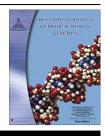


ORIGINAL ARTICLE

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net



Some aspects of genetics and pharmacogenetics understanding by pharmacy students in Ukraine



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Received 27 September 2014; accepted 22 October 2014 Available online 18 November 2014

KEYWORDS

Pharmacogenetics; Genetics; Personalized medicine; Pharmacy students; Ukraine **Abstract** *Background:* Prescription and administration of drugs are still carried out without taking into consideration the individual's needs of a particular patient on the post-Soviet territory. A pharmacist may play a crucial role in the field of pharmacogenetics development in any country, nevertheless his/her role is uncertain even in the countries where pharmacogenetics is intensively developed. The aim of the present work is to analyze students' awareness about pharmacogenetics in the National University of Pharmacy (NUPh) since its development is delayed in Ukraine.

Methods: Field investigations have been used in this work. The material analysis based on questioning 637 students of the 1st–4th year majoring in pharmacy has been carried out.

Results: The analysis of the future pharmacists' awareness in the field of genetics and pharmacogenetics, as well as the study of the sex specificity of this awareness, has been carried out for the first time in Ukraine. It has been stated that more than 70% of the students questioned got the information about pharmacogenetics in University for the first time. However, only more than one-third of respondents (37.7% of males and 43.9% of females) correctly understand the idea of this discipline. About half of the students questioned thought that pharmacocorrection of hereditary diseases was impossible. It has been shown that on the whole females were more informed about pharmacogenetics than males. So, they can become more active persons of pharmaceutical market in future.

Conclusion: The awareness about pharmacogenetics and its role in personalized medicine is not satisfactory both in Ukraine and other countries. Thus, it is necessary to pay more attention to the aspects of pharmacogenetics when training competent up to date specialists in the field of pharmacy. Effective development of the appropriate infrastructure in pharmacogenetics testing and its introduction among the population of Ukraine are also necessary.

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1. Introduction

Unfortunately, prescription and administration of drugs are still carried out without taking into consideration the individual's needs of a particular patient on the post-Soviet territory.

http://dx.doi.org/10.1016/j.ejmhg.2014.10.004

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At the same time, investigations into the field of personalized medicine are intensively carried out in the western world. The problem of the individual's approach to treatment is crucial in modern medicine. It is connected with the range of important discoveries in the field of molecular mechanisms of drug action. These discoveries are related to the levels of pharmacodynamics (receptors) and pharmacokinetics (enzymes). A series of new interdisciplinary subjects appeared not known so far, such as pharmacogenetics, pharmacogenomics, pharmaceutical biotechnology, etc. Thus, it is necessary to develop educational programs for pharmaceutical and medical students, as well as for specialists in advanced training, who work in the health care system [1]. The mentality changes of a future pharmacist and his/her adaptation to biological introduction, particularly genetic novation, are needed. There is a positive experience of interaction between geneticists, clinicians and pharmacists though it is rather insufficient.

Pharmacogenetics studies interindividual differences in relation to drugs due to genetic variation between people and, therefore, it is an important part of personalized medicine. Relevancy of pharmacogenetic tests is obvious due to occurrence of adverse reactions when underestimating the genetic polymorphism system, including variations in drug metabolism. For example, Holland scientists showed that in 39.5% cases adverse reactions appeared as a result of genetic factors, and the necessity of genetic expertise was initiated directly by the medical staff [2]. Adverse reactions due to genetic variations are particularly obvious in cancer patient treatment [3], and in recent years pharmacogenetic information is intentionally included into specifications of common drugs. Thus, the Food and Drug Administration takes into control this procedure in the USA [4]. The examples of drugs labeled with pharmacogenetics information include cytostatics 6-mercatopurine and irinotecan [5]. The personalized administration of drugs has become the applied aspect of the analysis results of human genetic polymorphism. There are some perquisites for gradual introduction of pharmacogenetic tests and genetic passports as a pharmaceutical service. Among them there is decoding of the human genome [6], and, consequently, understanding of genetic influence on drug metabolic pathways in the body.

The main and wide spread type of pharmacogenetic polymorphism is SNP (single nucleotide polymorphism). It studies differences in genetic material of DNA separate nucleotides (adenine, thymine, guanine and cytosine). SNP occurs in the human genome practically over each 300-400 b.p. Less significant are STRs (short tandem repeat), VNTRs (variable number tandem repeat) and other types of genetic polymorphism. Interpopulation pharmacogenetic polymorphism is more pronounced, especially, between the individuals of different races and ethnic groups. The differences between individuals within a population may also be quite obvious and clinically significant due to possibility of adverse reaction development because of either variations in pharmacodynamics or pharmacokinetics. A great number of papers are devoted to polymorphism of enzyme gene CYP2D6, which takes part in metabolism of many drugs, including narcotic analgesics and antidepressants. For example, the role of CYP2D6 in codeine metabolism is well-known. A person who doesn't have potency of this enzyme (a poor metabolizer), practically doesn't feel the analgesic effect of codeine, while ultra-rapid metabolizers are subjected to serious opioidergic effects, even to lethal

outcomes [7]. It has been shown that in some populations not less than 50% of people can have at least one of two alleles of CYP2D6 with the reduced functional activity, which prevents codeine turning into active metabolite morphine and makes codeine analgesia ineffective [8]. CYP2D6 polymorphism also predetermines the therapeutic effect of oxycodone and hydrocodone [9]. SNP-genotyping of patients receiving tramadol as a post-operative analgesic in one of the Asian populations showed that 27% of them were moderate, 70% – quick and 2.9% – ultra-rapid metabolizers. Nevertheless the profiles of adverse reactions in different groups significantly differed. The widespread alleles were CYP2D6*1 and CYP2D6*10 [10].

Pharmacogenetics suggests three possible areas of activity: (1) development of methods and identification of areas of research, (2) evaluation of pharmacogenetic tests in clinical practice, and (3) conducting educational activities and infrastructure development for the pharmacogenetic test introduction [11].

The main role in pharmacists' competence to modern requirements is their constant qualification growth although in some cases pharmacists do not realize the importance of advanced training. In particular, there is evidence concerning the effect of advanced training reflected in the employment history on the competency of pharmacists. Pharmacists with work experience from 0.1 to 21 years took part in the investigation, which was held in the UK. The results showed that registration of certificates of professional development didn't influence pharmacist's activity. The most experienced participants of the investigation could less explain changes in their practical activity after trainings. The conclusion about the necessity of further investigations into the role clarification of the self-regulatory pharmacist's behavior was made [12]. In Scotland, 543 pharmacists took part in the investigation into time recording spent on advanced training. It has been shown that 9.8% of respondents have never passed advanced training. According to the sector of employment the rest of the respondents spent on average from 45 to 68 h for their qualification improvement [13]. The complex study as to relationship assessment of pharmacists' professional development has shown that such events are not approved by pharmaceutical community everywhere and not exclusively, especially in cases of qualification rechecking. Totally 22 works made from 2000 to 2010 were included into analysis in the UK [14]. Canadian researchers consider intra- and interdisciplinary cooperation necessary in conducting activities to advanced training of specialists working in the health care system [15]. It has been shown that two main motivational factors of curricula among students of pharmacy higher schools were knowledge and experience gaining, as well as a wish to get special skills [16]. These data clearly testify that not all events as to pharmacists advanced training are necessary and useful to subjects of such interaction.

The first step toward development of pharmacogenetic test protocols introduction into clinical practice was made in 2001, when with antidepressant administration, physicians began to recommend genotyping of the cytochrome gene CYP2D6. However, in spite of the early optimism, an up to date pharmacogenetic test is limited by the use of only a few clinical directions, in particular, cancer and psychiatry [17]. It is important to understand that before the introduction of a specific pharmacogenetic test into medical practice, it is necessary to conduct randomized clinical trials to evaluate its suitability

as a laboratory test, development of clinical guidelines for its use and educational programs for the corresponding specialists [18]. Similar clinical studies have been performed for some drugs, particularly for warfarin [19]. In some cases, a personalized approach for one disease should include a number of pharmacogenetic tests because the disease is multifactorial; for instance, typing of several genes related to treatment of schizophrenia [20].

Thus, on the basis of the world experience analysis concerning modern biopharmaceutical technology introduction with the aim of personalized medicine, we can make a conclusion about a multifaceted and significant role of a pharmacist in the system organization, providing pharmaceutical service to the population and developing the accurate algorithm. Further investigations propose in-depth analysis of the situation in Ukraine with the aim of the possibility of the country's pharmacogenetic infrastructure development. The range of problems presented confirmed by visual examples determines the vector and the prospects for further studies of the population genetic structure in relation to pharmacogenetic significant features connected with the therapeutic efficiency of narcotic drug administration among the polyethnic local population in order to improve the quality of pharmaceutical services.

The aim of the present work is to analyze the students' awareness about pharmacogenetics in the National University of Pharmacy (NUPh).

2. Subjects and methods

2.1. Design and questionnaire

Field investigations were used in this work. Questioning of NUPh students (Kharkov, Ukraine) was conducted. The questionnaire consisted of two parts: socio-demographic and basic. In the socio-demographic part of the questionnaire there was information about sex, age, address, educational level, respondents' profession and number of people in his/her family working in the field of health care system. The basic part of the questionnaire consisted of the questions directed to understanding of the role of the genetic factor in the process of pharmacocorrection. Only some questions of the basic part of the questionnaire have been used for the current analysis.

2.2. Subjects

Gathering of information was conducted taking into consideration the ethical requirements while working with a human. All the participants of the study gave informed consent to anonymous questioning. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The material analysis based on questioning 637 students of the 1st–4th year majoring in pharmacy and studying some topics on human genetics and pharmacogenetics in the "Biology and Genetics Principles" course (the first year) has been carried out. According to the specific character of studying, the contingent selection has been shifted to female side. Among the students questioned there were 557 females (87.4%) and 80 males (12.6%). The age of the students questioned is from 17 to 23 years. In different age groups females and males were presented as: 17 years old -7.5% and 11.5%, 18 years old -31.2% and 25.0%, 19 years old -28.7% and 25.3%, 20 years old -18.7% and 27.5%, 21 years old -10% and 10.2%, 22 years old -2.5% and 0.5%, 23 years old -1.2% and 0%, respectively. 98.8% of males and 99.5% of females questioned lived in Ukraine (the rest of the respondents lived in Russia and Kazakhstan or stayed in Ukraine temporarily).

Among males, 46.4% lived in large cities with a population of more than 1 million people, 34.5% – in big towns (population of 250–500 thousand) and in towns (population of 100–250 thousand), and 19.1% – in small towns (up to 50 thousand) and in rural areas. Among the females questioned, 41.7% lived in large cities, 38.5% in big towns and 19.8% in small towns and rural areas.

38.1% of the males and 42.4% of the females questioned have family members, who work in the field of medicine or pharmacy.

2.3. Statistical analysis

The relationship between qualitative characteristics was evaluated using the criterion χ^2 . Conclusions to statistic hypotheses were made at a significance level of $p \leq 0.05$. Microsoft Excel and Statistica 6.1 programs were used in the study.

3. Results and discussion

Basic socio-demographic characteristics of males and females selection were put together. Therefore, any significant differences could be stipulated only by sex of an individual.

As many atypical human reactions to drugs are due to a genetic factor, it is reasonable to include the question about the possibility of pharmacocorrection for understanding hereditary conditions (diseases). The results of the study showed that the majority of the males questioned believed that it was impossible to correct hereditary diseases using drugs (51.2%). 41.4% of females thought that hereditary diseases could be treated with drugs (Fig. 1). Nevertheless, any significant differences between peculiarities of females' and males' answers to this question haven't been found ($\chi^2 = 2.70$, y = 2, p = 0.26).

Analyzing answers to the question about the notion of pharmacogenetics it has been shown that this concept is understood differently by males and females (Table 1), and differences obtained are statistically important ($\chi^2 = 13.84$, $\nu = 6$, p = 0.03). Thus, 11.8% of the males and 6.4% of the females questioned have not heard anything about pharmacogenetics. 14.1% of the males and of the females 25.2% have heard about it, but do not know exactly what pharmacogenetics studies. The right answer about the notion of pharmacogenetics was given by one third of the males (37.7%) and females questioned (43.9%).

Unfortunately, up to date even in developed countries health professionals, including pharmacists, do not have sufficient knowledge of the correct drug administration and dosing, as well as interact ineffectively with colleagues (physicians, genetic consultants, etc.) [21]. However, there is a positive experience of gradual pharmacogenetic test introduction into practical medicine. Thus, a pilot program of the personalized approach to clopidogrel antiplatelet administration consisted of two stages. At first, patients visiting a pharmacist for a

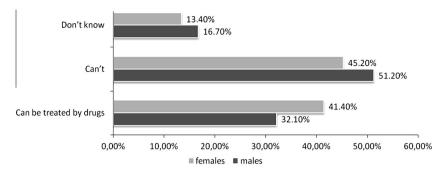


Figure 1 Analysis of the possibility of hereditary diseases' pharmacocorrection among males and females.

Table 1 Distribution of answers to the question "What does pharmacogenetics study?" among respondents of different sex.

Sex	What does pharmacogenetics study?										
_		· · · · · · · · · · · · · · · · · · ·	•	The influence of drugs on a human	*	The possibility of gene mutation appearance as a result of drug administration	The body's response to drugs due to its genetic peculiarities				
Male (%)	11.8	14.1	17.6	3.5	4.7	10.6	37.7				
Female (%)	6.4	25.2	9.7	4.5	3.6	6.7	43.9				
Note. $\chi^2 = 13.84, v = 6, p = 0.03.$											

certain drug were offered to take part in the pharmacogenetic test. After receiving the consent, a specialist conducts a noninvasive collection procedure of the biological material (buccal epithelium of the oral cavity) for genotyping of the cytochrome gene CYP2C19, which is responsible for metabolism of the corresponding compound. After receiving the test results, the pharmacist got the results' interpretation from a physician and properly selected a dose for the patient [22]. In Spain, the monitoring protocol of anticonvulsants, including the corresponding pharmacogenetic tests, have been developed and approved [23]. The pharmacogenetic test in one of the U.S. clinics included 136 corresponding analyses performed within the year. Conducting educational seminars for pharmacists was included into organizational activities. Pharmacogenetic monitoring developed was smoothly integrated into the pharmacokinetic control system of the clinic. The results of pharmacogenetic tests were sent to a coordinating pharmacist, who had to give a written interpretation of analysis and to select the individual's treatment [24]. In some cases besides a positive description of the pharmacogenetic experience, attempts of the economic efficiency of pharmacogenetic testing are needed to be undertaken to assess a reduction of adverse reactions frequency, particularly, when administering warfarin [25].

In our study it has been stated that females – future pharmacists are more progressive as to awareness of pharmacogenetics ideas. Consequently, as females are more informed about genetic peculiarities of the organism and its response to drugs, they probably will advise visitors of the chemist's to conduct these tests in future. Besides, females as a subject of the pharmaceutical market potentially more often can be consumers of its production themselves (according to pharmacogenetics tests), therefore, with their knowledge they are less likely to have side effects due to incorrect treatment. In connection with this, the male population can be classified as potential risk group of increased frequency of atypical reactions.

When studying the information sources concerning pharmacogenetics it has been shown that most students received information about this notion in the University. Moreover, any significant differences between males and females have not been found ($\chi^2 = 2.23$, $\nu = 5$, p = 0.82). In particular, the curriculum for the discipline "Biology and Genetics principles" for the 1st year students of specialty "Pharmacy" in NUPh pays some attention to pharmacogenetics; it considers topics related to population genetics and hereditary diseases. According to the questionnaire data 70.7% of males and 72.9% of female respondents heard about pharmacogenetics superficially in University; 13.4% of males and 10.5% of females knew nothing about this notion at all (Table 2).

For discussion, one can give some examples about the specialists' awareness of pharmacogenetics and pharmacogenetics testing and related questions in some other samples.

New biotechnological approaches of study in pharmaceutics are differently treated by pharmacists. 580 U.S. pharmacists expressed positive attitudes toward pharmacogenetic testing at on-line questioning. The majority of the participants questioned (87%) thought that this diagnostic procedure promotes a decrease in the number of adverse reactions, and optimization of the drug dose. More than half of the participants questioned (57%) thought that patient consulting and explaining the results of pharmacogenetic tests to them were included in their tasks. At the same time the majority of the participants questioned (65%) expressed the apprehension that pharmacogenetic tests could be used with the aim of medical insurance annulation [26]. For comparison, we can use the results of questionnaires conducted in the USA among genetic consultants and clinical geneticists. It has been shown that 12% of genetic consultants and 41% of clinical geneticists promoted pharmacogenetic test conducting in patients; it is a relatively

Sex	The source of information about pharmacogenetics							
	Don't have any information	Have heard in University (superficially)	Studied in University (as a discipline)	Got to know from friends	Got to know from media			
Male (%)	13.4	70.7	3.7	3.7	8.5			
Female (%)	10.5	72.9	5.6	4.9	6.1			
Note. $\chi^2 = 2.23, v =$	5, p = 0.82.							

 Table 2 Distribution of answers to the question "Where did you get information about pharmacogenetics?" among males and females.

high level at this early stage of mass diagnostics introduction. Almost all questioned participants had an idea about pharmacogenetic, although only 28% of consultants and 58% of clinical geneticists were well prepared in the field of pharmacogenetic testing. About half of genetic consultants (52%) and clinical geneticists (46%) thought that introduction of a pharmacogenetic test into clinical practice was their task, although 17% and 19% of the participants questioned from these groups did not consider this activity as a component of their work [27]. Explanatory work, accessible students and practising pharmacists' education on specific pharmacogenetic methods, particularly warfarin dosing on the basis of the patient genotyping, have shown high effectiveness. So, the competence level of the participants under study determined after filling test sheets was 97 \pm 3%. Thus, even short training courses may be effective for personalized diagnostics and interpretation of pharmacogenetic test results [28]. Other authors studied the effectiveness of advanced training on pharmacogenetics, which was taught to 272 pharmacists within 2 months. However, the investigation results showed that the average improvement was only 0.7 points on the test system of 11 questions of multiple-choice [29]. Questioning of 284 Canadian practicing pharmacists regarding their pharmacogenetics vision and its role in the introduction into medical practice has shown that more than 95% are ready to recommend conducting pharmacogenetic tests to potential customers, but only a small number of respondents (7.7%) had the necessary knowledge for this. Majority of pharmacists (96.6%) showed the necessity of additional pharmacogenetic training [30]. The cross-sectional study of the Australian pharmacists showed their weak background in the pharmacogenetic field. An inverse relationship between awareness level and work experience was found. Thus, pharmacists with the greatest work experience had less knowledge relative to pharmacogenetic testing. Most respondents thought that it was more optimal to conduct the corresponding courses and seminars while studying at the University, but not in the post graduate system of studying and advanced training [31]. Available data as to the patients' relation to pharmacogenetic testing in general showed their concern. A randomized telephone questioning of the US population revealed that 90% of the respondents were extremely positive about the possibility that the medical personal would have their results of pharmacogenetic tests. Fewer respondents questioned (74%) approved such results provided by pharmacists [32]. Questioning of people suffering from chronic diseases or having sick family members showed a positive attitude toward pharmacogenetic tests conducting and most have the complete awareness of physicians and pharmacists [33].

Our analysis has shown that even among future pharmacists the awareness about pharmacogenetics and its role in personalized medicine is not satisfactory both in Ukraine and other countries. Thus, it is necessary to pay more attention to the aspects of pharmacogenetics when training competent up to date specialists in the field of pharmacy. Effective development of the appropriate infrastructure in pharmacogenetics testing and its introduction among the population of Ukraine are also necessary.

4. Conclusion

The analysis of the future pharmacists' awareness in the field of genetics and pharmacogenetics, as well as the study of the sex specificity of this awareness, has been carried out for the first time in Ukraine. It has been stated that more than 70% of the students questioned got the information about pharmacogenetics in University for the first time. However, only more than one-third of respondents (37.7% of males and 43.9% of females) correctly understand the idea of this discipline. About half of the students questioned thought that pharmacocorrection of hereditary diseases was impossible. It has been shown that on the whole females were more informed about pharmacogenetics than males. So, they can become more active persons of pharmaceutical market in future.

Acknowledgments

Authors are grateful to the rector of NUPh, corr-mem. of the NAS of Ukraine, Prof. V.P. Chernykh; the head of Department of Human Physiology and Anatomy, Prof. L.N. Maloshtan; the head of Department of Microbiology, Virology and Immunology, Prof. N.I. Filimonova; the head of Department of Pharmacology, Prof. S.Yu. Shtrygol; the head of Department of Management and Marketing in Pharmacy, Prof. V.V. Malyi for their assistance in conducting this research.

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