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GENETIC ALGORITHM FOR MAKING PHARMACOTHERAPY DECISION IN THE PATIENTS WITH MULTIMORBIDITY: APPROACHES FOR CLINICIANS

ALGORYTM GENETYCZNY UŁATWIAJĄCY PODEJMOWANIE DECYZJI CO DO FARMAKOTERAPII U PACJENTÓW Z WIELOMA CHOROBAMI WSPÓŁISTNIEJĄCYMI: PRAKTYCZNE ASPEKTY DLA KLINICYSTÓW

Viktor M. Bobyryov, Sergij K. Kulishov, Andrij V. Vakhnenko, Olena V. Vlasova
THE HIGHER STATE EDUCATIONAL INSTITUTION OF UKRAINE, UKRAINIAN MEDICAL STOMATOLOGICAL ACADEMY, POLTAVA, UKRAINE

ABSTRACT

Purpose of our investigation was to propose and verify the algorithm for making pharmacotherapy decision in the patients with multimorbidity.

Material and methods: Object of investigation: patients with multimorbidity. Observations were conducted according to European Guidelines. We proposed and tested genetic algorithm for making pharmacotherapy decision for such patients. It is necessary to mention, that each person is representing a variant of treating with certain pathology. Chromosome of this variant is composed from genes, where each gene is certain group of drugs. The sequence of solutions of this problem comes down to the selection of drugs for the di-morbid conditions as the descendants of mono-morbidity. At the next stage of selection continues the most successful combinations of drugs for multimorbid conditions as descendants di-morbid and monomorbid conditions. When breeding pairs must take into account the mutual potentiating pathogenic and / or sanogenetic effects.

Results: We had optimal patient's treatment as a result of crossing genes, groups of drugs and obtaining their offspring with the best combination without absolute contraindications and minimal relative contraindications.

Conclusion: Thus, genetic algorithm for making pharmacotherapy decision in the patients with multimorbidity showed effectiveness of drugs choosing.

KEY WORDS: genetic algorithm, multimorbidity, pharmacotherapy

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PREREQUISITES THE APPLICATION OF GENETIC ALGORITHM FOR MAKING TREATMENT DECISIONS IN THE PATIENTS WITH MULTIMORBIDITY

The decisive argument using genetic algorithms is closely related to the question of how the search space is explored [1]. If this space is easy to analyze and its topology allows the use of specialized search technology, the use of genetic algorithms is not efficient in terms of cost of computing resources [1]. If the search space can not be analyzed and structured enough, and if there is an effective method of genetic mapping of this space, the genetic algorithm is surprisingly impressive search method in large and complex areas [1].

Matthew Wall [2] was initiated of genetic algorithm library (GALib). It may help us in transformation of the optimal intermediate decisions in the final creative diagnostic and treatment decisions.

Genetic algorithm is used for solving different problems that do not have the solutions for the exhaustive search for polynomial time. Therefore, it is evolutionary calculations, i.e. genetic algorithm preferably used in making diagnostic and therapeutic decisions [3, 4].

The modern world, highly developed industrial countries, pay attention to the problem of multimorbidity. The main reason for this attention is the aging of populations, an increasing of the life expectancy, the number of old people and long-livers in the age structure of the population [5].

Multimorbidity is an integrated system state to perturbation and feedback of the person's genomic, proteomic, metabolomic, neuroendocrine, immune and bioenergetics networks [6]. An integrated understanding of multimorbidity invites health professionals to consider the multiple consequences of any biomedical intervention and underscores the potential beneficial effects of implementing stress-reducing biobehavioural interventions for patients and communities [6].

Comorbidity and multimorbidity represent one of the greatest challenges to academic medicine [7]. Many disorders are often comorbidly expressed in diverse combinations. In clinical practice comorbidity and multimorbidity are underrecognized, underdiagnosed, underestimated and undertreated [7]. Comorbidities and multimorbidities are indifferent to medical specializations, so the integrative

and complementary medicine is an imperative in the both education and practice [7].

Shifting the paradigm from vertical/mono-morbid interventions to comorbidity and multimorbidity approaches enhances effectiveness and efficiency of human resources utilization [7]. Comorbidity and multimorbidity studies have been expected to be an impetus to research on the validity of current diagnostic systems as well as on establishing more effective and efficient treatment including individualized and personalized pharmacotherapy [7].

Purpose of our investigation was to propose and verify the algorithm for making pharmacotherapy decision in the patients with multimorbidity.

THE METHODOLOGY OF APPLYING GENETIC ALGORITHM FOR MAKING TREATMENT DECISIONS IN THE PATIENTS WITH MULTIMORBIDITY

There are standards for the treatment of concrete diseases, but we have problems with multimorbidity [8,9,10,11,12,13]. Treatment program for the patients with multimorbidity must be without polypharmacy, without iatrogenic origin pathology [8,12].

Based on these data, we considered the possible application of genetic algorithm formulation of patient treatment programs with multimorbidity based on existing standards for monomorbid cases [12]. Thus, it is necessary to make a population, each person which represents a variant of treating a patient with certain pathology. Chromosome of this variant is composed from five genes, where each gene has certain group of drugs. Considered to that the application of more than 5 drugs increases the risk of iatrogenic, medical complications, disease, based on these provisions, and it was proposed to limit the genes on chromosome by 5 [12]. The goal of treatment is to achieve a compiling of individual treatment regimens multimorbid states that were selected medications without contraindications to their use for each component of the multimorbidity. Ideally, after the chosen child-chromosome genes with 5 groups of drugs need to think about the possible reduction of medication as a result of mutations up to monotherapy.

The sequence of solutions of this problem comes down to the selection of drugs for the di-morbid conditions as the descendants of mono-morbidity. At the next stage of selection continues the most successful combinations of drugs for multimorbid states as descendants di-morbid and monomorbid states. Breeding pairs must take into account the mutual potentiating pathogenic and / or sanogenetic effects [12]. Selection of following pairs is based on the rating of the treatment schemes, which focuses on the synergistic effects on multimorbidity processes, multi syndrome effect on each drug "gene" [12].

After the selection of the optimal therapeutic solutions of multimorbidity concrete state can be carried out to check the quality of selection at the level of the constituent syndromes.

IMPLEMENTATION OF GENETIC ALGORITHM FOR MAKING DIAGNOSIS AND TREATMENT DECISIONS

Example of implementation:

Patient Y., male, 65 years old, with combination of:

- chronic ischemic heart disease, diffuse cardiosclerosis, paroxysmal atrial fibrillation;
- essential hypertension 2nd stage, 2nd degree, with a moderate risk of complications, hypertensive heart, 1st functional class of heart failure by NYHA;
- chronic acalculous cholecystitis;
- pollinosis, allergy to Weed (Ragweed, Sunflower, Artemisia, etc.), allergic rhinitis, allergic conjunctivitis.

Methods of investigation: monitoring of ECG and blood pressure, ultrasound investigation of heart, organs of abdominal cavity were used for verification of diagnosis genotyping (PCR, gel electrophoresis) of Apolipoprotein E on Alleles; total immunoglobulin E, immunoglobulin E to the harmful plants and food allergens; daily monitoring of ECG and blood pressure, ultrasound investigation of heart, organs of abdominal cavity were used for verification of diagnosis.

Results of investigation: in this patient were detected paroxysmal atrial fibrillation, left ventricular hypertrophy, E3/E2 Allele of Apolipoprotein E; 121 IU / ml total immunoglobulin E (normal - up to 100.0); apolipoprotein A-1 – 1,3 g / l (normal: 1,04 – 2,02); apolipoprotein B – 1,24 g / l (normal: 0,66 – 1,33); cholesterol 5,54 mmol / l; triglycerides 1,21 mmol / l; high density lipoprotein (HDL) – 1,13 mmol / L, low density lipoproteins (LDL) – 4,06 mmol / l, very low density lipoproteins (VLDL) – 0,35 mmol / L; atherogenic factor – 3,9 U (normal: up to 3,0), high level of immunoglobulin E to pollen of ragweed, artemisia.

Find: to draw up a program of treatment of such patients in order to maximize the improvement of its quality of life.

Solution: Create a population of standards for treatment of certain disease entities, mono-morbid conditions.

Standard treatment for arrhythmic form of coronary heart disease, atrial fibrillation are such groups as calcium channel blockers, beta-blockers, antiplatelet agents, statins.

Standard treatment for essential hypertension stage II, 2nd degree with moderate risk are such drugs as calcium blockers, diuretics, beta-blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors.

Standard treatment for chronic acalculous cholecystitis are such groups as antibiotics, ursodeoxycholic acid, modulators of smooth muscle tone - cholekinetics; choleretics, analgetics.

Standard treatment for pollinosis, allergy to Weed (Ragweed, Sunflower, Artemisia, etc.), allergic rhinitis, allergic conjunctivitis are such groups as membrane stabilizators, calcium blockers, antihistamines.

Breeding couples - from chromosomes standards of treatment of coronary artery disease and essential hypertension; standards of chromosomes treatment of coronary artery disease and chronic acalculous cholecystitis; chromosomes of essential hypertension standards treatment and chronic acalculous cholecystitis; treatment standards for coronary artery disease and pollinosis, allergy to Weed (Ragweed,

Sunflower, Artemisia, etc.), allergic rhinitis, allergic conjunctivitis; etc. As a result, multi-point crossover pairs of chromosomes will have a pair of offspring - solutions for di-morbid states treatment problems. The next stage is a search, selection of di-morbid states treatment standards for selection of pairs and after it to make treatment decisions for three- and more multimorbid states. After the chosen child -chromosome with 5 genes of 5 drug groups for the treatment of a concrete multimorbidity states need to think about the possible reduction of drugs by mutating.

The genetic algorithm is allowed us to determine the treatment characteristics of such pathology, to select drugs and their combinations, that, with minimum amount can influence on maximum number of symptoms, syndromes. Treatment included Mediterranean diet with the transition to a vegetarian diet in the period of flowering weeds, drugs such as angiotensin-2 receptors blockers; calcium channel blockers, modulators of the coagulation cascade and lipid metabolism, membrane stabilizers, mast cell stabilizers. The use of evolutionary algorithms contributed to the identification of structural components of the syndromes in patients with multimorbidity, making optimal treatment decisions with positive results.

In this study, the analysis of the genetic algorithm on a given clinical data on the composite syndromes certain nosologic units of multimorbidity. The formal-logical solutions aim of differentiation treatment of multimorbid states in accordance with existing standards for optimizable and competing criteria are:

- minimizing errors of group drugs inclusion with absolute and may be relative contraindicated for use;
- The lowest ammount of selected drugs with maximum therapeutic effect.

It is believed that the more taken into consideration sign-tests, the more realistic to expect greater accuracy, and vice versa. Thus it is necessary to find a compromise solution that is satisfactory for both criteria.

We consider, that genetic algorithm help us with solving of diagnostic and treatment multimorbidity problems, peculiarities of patient management with age dependent pathology.

The essence of good prescribing is to pick the most appropriate drug for the disease in question, taking pathophysiology in account [14]. Drugs act on a wide variety of targets: receptors, transport processes, enzymes, by others miscellaneous effects [14]. Following administration, disposition of drugs in the body is determined by drug absorption, distribution, metabolism and excretion [14]. Taken together, these processes define pharmacokinetics of drug. Drug therapy monitoring, also known as Therapeutic Drug Monitoring, is a means of monitoring drug levels in the blood [14]. Many different factors influence on blood drug levels, the following points should be taken into consideration during Therapeutic Drug Monitoring: the age and weight of the patient; the route of administration of the drug; the drug's absorption rate, excretion rate, delivery rate, and dosage; other medications taken by the patient; other diseases the patient has; the patient's compliance regarding the drug treatment regimen; and the laboratory methods used to test for the drug [14]. Therapeutic Drug Monitoring is a practical tool that can help the physician provide effective and safe drug therapy in patients who need medication [14]. Monitoring can be used to confirm a blood drug concentration level that is above or below the therapeutic range, or if the desired therapeutic effect of the drug is not as expected [14]. If this is the case, and dosages beyond normal have to be prescribed, Therapeutic Drug Monitoring can minimize the time that elapses [14].

Therapeutic Drug Monitoring is important for patients who have other diseases that can affect drug levels, or who take other medicines that may affect drug levels by interacting with the drug being tested [14]. Therapeutic drug monitoring refers to the individualization of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window) [14]. There are two major sources of variability between individual patients in drug response [14]. These are variation in the relationship between: dose and plasma concentration (pharmacokinetic variability); drug concentration at the receptor and the response (pharmacodynamic variability) [14]. Several methods have been developed to improve the prediction of individual dose requirements based on sparse data for individual patients [14]. These are based either on calculation of clearance and volume of distribution from one or a few timed drug concentrations, or by a Bayesian feedback method [14]. This latter method is based on differences between "typical" population parameter values and those predicted for the individual patient from measured drug concentrations [14].

Our algorithm of using principles of Cantor von Koch sets for exploratory fractals clinical pharmacological data analysis is based on the principles of genetic algorithm [14]. It's based on the grouping data, formation of categorical variabilities in the form of subgroups as iteration process [14] as for receiving Cantor von Koch sets. It boils down to: selection of informative numerical dependent variabilities; transformation these informative numerical dependent variabilities to new categorical variabilities; formation of categorical variabilities in the form of subgroups as a result of an iterative process as for Cantor von Koch sets; statistical analysis of the data; determination of the distribution of variabilities; transformations that may be normalize from non-normal data; ANOVA - analysis of variance parametric data or nonparametric equivalent of ANOVA - Kruskal-Wallis testing; formulation of the conclusion [14]. Our algorithm of using Cantor von Koch sets principles for Exploratory Fractals Data Analysis of clinical pharmacological data will help to maximize insight, uncover underlying structure, extract important variables, develop models and determine optimal factor settings [14].

Conclusion: Thus, the criteria for the selection and evaluation are the number of syndromes and diseases in which can be determine the best group of drugs without absolute contraindications and minimal level with relative contraindication. More points of optimality criterions are the termination of breeding, the possibility to improve the quality of care and life.

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ADDRESS FOR CORRESPONDENCE
Sergii K. Kulishov
Osvityansky st. 6, f. 47,
36021 Poltava, Ukraine
Tel. +8(050)9963333
E_mail: kulishov@meta.ua

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