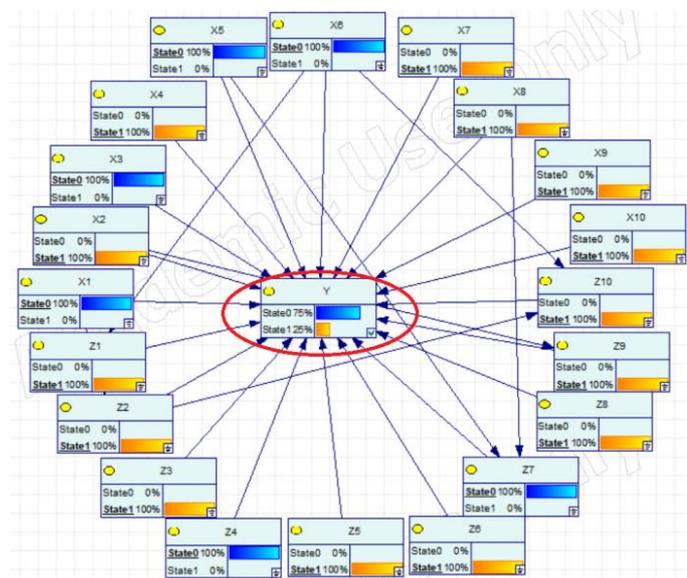


Fig. 3. Clinical Case Simulation Results 1

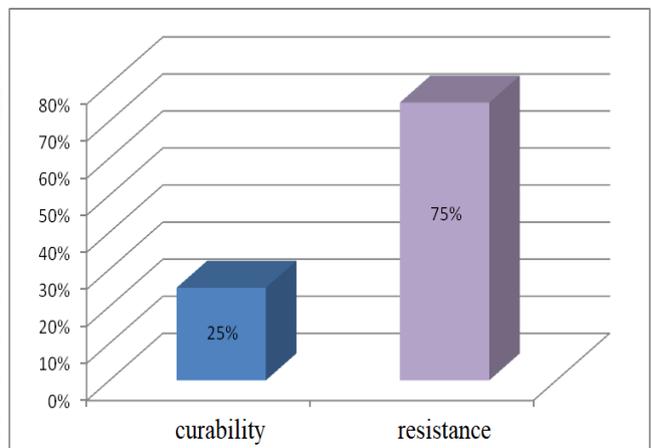
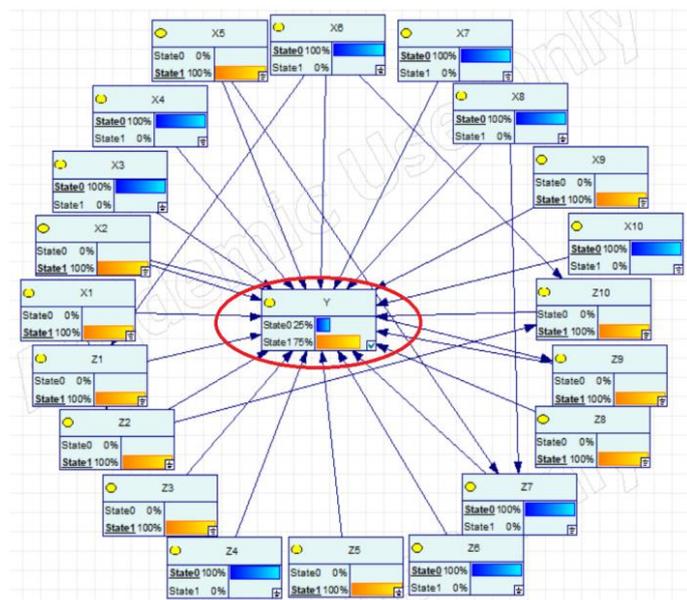


Fig. 4. Clinical Case Simulation Results 9

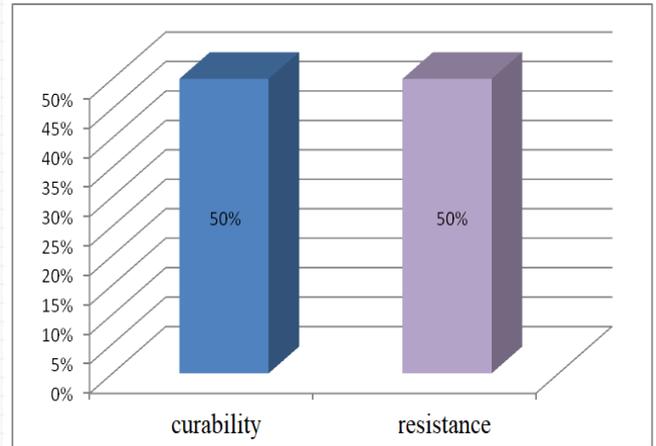
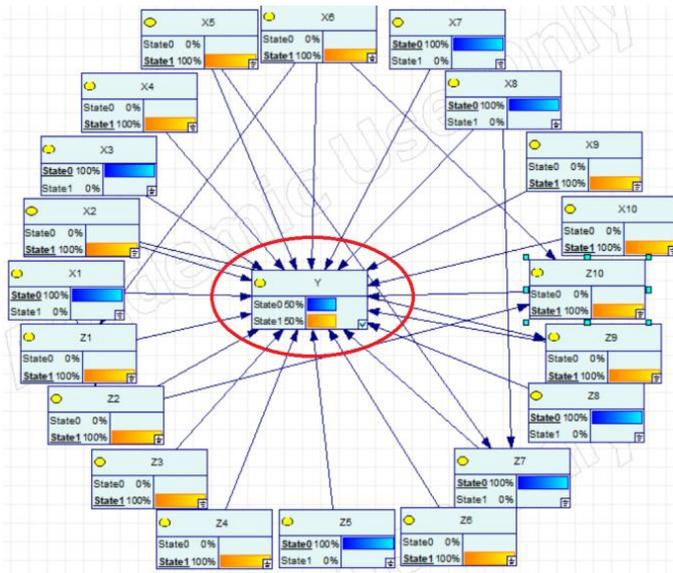


Fig. 5. Clinical Case Simulation Results 6

Consider a clinical case 9. As can be seen from table 2, a patient is 75% likely to be pharmacoresistant, that is, they need alternative methods for treating epilepsy, such as pharmacogenetics, electrophysiology, and also surgery for epilepsy when it is possible (Fig. 4).

Consider a clinical case 6. As can be seen from table 2, the patient has a controversial result. This result requires additional analyzes and research, as usually in such a situation the doctor will further clarify the clinical picture (Fig. 5).

As can be seen from table 2, in 6 cases, their 16 presence of pharmacological resistance was confirmed with a probability of 75% (red), in 9 cases out of 16 – we are talking more about the absence of pharmacological resistance (green). In the only case with patient No. 9, the probability of the presence/absence of drug resistance is 50% to 50%.

5. Discussion

BNs are interesting for representing knowledge because they allow both top-down and bottom-up, they easily capture the opinions of experts and can be trained on data, updated and personalized.

Pharmacoresistance is:

- high-amplitude slow-wave bilateral activity on the background EEG;
- lack of response to the first drug intake;
- diffuse changes on EEG;
- symptomatic epilepsy;
- the presence of several foci on the EEG;
- more than 10 attacks before treatment.

The results of the analysis of clinical observations of the symptoms of patients and laboratory studies are shown in Fig. 6.

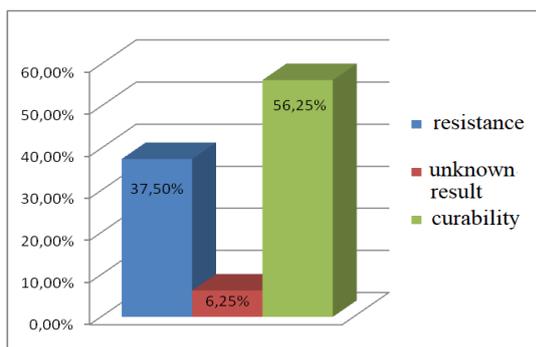


Fig. 6. The results of the analysis of clinical observations of the symptoms of patients

6. Conclusions

The paper proposes a model of a static Bayesian network for solving the problem of predicting the effectiveness of drug therapy for such diseases as epilepsy. The simulation results showed that 56.25% of patients are amenable to standard treatment, 6.25% have a controversial result and in this case need additional examination, but 37.5% of patients need alternative methods of treatment of epilepsy, such as: pharmacogenetics, electrophysiology, as well as surgery for epilepsy when possible.

In our future research, we apply the proposed model to the diagnosis of other diseases.

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Ph.D. Mariia A. Voronenko

e-mail: mary.voronenko@gmail.com

Docent of the Department of Informatics and Computer Science, Kherson National Technical University, Kherson, Ukraine.

Area of scientific interests: combined iterative algorithms, Group method of data handling, Inductive modeling of complex systems, computer intelligence systems, Bayesian networks

<http://orcid.org/0000-0002-5392-5125>

**M.Sc. Ulzhalgas M. Zhunissova**

e-mail: ulzhalgas@list.ru

Master of Science, Senior teacher of the Department of Biostatistics, Bioinformatics and Information Technologies, Astana Medical University, Kazakhstan.

Science interests: data processing, medical data, machine learning methods, neural networks, Bayesian networks, evolutionary algorithms, clustering, information technology.

<http://orcid.org/0000-0001-5255-9314>

**Ph.D. Saule Smailova**

e-mail: Saule_Smailova@mail.ru

Saule Smailova is currently a lecturer at the Department of Information Technology. She is a co-author over 60 papers in journals, book chapters, and conference proceedings. Member of Expert Group in the Computer Science specialization of IQAA. Her professional interests are teaching, artificial intelligence, software engineering, data processing.

<http://orcid.org/0000-0002-8411-3584>

**Luidmyla Lytvynenko**

e-mail: llytvynenko58@gmail.com

Psychiatrist, Kherson City Psychiatric Center. Research interests: medical information systems, diagnosis and treatment of psychiatric diseases, epileptology, pharmacoresistance.

<http://orcid.org/0000-0001-8445-5704>

**Prof. Nataliia Savina**

e-mail: n.b.savina@nuwm.edu.ua

Conduct scientific, technical and innovative activities of the university, including the implementation of research results. Promotes the development of scientific relations with other universities, scientific institutions, centers and other enterprises, institutions and organizations. Organizes scientific relations with International centers, funds, programs, other foreign institutions. He has awards from the university, city and regional authorities, the Ministry of Education and Science of Ukraine, departmental awards.

Science interests: opinion and forecasting of investment efficiency in logistics projects, logistic and economic systems, and human capital.

<http://orcid.org/0000-0001-8339-1219>

**Ph.D. Pavlo P. Mulesa**

e-mail: pavlo.mulesa@uzhnu.edu.ua

Head of the Department of Cybernetics and Applied Mathematics, Uzhgorod National University, Uzhgorod, Ukraine.

Area of scientific interests: decision making systems and methods, data mining, data visualization, neural networks and artificial intelligence.

<http://orcid.org/0000-0002-3437-8082>

**Prof. Volodymyr Lytvynenko**

e-mail: immun56@gmail.com

Doctor of Science, Head of the Department of Informatics and Computer Science, Professor, Kherson National Technical University.

Science interests: Modeling of complex systems in economics, biology, medicine, machine learning methods, neural networks, Bayesian networks, evolutionary algorithms.

<http://orcid.org/0000-0002-1536-5542>

