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# An attempt to simplify clinical diagnostics of poisoning in the field using the binary discrimination method

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## ABSTRACT

**Introduction.** The lack of analytical determination of toxic chemicals in biological environments and environmental objects complicates the assessment of the prognosis of the poisoned person's condition and the choice of medical tactics at the advanced stages of medical evacuation. This problem is extremely relevant in cases of poisoning with fast-acting substances in conditions where therapeutic measures are severely limited in time. Taking this into account, an attempt was made to develop a diagnostic algorithm based on the mathematical method of binary discrimination of objective signs of poisoning.

**Material and methods.** Tables of 56 bivariantly manifesting (yes/no) signs of 89 etiological types of poisoning were compiled taking into account national guidelines and the authors' experience in the presence of analytical confirmation of the diagnosis. Using the discriminant binarization method, sets of 11 signs were selected that unambiguously determine all types of poisoning and a decision rule was compiled for their express diagnostics at the advanced stages of medical evacuation.

**Results.** Assessments of the presence or absence of objective manifestations of intoxication in the format of a reduced matrix made it possible to formulate a version of a decision rule for diagnosing poisoning with the most common types of military, industrial and medicinal toxicants, modern narcotic and psychotropic drugs, and substances of natural origin. The compiled algorithm is currently being tested to determine the objective characteristics of prognostic significance in the context of providing medical care of unknown structure toxic agent intoxication.

**Limitations.** Binary discrimination acceptability for data objectification on a probable toxic chemical class does not apply to home foodborne intoxications and iatrogenies, and their methodic interpretabilities are limited by preventive prescription of symptomatic therapeutics.

**Conclusion.** The method of multiple binary discrimination of alternatively expressed features is applicable in the formation of express assessments of the state and prognosis of the course of the disease allows reducing redundant information and compiling primary diagnostic algorithms applicable until analytical confirmation of the etiology of poisoning is available.

**Keywords:** *symptoms of poisoning; binary; discrimination; matrix of manifestations of independent features; diagnostic algorithm*

**Compliance with ethical standards.** The study does not require the provision of an opinion from the biomedical the ethics committee.

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## Introduction

The most effective way to treat poisoning is the timely use of antidote (etiotropic) therapy [1], however, in the definition of the antidote itself (from Latin given as a remedy) has a purpose that presupposes its use only with an established etiology of poisoning. Currently, the expansion of the list of toxic chemicals, including dual-use drugs, and changes in the forms and order of chemical risks in the absence of analytical confirmation have determined the need to analyze the etiology of the lesion when choosing rational pharmacotherapy tactics [2], including at the early stages of evacuation.

It is known that the symptoms of poisoning are often nonspecific and, depending on the severity and period of intoxication, it is characterized by polysyndromicity, idiosyncrasy and multimodality of manifestations. Traditionally, analytical studies with the detection of a toxic chemical or its metabolites in the biological environment of a poisoned organism [3], on clothing and in environmental objects are considered the gold standard for the diagnosis of poisoning. However, quickly implemented analysis algorithms have been developed only for a narrow range, mainly for combat poisons (organophosphorus poisons, pulmonotoxicants, substances of general toxic action), whereas for the rest of a wide range of toxicants, especially for poisoning with complex matrices of substances, the analysis procedure can take several days, exceeding the duration of the toxicogenic phase of poisoning [4]. In this regard, in order to form a rational pharmacotherapy strategy at the stages of primary pre-medical and medical health care, and even specialized health care, it is advisable to develop rapid diagnostic algorithms that take into account the totality of the body's responses to the effects of poisons. Undoubtedly, the initial assessments require clarification as the laboratory and instrumental examination of patients progresses.

Currently, in medical practice, mathematical analysis methods in the form of artificial intelligence systems and neural network models of decision-making tactics have increasingly been used in the diagnostic process [5, 6]. The development of such systems and models requires time to refine and optimize algorithms to prevent the negative effect of "overtraining", and the doctor's experience in identifying possible contradictions in the diagnosis and knowledge of the differential diagnostic criteria of syndrome-like conditions. At the present stage in medical toxicology, such diagnostic approaches go through only the initial phase of forming a system of initial data [7] and, importantly, they are presented in a form suitable for analysis [8].

*The purpose of this work* is to determine the suitability of diagnostic algorithms based on the binary discrimination method to improve the efficiency of sorting the affected at the advanced stages of medical evacuation and prescribing necessary medicines to them. The proposed approach ensured that the necessary and sufficient sets of poisoning signs reflecting the etiology of the process were isolated from a variety of options (more than 1025 combinations of predictors) and applied to create a decisive rule.

## Material and methods

Based on the results of the analysis of the primary medical documentation of 274 cases of poisoning with toxic chemicals, the variants of manifestations, the duration of evacuation and the outcomes of poisoning were traced in relation to the results of analytical control of the chemical composition of samples of biological media and clothing.

In many applied sciences, there is a task of finding ways to discriminate between types ( $t_i$ ), each of which is described by a certain set of binary (presence/absence) characteristics ( $a_{ij}$ ):

$$A = \begin{pmatrix} t_{i_1} & a_{11} & \dots & a_{1N} \\ t_{i_2} & a_{21} & \dots & a_{2N} \\ \vdots & \vdots & & \vdots \\ t_{i_M} & a_{M1} & \dots & a_{MN} \end{pmatrix}, \quad (1)$$

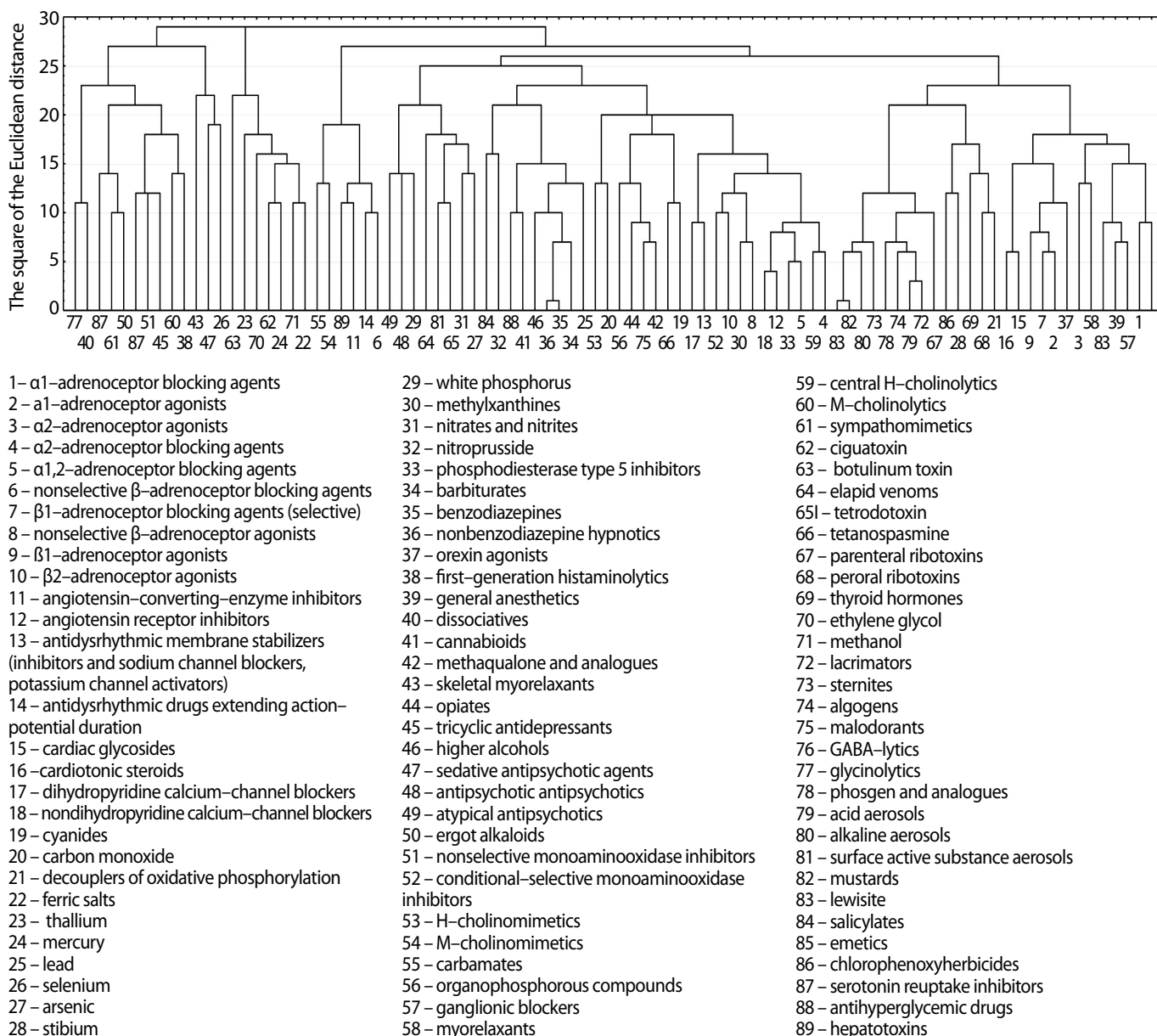
where in the simplest version, the number of lines  $M$  corresponds to the number of types of poisoning etiology variants, and  $N$  is the number of (considered, measured, available) characteristics of each type, and for any  $m, n$  the equality is valid

$$a_{mn} = \begin{cases} 0 \\ 1 \end{cases}, \text{ (we will call such characteristics binary).}$$

Thus, we developed a method for separating types according to the matrix (1), that is, a method that (ideally) allows us to determine the value  $t_{im}$  of this row using any row  $L = (a_{m1} \dots a_{mN})$  of a submatrix.

$$A_0 = \begin{pmatrix} a_{11} & \dots & a_{1N} \\ \vdots & & \vdots \\ a_{M1} & \dots & a_{MN} \end{pmatrix}. \quad (2)$$

Obviously, the lines are different for different types, and the signs for one type are indicated in this task in one line. In reality, several lines may belong to the same type, reflecting different possible reactions to the same toxic chemical.



Hierarchical clustering of the complete matrix of poisoning etiology types (squared Euclidean distance).

The separation of all types was carried out according to a binary number formed by the values of the characteristics. To separate the types, we found the simplest possible function that takes on different values for each of them. The types were separated after converting the corresponding characteristic strings into binary numbers, but the number of characteristics  $N$  may be excessive –  $2^N \gg M$ . Taking into account the above circumstances, a separating function was formed based on a binary number determined by the values of the characteristics in the part of the columns found, reduced by discrimination of the matrix.

Thus, calculating a binary number over the entire row of sample characteristics and then comparing the values obtained between the samples allows you to completely separate the types if there are no

identical rows corresponding to different types; if there are such rows, then it is impossible to separate the corresponding types without introducing new characteristics. In some cases, to separate the  $M$ -types, a binary number was formed not over the entire row of characteristics, but only according to the values located in the selected  $K$ -columns of characteristics. There can be no fewer columns than  $[Log_2 M] + 1$  (square brackets mean taking the integer part of the number – the largest integer that does not exceed this number).

The initial matrix of poisoning symptoms corresponding to a specific etiology was compiled using clinical guidelines [4, 9] and the results of our own analytical studies confirming the presence or absence of an etiological factor. The circumstances

**Option for forming a decision rule based on a reduced (11 manifestations: hypotension, bradycardia, tachypnea, dyspnea, diarrhea, hallucinations, headache, dizziness, nausea, visual disturbances, skin redness) matrix of poisoning etiology types based on binary discrimination**

[illegible]

*Note.* 1 –  $\alpha$ 1-adrenoceptor blocking agents, 2 –  $\alpha$ 1-adrenoceptor agonists, 3 –  $\alpha$ 2-adrenoceptor agonists, 4 –  $\alpha$ 2-adrenoceptor blocking agents, 5 –  $\alpha$ 1,2-adrenoceptor blocking agents, 6 – nonselective  $\beta$ -adrenoceptor blocking agents (selective), 8 – nonselective  $\beta$ -adrenoceptor agonists, 9 –  $\beta$ 1-adrenoceptor agonists, 10 –  $\beta$ 2-adrenoceptor agonists, 11 – angiotensin-converting-enzyme inhibitors, 12 – angiotensin receptor inhibitors, 13 – antidiarrhythmic membrane stabilizers (inhibitors of  $\text{Ca}^{2+}$  channel blockers), 14 – antidiarrhythmic drugs extending action-potential duration, 15 – decouplers of oxidative phosphorylation, 16 – cardiotonic steroids, 17 – dihydropyridine calcium-channel blockers, 18 – nondihydropyridine calcium-channel blockers, 19 – cyanides, 20 – carbon monoxide, 21 – decouplers of oxidative phosphorylation, 22 – ferric salts, 23 – thallium, 24 – mercury, 25 – lead, 26 – selenium, 27 – arsenic, 28 – stibium, 29 – white phosphorus, 30 – methylxanthines, 31 – nitrates and nitrites, 32 – nitroprusside, 33 – phosphodiesterase type 5 inhibitors, 34 – barbiturates, 35 – benzodiazepines, 36 – nonbenzodiazepine hypnotics, 37 – orexin agonists, 38 – first-generation histaminolytics, 39 – general anesthetics, 40 – dissociatives, 41 – cannabinoids, 42 – methaqualone and analogues, 43 – skeletal myorelaxants, 44 – opiates, 45 – tricyclic antidepressants, 46 – higher alcohols, 47 – sedative antipsychotic agents, 48 – antipsychotic antipsychotics, 49 – atypical antipsychotics, 50 – ergot alkaloids, 51 – nonselective monoamine oxidase inhibitors, 52 – conditional-selective monoamine oxidase inhibitors, 53 – H-cholinomimetics, 54 – M-cholinomimetics, 55 – carbamates, 56 – organophosphorus compounds, 57 – ganglionic blockers, 58 – myorelaxants, 59 – central H-cholinolytics, 60 – M-cholinolytics, 61 – sympathomimetics, 62 – ciguatera, 63 – botulinum toxin, 64 – elapid venoms, 65 – tetrodotoxin, 66 – tetanospasmin, 67 – parenteral ribotoxins, 68 – peroral ribotoxins, 69 – thyroid hormones, 70 – ethylene glycol, 71 – methanol, 72 – lacrimators, 73 – sternites, 74 – algogens, 75 – malodorants, 76 – GABA-lytics, 77 – glycinolytics, 78 – phosgen and analogues, 79 – acid aerosols, 80 – alkaline aerosols, 81 – surface active substance aerosols, 82 – mustards, 83 – lewisite, 84 – salicylates, 85 – emetics, 86 – chlorophenoxherbicides, 87 – serotonin reuptake inhibitors, 88 – antihyperglycemic drugs, 89 – hepatotoxins.

The shaded cells reflect the value of the feature used to form the diagnostic decision. The non-shaded cells contain information that does not affect the diagnostic decision, either because there is no variation in the feature values within the group, or because the data is redundant and the previous step was unambiguous.

of poisoning, the presence and dynamics of somatic status and complaints were taken into account, visual manifestations of acute poisoning and data from instrumental (laboratory) studies were recorded. In total, the data matrix contained 89 variants ( $M$ ) of the etiology of poisoning, the manifestations of which were described by 56 independent binary signs ( $N$ ). The processing of this matrix involved the search for various matrices of the type  $A_0$  with dimensions  $M \times K$  and the determination of  $K$ -signs that fully determine all  $M$  variants of the etiology of poisoning and the construction of a diagnostic algorithm. The complexity of discrimination is associated with the duration and deterministic power of computing systems.

## Results

Attempts to determine the etiological types of poisoning using multidimensional grouping and classification methods have been ineffective. The use of the method of factor analysis based on the identification of the main components did not allow us to group the types of etiology of poisoning and classify their groups. The results of the cluster analysis, taking into account the full matrix of manifestations of etiological poisoning variants, are shown in the Fig.

Despite the possibility of distinguishing groups of toxicants, the numerical contribution of several specific features to the determination makes it difficult to apply this algorithm in practice for the classification of etiological types.

As a result of binary discrimination, at least 4 combinations of 10 signs with bivalent manifestations (yes—no) were identified, ensuring the separation of 88 of the 89 etiological types and at least 7 combinations of 11 signs determining the separation of all the types of poisoning under consideration. Further examination of the blindly obtained combinations of signs revealed the simultaneous presence of mutually exclusive manifestations in their composition, for example, the simultaneous presence of tachycardia and bradycardia, hypertension and hypotension, tachypnea and bradypnea, diarrhea and constipation, dry skin and hyperhidrosis, etc. Such combinations were excluded from further consideration. When reducing symptoms, combinations containing criteria for the presence or absence of not only complaints, but also objective characteristics of intoxication, which are subject to reference assessment and dynamic control at the stages of medical evacuation, were also chosen to a greater extent.

As a result of the calculations, a numerical combination of 11 signs was selected, the totality of which reflected the presence of hallucinations,

hypotension, bradycardia, tachypnea, shortness of breath/difficulty breathing, diarrhea/diarrhea, redness of the skin, headache, dizziness, visual disturbances. It should be noted that there are a number of objective signs such as the presence of hyperkinesis, changes in pupil diameter, etc. It was not included in the system of estimated indicators based on the results of calculations, although it is advisable to indicate these objective signs in the final formulations defining the etiology of poisoning in the formation of the algorithm.

A working version of the diagnostic algorithm based on these features is shown in the Table. Developing such algorithms is a difficult task with several assumptions.

Firstly, the course of poisoning and the appearance of its complications, as well as modification by the administered drugs, presuppose a change in symptoms, which may not fully correspond to the static cross-section set during the formation of initial data, which reduces the diagnostic value of the work performed.

Secondly, in accordance with Table part of the diagnostic information can be considered redundant, although when forming a clinical diagnosis, all manifestations of the clinical picture of poisoning are evaluated in a complex. Recognizing the sufficiency of the objective criteria chosen in binary discrimination for the separation of etiological types, the formed "zero" variants of poisoning types (for example, the clinical picture of tetanospasmin poisoning) does not indicate the absence of intoxication as such, but with the assumption of abstractness describes only the place of the etiological type in the formed system of signs.

The specified algorithm can be implemented using hardware complexes and special tables in conditions of advanced stages of medical evacuation. The implementation of any numerical method involves the calculation and evaluation of the characteristics of specificity and sensitivity, the values of positive (PPV) and negative (NPV) predictive thresholds [10]. The calculation of these characteristics is possible as the developed algorithm is tested, the expert evaluation of which must be continued until a statistically significant sample is reached.

## Discussion

The increase in the share of newly created toxic chemicals, the replenishment of the range of dual-use products, the change in forms and the increase in cases of practical implementation of chemical risks in war zones in the absence or unavailability of permanent analytical control lead to caution in terms of ensuring chemical safety and the readiness of the

medical service to adequately respond to emerging threats. Taking into account the increased proportion of chemical damage to military forces performing tasks in the zone of a Special military operation, as well as in the absence of a «classic» focus of chemical contamination, the primary task of diagnosing the nature of the probable agent that caused poisoning is assigned to medical personnel. Given the frequent nonspecificity of poisoning symptoms and the dependence on the severity and period of intoxication, it is characterized by polysyndromicity, idiosyncrasy and multimodal manifestations. The reduction of diagnostic errors should be achieved by optimizing decision-making algorithms for sorting and stage-by-stage treatment of people with signs of a toxic reaction.

A rational strategy for pharmacotherapy at various stages of medical care can be the development of rapid diagnostic algorithms that take into account the totality of emerging body responses to the effects of poisons. Among them, one of the most accessible is the binary discrimination model, which is devoid of the disadvantages of complex models (duration of information processing, possible effect of "overtraining", etc.) and does not require additional skills from a doctor. The model considered in this paper was superior to models based on multidimensional grouping and classification methods, and, unlike factor analysis, provided clustering of the types of poisoning etiology, taking into account their group affiliation. Of the entire sample of data describing all types of poisoning, combinations containing objective characteristics of intoxication that are subject to reference assessment and dynamic control at the stages of medical evacuation were the most significant. According to the magnitude of the numerical estimates, a combination of 11 signs was determined, the totality of which reflected the presence of hallucinations, hypotension, bradycardia, tachypnea, shortness of breath/difficulty breathing, diarrhea/diarrhea, redness of the skin, headache, dizziness, visual disturbances. Hyperkinesis, changes in pupil

diameter, and a number of other alternative indicators that are not included in the system of estimated indicators should be taken into account in the final formulations defining the etiology of poisoning, as well as continue their expert assessment in newly identified cases of poisoning until a statistically significant sample is reached.

A working version of the diagnostic algorithm, compiled on the basis of these signs, can be implemented using hardware complexes and special tables in the conditions of advanced stages of medical evacuation for military personnel who did not receive medications that modify the course of poisoning or the appearance of its complications. Despite the apparent redundancy of diagnostic information, for example, in intra-group separation (the clinical picture of tetanospasmin poisoning), the completeness and accuracy of the objective criteria selected in binary discrimination is confirmed by the comparability of responses within the etiological type with the formed system of signs.

**Limitations.** The acceptability of binary discrimination to objectify data on a probable class of toxic chemicals does not apply to household food poisoning and iatrogenia, and the methodological possibilities of their interpretation are limited in the context of preventive prescribing of symptomatic therapy.

## Conclusion,

Formalized algorithms and assessments of symptoms are aimed at helping primary care physicians to diagnose the etiology of intoxication and to timely apply antidote therapy if necessary, taking into account the time of intoxication and the determination of its nature. The conducted research helps to identify approaches to the creation of medical protective equipment, identifying possible forms of their use, taking into account the equipment of the stages of medical evacuation.

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