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Introduction

The Importance of Evidence: The Legacy of Archie Cochrane

The establishment of Cochrane Russia within the Kazan Federal University is a great triumph. Even more significant, perhaps, it is indication of the determination of the medical leadership in Tatarstan to contribute to the scientific factual basis for judgments and interventions in the practice of medicine. The faculty of the university is to be congratulated for showing its interest in the quality of the evidence in medicine and, as a result, for having been selected to serve as the Russian Branch of the Nordic Cochrane Centre.

Archie Cochrane was a complex individual – as are essentially all who eventually make substantial contributions to humanity. He early chose a path toward psychiatry and psychoanalysis in Vienna in the shadow of Sigmund Freud. As he noted much later, he "...couldn't test its hypotheses."

Archie Cochrane turned toward socialism as he was deeply impressed by the aspect of unemployment in the 1930's. He joined the International Brigade in the Spanish Civil War and took part in at least five major battles. He returned to London and qualified as a doctor at University College Hospital and settled into research only to face a new challenge, the outbreak of World War II. On active duty, he was shortly taken prisoner where he remained for the next four years. In this setting, he served as the physician for thousands of prisoner patients suffering from tuberculosis and diphtheria and a variety of other disorders. It was this experience that led him to epidemiology and to an intellectual curiosity about what does and does not work in medicine. He wondered why certain of the patients survived. He concluded that it had little to do with therapy in contrast to the recuperative processes of the human organism.

With very few therapeutic or even analgesic agents to use, he was drawn to observations as to what was effective and what was not. In later years, during a lecture in Germany, he thanked the audience for leading him into the productive fields of epidemiology and thinking about the health of the community.

Between 1951 and 1968, he watched the birth of the National Health Service and a substantial increase in the number of medical resources in the UK. Requests for pathology tests increased three-fold and the number of x-ray units doubled. This propelled him to question the usefulness or perhaps wastefulness of some of what medicine did. He focused in this on type II diabetes, hypertension and the very active practice of tonsillectomy in children. It was this experience that spawned his most famous book, Effectiveness and Efficiency in the National Health Service. He eventually returned to his home territory in Wales and to the epidemiological study of pneumoconiosis among Welsh coal miners.

In all of this, he believed that much of medicine did not have sufficient evidence to justify its use. This, of course, was a serious challenge to practitioners and to their institutions. Cochrane expressed an unwavering position that controlled clinical trials were a requisite for judging effectiveness.

Archie Cochrane was always humorous, self-effacing and self-deprecating. Cochrane liked to think of himself as a heretic. At one point late in his career, he was heard to say, "I am getting rather old and we don't seem to be producing any young heretics."

I briefly knew Archie Cochrane and can attest to his ingenuous and generous personality. During one of his visits to the United States in the 1970's, I had the pleasure of bringing him and his points of view to the attention of the leadership of the National Institutes of Health in Washington.

His legacy, rigorous attention to the evidentiary basis of medicine, is now established. The Cochrane Library and the Cochrane collaboration represent the data bases for medicine. The vision of the Cochrane Collaboration is stated as a "...world of improved health where decisions about health and health care are informed by high quality, relevant and up-to-date synthesized research evidence."

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Mild anemia as a protective factor against pregnancy loss

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BACKGROUND: Iron deficiency anemia is traditionally considered to be a pathological condition during pregnancy. According to the standards, prescription of iron supplements to pregnant women is required at hemoglobin levels of 110 g/l and lower. Numerous studies at different periods showed the relationship of anemia and premature birth [5], preeclampsia [1], low birth-weight [2]. Meanwhile, physiological hemodilution carries in pregnancy an important adaptive function. It is well known, that in the second half of pregnancy physiological hypercoagulability develops (increased activity of the plasma clotting factors, platelet aggregation, decreased activity and blood concentrations of physiological anticoagulants) aimed at implementing adequate hemostasis in labor. Under these conditions, moderate hemodilution is an effective mechanism for preventing the development of severe disseminated intravascular coagulation (DIC) in labor, during surgery, in various forms of obstetric pathology.

OBJECTIVE: To study the effect of anemia of varying severity on the pregnancy course and outcomes.

METHODS: We conducted a "case-control" study based on cohort. The study included 421 pregnant women who received outpatient care under the monitoring of pregnancy in the antenatal clinic of the South Ural State Medical University and the antenatal clinic of Chelyabinsk Clinical Hospital №6. The inclusion period was from January to March 2014. Inclusion criteria were: confirmed pregnancy, informed consent to participate in the study. Exclusion criteria were multiple pregnancy, induced pregnancy, late first appearance in the antenatal clinic (after 25 weeks' gestation), change of residence and medical supervision during pregnancy, the presence of severe mental disorders, severe somatic diseases in decompensation stage, HIV infection, cancer, active tuberculosis. Study design complies with the legislation of the Russian Federation, international ethical standards and was approved by the Ethics Committee of the South Ural State Medical University. Prospective observation was conducted. All pregnancy complications were registered, in particular, preeclampsia, placental insufficiency (violation of utero-placental blood flow), the presence and severity of anemia during pregnancy, as well as outcomes: the duration and mode of delivery, fetal weight at birth. The criteria for the diagnosis of anemia during pregnancy were: decrease of hemoglobin levels below 110 g/l. All pregnant women with confirmed anemia were treated with iron supplements. After the completion of follow-up the odds ratios analysis of presenting anemia was performed in subgroups: 1) a patient gave birth to a live child, and patient with the loss of the fetus at various stages of gestation; 2) patients who have given birth in time, and patients with premature birth; 3) patients with placental insufficiency (violation of utero-placental blood flow) during pregnancy and patients without placental insufficiency; 4) patients with preeclampsia and patients without pre-eclampsia; 5) patients who have delivered live births weighing less than 2,500 grams and birth weight over 2500. In each case, odds ratios (ORs) and confidence intervals (95% CI) were calculated. Statistical calculations were performed using the software package SPSS 22.0.

RESULTS: Among all patients ($n = 421$) anemia of varying severity has been diagnosed in 190 (45.13%), including mild anemia in 161 (38.24%), moderate or severe anemia - in 29 patients (6.88%). In 16 (3.8%) cases, the pregnancy resulted in miscarriage or fetal death. Premature birth of live fetus before 34 weeks of gestation was recorded in 13 cases (3.2%; $n = 405$). Preeclampsia was diagnosed in 15 women (3.56%). Live births with weights less than 2,500 g were registered in 23 cases (5.67%; $n = 405$).

An analysis of odds ratios was performed to compare the groups of women with anemia of any severity and without anemia, with mild anemia compared with women without anemia, and moderate/severe anemia compared to women with mild anemia or without anemia.

According to our results, there was a statistically significant reduction in the chance of having anemia of any severity in patients whose pregnancy was completed by fetal loss. For mild anemia odds ratio in these subgroups was even lower. Thus, the odds of having mild anemia in the group of women who completed a pregnancy to a live birth, was 90.3%, which may indicate a protective role of mild anemia against the loss of the fetus.

In all other cases, statistically significant results were not received. Thus, we didn't receive significant positive association between anemia and development of preeclampsia, placental insufficiency during pregnancy, low birth weight and premature birth. There are other publications that show a protective role of anemia in pregnancy. Case control study [3] showed a protective role of anemia against the development of pre-eclampsia ($n = 636$, $p = 0{,}01$). In [4] anemia was a protective factor against stillbirth. There is evidence [6] of the higher risk of stillbirth in women with high hemoglobin level (146 g/l and above), while the link of the risk of stillbirth with anemia has not been confirmed ($n = 1404$).

CONCLUSIONS: Our data suggest a protective role of mild anemia during pregnancy in relation to pregnancy loss.

Keywords: Anemia, pregnancy, pregnancy loss, mild anemia, protective factor

Conflict of interest statement: None.

References

[1] Endeshaw M, Abebe F, Bedimo M. Diet and Pre-eclampsia: A Prospective Multicentre Case-Control Study in Ethiopia. Midwifery. 2015;31(6):617-24. doi: 10.1016/j.midw.2015.03.003. Epub 2015 Mar 10.
[2] Haider BA, Olofin I, Wang M, Spieqelman D, Ezzati M, Fawzi WW. Anemia, prenatal iron use, and risk of adverse pregnancy outcomes: Systematic review and meta-analysis. BMJ. 2013;346:f3443. doi: 10.1136/bmj.f3443
[3] Kashanian M, Baradaran HR, Bahasadri S, Alimohammadi R. Risk factors for pre-eclampsia: A study in Tehran, Iran. Arch Iran Med. 2011;14(6). P. 412-5.
[4] Stephansson O, Dickman PW, Johansson A, Cnattinquis S. Maternal hemoglobin concentration during pregnancy and risk of stillbirth. JAMA. 2000;284(20). P. 2611-7.
[5] van den Broek NR, Jean-Baptiste R, Neilson JP. Factors associated with preterm, early preterm and late preterm birth in Malawi. PLoS One. 2014;9(3):e90128. doi: 10.1371/journal.pone.0090128. eCollection 2014
[6] Zhang Q, Ananth CV, Rhoads GG, Li Z. The impact of maternal anemia on perinatal mortality: A population-based, prospective cohort study in China. Ann Epidemiol. 2009;19(11):793-9. doi: 10.1016/j.annepidem.2009.06.002. Epub 2009 Aug 3.

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Acute kidney injury in neonatal intensive care: Medicines involved

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BACKGROUND: The incidence of acute kidney injury (AKI) in neonates in the intensive care units and neonatal intensive care (NICU) according Plotz et al. ranges from 8% to 22% [3]. According to Andreoli, neonatal death due to AKI in NICU amounts up to 10–61% [1]. It should be in the reasons of AKI emphasize

The role of certain drugs, which are widely used in modern neonatology: nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (aminoglycosides, glycopeptides, carbapenems, 3rd generation cephalosporins), furosemide, enalapril, in contributing to AKI should be emphasized [2].

OBJECTIVE: To identify risk factors for acute kidney injury in neonates in intensive care units and intensive care.

METHODS: We performed a prospective observational case-control study of full-term newborns who were treated in the intensive care unit and neonatal intensive care of the "Children's city hospital №1" Kazan and NICU №3 "Children's Republican Clinical Hospital" in 2011–2014 years.

The study included 86 term infants in critical condition, who were hospitalized to the NICU on the first days of life, - the main group. The main criterion of AKI in neonates according to neonatal AKIN classification (2011) is a serum creatinine concentration ≥1.5 mg/dL. We subdivided the main group into two subgroups:

subgroup I, AKI+ consisted of 12 term infants in critical condition with the serum creatinine level ≥ 1,5 mg/dL at the age of not younger than 48 hours after birth, which was 14% of all full-term newborns who were at the NICU;

subgroup II, AKI- consisted of 74 term infants in critical condition with the serum creatinine level <1.5 mg/dL at the age of not younger than 48 hours after birth.

The control group was formed by random sampling, it consisted of 26 somatically healthy term infants. We used conventional methods for evaluating renal function, and enzyme immunoassay (ELISA) for the urine biomarker of AKI, IL-18.

Statistical analysis was performed using SPSS, Statistics 20, and the IBM and Microsoft Office Excel 2007. The study results were subjected to statistical analysis using parametric and non-parametric methods of analysis. We present the findings as arithmetic means (M) with, standard deviation (σ) and standard error of the mean (m) according to standard formulas.

RESULTS: All children were admitted to primary and emergency care with subsequent transfer to the NICU at 1-2 days of life and further treatment in the department of pathology of newborns (DPN). The duration of hospitalization of infants at the NICU for the main group averaged 5,9 ± 0,44 days; at the DPN (subsequent stage of nursing) - 11,42 ± 0,51 days; for the subgroup I, AKI+ newborns these

were 7,83 ± 1,23 days and 13,75 ± 3,34 days, respectively; for the subgroup II, AKI– newborns these were 5,58 ± 0,47 (3-30) and 11,04 ± 0,3 (0–47) days, respectively. Neonates received daily average of 16,5 ± 0,3 various medicines while at NICU and 9,1 ± 0,7 while at DPN. Overall, over the entire period of hospitalization neonates of the main group received on average 25,6 ± 1,8 medicines. Of these, 2,9 ± 0,4 drugs were antibiotics, possessing nephrotoxic properties (aminoglycosides, cephalosporins, carbapenems, fluoroquinolones). Children of the main group in 100% ($n=86$) of cases were treated with 3rd generation cephalosporins (ceftriaxone, cephaperazone/sulbactam (sulperazon)), in 55% od cases ($n=47$) – with aminoglycosides (amikacin, gentamicin), in 1% ($n=1$) – with vancomycin, in 7% ($n=6$) – with carbapenems. Diuretics were prescribed to 57% ($n=49$) of infants. Often, patients were treated with a combination of nephrotoxic medications. Aminoglycoside were prescribed statistically more often to neonates of the subgroup I, than of the subgroup II ($p<0.01$). Diuretic drugs were used more frequently and for longer periods of time in neonates of the subgroup I (AKI +), than in newborns of the subgroup II (AKI–), namely, in 83% ($n=10$) for 4,6 ± 1.34 days versus 53% of cases ($n=39$) for 2.84 ± 0.49 days, respectively ($p<0.05$). IL-18 urine level in neonates of subgroup I (AKI +) was 2 times higher than that in neonates of the subgroup II (AKI–), and 13 times higher than in neonates of the control group.

The fact that the IL-18 urine level increased with progression of kidney damage, caused by nephrotoxic therapy, suggests that a significant role in the development and progression of AKI in neonates at NICU belongs to drug therapy.

CONCLUSIONS: Full-term newborns in intensive care units are at high risk of AKI when they are treated with aminoglycosides in combination with diuretics for longer than 4.5 days.

Keywords: Risk factor, acute kidney injury, neonates, intensive care

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References

[1] Andreoli SP. Acute renal failure in the newborn. Semin Perinatol. 2004;28 (2): 112-3. doi:10.1053/j.semperi.2003.11.003
[2] Morgan CJ, Zappitelli M, Robertson CM et al. Risk factors for and outcomes of acute kidney injury in neonates undergoing complex cardiac surgery. J Pediatr. 2013;162(1):120-7.e1. doi: 10.1016/j.jpeds.2012.06.054. Epub 2012 Aug 9.
[3] Plotz FB, Bouma AB, van Wijk JA, Kneyber MC, Bokenkamp A. Pediatric acute kidney injury in the ICU: An independent evaluation of pRIFLE criteria. Intensive Care Med. 2008;34(9):1713-7. doi: 10.1007/s00134-008-1176-7. Epub 2008 Jun 3.

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Pharmacists' knowledge of the safety of antibiotics for systemic use

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BACKGROUND: Patients decide to take antibiotics themselves in 21% of cases of acute respiratory viral infections, influenza and acute respiratory infections [1]. The main factor of drug purchase at a pharmacy is pharmacist's recommendation. In 14% of cases of purchase of antibiotics, patients describe the symptoms and do not name a specific drug. This provides opportunity for drug selection at a pharmacy [2]. In these circumstances the role of pharmacists in ensuring the rational use of antimicrobial agents increases significantly.

OBJECTIVE: To evaluate the knowledge of pharmacists about antibiotics for systemic use.

METHODS: Pharmacoepidemiological study was based on surveying pharmaceutical workers using a questionnaire. The questionnaire included 2 groups of questions: general questions aimed at identifying the socio-demographic characteristics of respondents (gender, age) and professional status (level of qualification, work experience), as well as specific questions aimed at identifying perceptions and knowledge of respondents about the studied group of drugs (range of used drugs, the factors determining and limiting the choice of drug, properties of individual drugs, etc.). The study involved 182 pharmaceutical workers at the age of 20 to 52 years. When processing the received data, we used Microsoft Excel and BioStat, and methods of nonparametric statistics (χ^2-test). The survey was conducted anonymously, informed consent of the participants was not required. According to the recommendations of Ethical Committee of Saratov State Medical University n.a. V.I. Razumovsky (protocol No. 8 from 01.04.2014) the study is consistent with the basics of medical ethics.

RESULTS: Interviewed pharmaceutical workers were mostly women (97%) with secondary pharmaceutical education (84%). The average age of the respondents was 27.0±0.5 years. The work experience of the respondents ranged from 0.5 to 34 years (average experience 5.64±0.41 years).

Almost all pharmacists (97%) reported that they dispense antimicrobial drugs every day and consult patients about the choice and characteristics of antibiotic (99.5%). However, only 20% of the respondents indicated that they refuse to recommend antibiotics to the pharmacy visitors and send them to the doctor. Most often pharmaceutical employees recommended azithromycin (45%), amoxicillin in combination with clavulanic acid (41%), amoxicillin (26%). According to respondents, the choice of recommended antibiotic mostly depends (score on a scale of 1–5) on pharmacological characteristics of the drug: the effectiveness (of 4.66±0.04) and safety (4.16±0.07). Thus, pharmaceutical specialist should be knowledgeable about characteristics of antimicrobial agents to conduct proper consultation.

According to the results of self-assessment of respondents' knowledge about antibiotics it is at an average level. 36.3% of respondents state that they are familiar with the range and features of most of the drugs. 41.8% of professionals are familiar with the range of the most popular drugs and their

main features. Only 16.5% of respondents assess their knowledge about antibiotics at the highest level, indicating that they are fully familiar with the range and features of the drugs.

Aiming at identifying knowledge about the side effects of antibiotics pharmacists were asked to compare the most commonly prescribed drugs and their respective side effects, to position the drugs and groups of drugs in the range according to the degree of toxicity and to indicate which antibiotics can be used during pregnancy. Knowledge of pharmaceutical workers is mainly limited to the perceptions of non-specific side reactions that can occur when taking any antibiotic (dyspepsia, allergic reactions, headache, candidiasis). 54.9% of respondents rightly pointed out nonspecific reactions for all 7 mentioned drug, for individual drugs the proportion of correct answers varied from 65,4% (linezolid) to 81,3% (amoxicillin+clavulanic acid). The analysis revealed no relationship between respondents' answers and their qualifications ($\chi^2 = 0{,}053$; $p = 0{,}818$), work experience ($\chi^2 = 6{,}956$; $p = 0{,}096$) and self-assessed knowledge about antimicrobial drugs ($\chi^2 = 1{,}272$; $p = 1{,}000$). There were no respondents who correctly reported specific adverse reactions (hearing disorder for azithromycin, hemopoiesis oppression for linezolid, etc.) for each antibiotic. The proportion of correct answers ranged from 6,0% for the combination amoxicillin+clavulanic acid to 43,4% for cefixime and doxycycline. The relationship between knowledge of respondents and frequency of recommendations of the same group of drugs could not be determined.

Pharmacists assume that the safest antibiotics are macrolides (average rank place of $2{,}99 \pm 0{,}15$ of 8), cephalosporins ($3{,}12 \pm 0{,}15$) and penicillins ($3{,}38 \pm 0{,}22$), the most toxic are tetracyclines ($5{,}61 \pm 0{,}17$). It should be noted that average rank places are quite similar, which means serious differences of opinion between the specialists. When assessing the toxicity of individual drugs a combination of amoxicillin+clavulanic acid (average rank place of $2{,}92 \pm 0{,}29$ of 15) and ampicillin (of $4{,}88 \pm 0{,}36$) were considered as the safest, the most toxic were tetracycline ($10{,}13 \pm 0{,}30$) and gentamicin ($10{,}14 \pm 0{,}33$). These perceptions are generally consistent with the views on the safety of antibiotics in outpatient practice [3].

Half of the respondents (51,1%) correctly identified the antibiotics that can be used during pregnancy (FDA category B). 45,1% of respondents said that no antibiotics can be used during pregnancy. Only 2,7% of respondents named drugs contraindicated during pregnancy (category C and D) – gentamicin, doxycycline, ciprofloxacin.

CONCLUSIONS: The study identified gaps in the knowledge of pharmacists about the safety of antimicrobial agents. Views of professionals about antibiotics are mostly consistent with current data about the properties of drugs. However, detailed analysis shows that such views are not supported by clear knowledge of the properties of each drug and are mostly intuitive. In terms of the prevalence of self-medication with antibiotics and OTC dispensing of antimicrobial drugs it is necessary to improve the professional knowledge of pharmaceutical workers on antibiotics for systemic use.

Keywords: Antibiotics, safety, knowledge, pharmacists, pharmacoepidemiology

Conflict of interest statement: There was no conflict of interests.

References

[1] How do the Russians care about their health? [Internet]. Profi Online Research; 2009 [updated 20 Feb 2009; cited 27 Aug 2015]. Available from: http://profiresearch.ru/files/pr200209.pdf
[2] Increasing role of pharmacist in drug consumers' choice [Internet]. Synovate Comcon Healthcare; 2014 [updated 27 Aug 2015; cited 27 Aug 2015]. Available from: http://www.synovate.ru/default.asp?artID=2955
[3] Stetsiouk OU, Andreeva IV, Kolosov AV, Kozlov RS. Safety and Efficacy of Antibiotics Used in Outpatient Setting. Clinincal Microbiology and Antimicrobial Chemotherapy. 2011;13(1):67-84

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Antimicrobial use at a multi-disciplinary hospital

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BACKGROUND: The problem of antimicrobial resistance has become topical and alarming all over the world, including Kazakhstan. Nosocomial strains of microorganisms are widespread, being resistant to the majority of available antimicrobials. This results in longer periods of hospital stay, increases in financial expenditures, and sometimes, in lethal outcomes. The social importance of antimicrobial resistance is preconditioned by the spread of resilient strains of microorganism beyond the hospital environment, which leads to lower effectiveness of antibiotic therapy against infectious diseases and growth in their incidence [1, 2].

Our in-patient health facility is a multifunctional one. It provides therapeutic, surgical and oncology and hematology care including organ transplantation. Measures to reduce antibiotic resistance are very important.

OBJECTIVE: To develop a standardized approach to the use of antimicrobial drugs aimed at reducing of antimicrobial resistance, postoperative complications and mortality rates along with financial expenditures. The expected result of this approach should be the enhancement of quality of care.

METHODS: In September 2014 we developed and introduced a local protocol of the antimicrobials use, namely antibiotics for surgical prophylaxis and treatment, based on the evidence of international clinical guidelines evidence-based medicine approach, taking into account the microbial landscape and antibiotic resistance patterns to major pathogens: *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae* [3]. We planned to assess the effectiveness of this policy by the following criteria: the percentage of post-surgical sequela, the number of bed days, the percentage of resistant cases and antibiotic expenditures. In order to improve the quality of bacteriological studies, together with microbiologists we trained the medical staff on the methods of obtaining of biological material for microbiological testing.

RESULTS: We analyzed the indicators of antibiotic resistance from October 2014 to March 2015 (hereafter period I) on the basis of the data from the microbiological laboratory with data of April–August 2015 (hereafter period II). The analysis on the basis of other criteria has yet to be carried out. The biomaterial was obtained from different loci, including blood. The results of the oncology and hematology were analyzed separately. We received the following results of sensitivity of the listed microorganisms to various antimicrobials in the period I and the period II respectively expressed as percentages:

Staphylococcus aureus: Oxacillin – 95% and 100%, Azythromycin – 62% and 100%, Vancomycin – 100% and 100%, Levofloxacin/Moxifloxacin – 100% and 100%.

Pseudomonas aeruginosa: Ceftazidime – 34% and 67%, Piperacillin/Tazobactam – 91% and 84%, Cefepime – 59% and 81%, Amikacin – 95% and 100%, Meropenem – 100% and 100%, Ciprofloxacin – 97% and 100%.

Escherichia coli: Gentamicin – 93% and 96%, Piperacillin/Tazobactam – 86% and 92%, Ceftriaxone – 82% and 100%, Amikacin – 99% and 100%, Ciprofloxacin – 69% and 80%, Amoxycillin/Clavulanate – 44% and 46% respectively.

Klebsiella pneumoniae: Gentamicin – 50% and 100%, Piperacillin/Tazobactam – 95% and 100%, Cefepime – 100% and 100%, Ceftriaxone – 96% and 100%, Amikacin – 99% and 100%, Ciprofloxacin – 100% and 100%, Amoxycillin/Clavulanate – 22% and 23%.

Acinetobacter baumannii: Gentamicin – 83% and 83%, Piperacillin/Tazobactam – 33% and 58%, Cefepime – 0% and 33%, Ceftriaxone – 0% and 33%, Amikacin – 50% and 83%, Ciprofloxacin – 83% and 67%, Meropenem/Imipenem-Cilastin – 83% and 83%.

CONCLUSIONS: During the analyzed periods we observed some improvement in the sensitivity of the main pathogens to antibiotics. At the same time, the resistance of Acinetobacter *baumannii* to carbapenems and fluoroquinolones increased.

Limitations of the study: There are many other than antibiotic use factors, which influence these results. Further analysis is planned to be carried out. Nevertheless, this analysis makes us believe that we are, probably, on the right path for improving the use of antibacterial drugs.

Keywords: Antimicrobial, antibiotic, use, hospital, resistance

Conflict of interest statement: None.

References

[1] Antibiotic resistance – the need for global solutions. The Lancet Infectious Diseases Commission. 2013;13(12): 1057–98. doi: http://dx.doi.org/10.1016/S1473-3099(13)70318-9
[2] WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health. [Internet] 2014 April 30 [cited 2014 April 30]. Available from: http://www.who.int/mediacentre/news/releases/2014/amr-report/en/
[3] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283. doi: 10.2146/ajhp120568

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ABCB1 polymorphism and acenocoumarol safety in patients with valvular atrial fibrillation

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BACKGROUND: Oral anticoagulant drugs (AD) are commonly used to treat patients with thromboembolic diseases. The ADs have narrow therapeutic index and wide pharmacokinetic and pharmacodynamic interindividual variability. Some genetic variations could influence interindividual variability in response to AD. Acenocoumarol (AC) is a coumarin, vitamin K derivate with antagonistic activity, used as anticoagulant therapy mainly in Central Europe and Latin America. P – glycoprotein (PGP), a transporter encoded by the ABCB1 gene, plays a major role in the drug disposition [1]. PGP is expressed in normal tissues, where it performs a defensive role against potentially toxic substances in intestinal cells and endothelial cells of the brain capillary endothelium. ABCB1 – is highly polymorphic, C3435T polymorphism in exon 26 has been associated with the expression of PGP [2]. There is some evidence that PGP could influence coumarin sensitivity.

OBJECTIVE: To assess effects of the ABCB1 pilymorphisms on safety profile and dosing regimen of acenocoumarol in the patients with valvular atrial fibrillation.

METHODS: 50 patients (34 male and 16 female), 40–70 years of age were included. All patients received acenocoumarol at doses of 1–6 mg daily with a target international normalized ratio (INR) of 2.0 to 3.0. Genotyping for polymorphism marker C3435T of ABCB1 gen was performed using PCR and RFLP (restriction fragment length polymorphisms) techniques. Statistics were performed by Fishers exact tests. All enrolled patients provided written informed consent.

RESULTS: Genotype CC was found in 10 patients (20%), genotype CT in 25 patients (50%) and genotype TT in 15 patients (30%). In the CC group ($n=10$) bleeding was found in 1 patient (2%). There were 19 patients (38%) with bleedings in combined group of CT and TT genotype ($p=0.0366$). We compared the average doses of acenocoumarol in groups identified according to their genotypes: CC (3.45 mg/day), CT (2.64 mg/day), TT (3.07 mg/day) and found no significant differences.

CONCLUSIONS: ABCB1 CT and TT genotypes were found to be significantly associated with higher risk of bleeding. There was no influence of ABCB1 polymorphisms on dosing regimens of acenocoumarol.

Conflict of interest statement: The authors report no conflicts of interest.

Keywords: ABCB1 polymorphism, acenocoumarol, safety, valvular atrial fibrillation, bleeding

References

[1] Ling V. Multidrug resistance: Molecular mechanisms and clinical relevance. Cancer Chemotherapy and Pharmacology 1997 Vol 40(Is.1):S3-S8. doi: 10.1007/s002800051053
[2] Hoffmeyer S, Burk O, von Richter O. Functional polymorphisms of the human multidrug – resistance gene: Multiple sequence variations and correlation of one allele with P – glycoprotein expressions activity in vivo. Proc Natl Acad Sci USA 2000;97(7):3473-8. doi:10.1073/pnas.050585397
[3] De Oliveire Almeida VC, Ribeiro DD, Gomes KB, Godard AL. Polymorphisms of CYP2C9, VKORC1, MDR1, APOE and UGT1A1 genes and the therapeutic warfarin dose in Brazilian patients with thrombosis: a prospective cohort study. Mol Diagn Ther. 2014;18(6):675-83. doi: 10.1007/s40291-014-0121-4

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VKORC1 polymorphisms and warfarin maintenance dose in population of Sakha (Yakuts)

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BACKGROUND: Vitamin K antagonists are effective in the prevention and treatment of thromboembolic disorders. Warfarin is one of the most widely prescribed vitamin K antagonists in the world [1, 2]. It has a narrow therapeutic range and a given dose may result in a large inter-individual variation of response. Insufficient dose may fail to prevent thromboembolism, while an overdose increases the risk of bleeding. Patient-specific factors (e.g., age, body size, race, concurrent diseases, and medications) explain some of the variability in warfarin dosage, but genetic factors influencing warfarin response explain a significantly higher proportion of this variability [3]. Molecular analysis of the gene that encodes the target enzyme vitamin K epoxide reductase complex 1 (*VKORC1*) strongly suggests that its genetic variations greatly affect the individual response to oral anticoagulants [4–7].

OBJECTIVE: To evaluate effects of VKORC1 polymorphisms on warfarin dose excess anticoagulation (INR >4.0) in the population of Sakha (S) patients.

METHODS: 53 patients (29-women, 24-men) with atrial fibrillation (68%), congestive heart failure (60%), hypertension (49%) and cardiac valve replacement (26%) were recruited. The age range was 26–80 years, with a mean age of 62.87 ± 12.57 years.

International normalized ratio and plasma warfarin concentrations were determined. Genotyping was carried out by RT-PCR (real-time PCR). The three genetic polymorphisms of the gene *VKORC1* G3673A (rs9923231) were studied: normal *(GG)*, heterozygous *(GA)* and homozygous *(AA)*. Fisher exact probability test and chi-square test (with Yates correction) were applied to compare data among the *AA* and *GG* + *GA* groups; also Mann-Whitney test was used.

RESULTS: The median maintenance daily dose of warfarin among *AA* carriers was 3.0 mg/day [1.25–7.5 mg], while in *GG* and *GA* patients it was 3.13 mg/day [1.88–7.92 mg]. The mean daily warfarin dosage was higher in *GG* and *GA* genotype carriers 4.05 mg/day (SD ± 1.7) than in patients with *AA* genotype 3.13 (SD ± 1.5). Differences are of borderline significance ($p = 0.054$).

Of the 41 patients who required warfarin doses of less than 5 mg, 28 (63%) were found to be *AA* carriers and 14 (37%) were GG, GA carriers. Differences were not quite significant ($p = 0.072$). Among 31 homozygous polymorphism carriers 2 (4%) patients developed overanticoagulation (INR >4.0), while among 22 normal and heterozygous polymorphisms carriers only 3 (6%) patients developed overanticoagulation (INR >4.0). Differences were not statistically significant ($p = 0.36$).

CONCLUSIONS: No significant association between *VKORC1* polymorphisms and the frequency of excess anticoagulation (INR >4.0) was found. This may be explained by the number of cases included. *AA* polymorphisms compared to other polymorphisms shows borderline difference in the warfarin dose. The results can be used for the development of a pharmacogenetic-guided warfarin dosing algorithm.

Keywords: Polymorphisms of the VKORC1 gene on maintenance warfarin dose in the population of sakha (yakuts)

Conflict of interest statement: None.

References

[1] Gage BF. Pharmacogenetics-based coumarin therapy. Hematology Am Soc Hematol Educ Program. 2006:67–473. doi: 10.1182/asheducation-2006.1.467
[2] Lee JS, Cheong HS, Kim LH, Kim JO, Seo DW, Kim YH, et al. Screening of Genetic Polymorphisms of CYP3A4 and CYP3A5 Genes. Korean J Physiol Pharmacol. 2013;17(6): 479–84. doi: 10.4196/kjpp.2013.17.6.479
[3] Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: Current status and future challenges. Pharmacogenomics J. 2007;7(2):99–111. doi:10.1038/sj.tpj.6500417.
[4] Wiwanitkit V. Pharmacogenomic effect of cytochrome P450 2C9 polymorphisms in different populations.Clin Appl Thromb Hemost. 2006;12:219–22. doi: 10.1177/107602960601200211
[5] D'Andrea G, D'Ambrosio R, Margaglione M. Oral anticoagulants: Pharmacogenetics. Relationship between genetic and non-genetic factors. Blood Rev. 2008;22:127–40. doi: 10.1016/j.blre.2007.11.004
[6] Mlynarsky L, Bejarano-Achache I, Muszkat M, Caraco Y. Factor VII R353Q genetic polymorphism is associated with altered warfarin sensitivity among CYP2C9 *1/*1 carriers. Eur J Clin Pharmacol. 2012;68:617–27. doi: 10.1007/s00228-011-1143-z
[7] Yin T, Miyata T. Warfarin dose and the pharmacogenomics of CYP2C9 and VKORC1 - rationale and perspectives. Thromb Res. 2007;120:1–10. doi: http://dx.doi.org/10.1016/j.thromres.2006.10.021

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Congenital anomalies in Primorsky region

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BACKGROUND: According to WHO hereditary diseases and congenital malformations contribute significantly to the health of population. Thus, the problems of epidemiology, clinical presentation, diagnosis and treatment of congenital abnormalities are of interest for many researchers [2]. In addition, the dynamic accounting for the incidence of congenital malformations and hereditary diseases allows the researchers to assess the ecological situation in the region [1]. The occurrence of congenital anomalies in the world varies; it depends heavily on how carefully the data is collected [4]. Multifactorial or polygenic diseases develop under the influence of environmental factors in the presence of defective genes. They can constitute up to 90% of all chronic pathology [2–5].

OBJECTIVE: To determine the incidence of congenital anomalies under the influence of environmental factors.

METHODS: The study used the methodology of system evaluation of congenital anomalies incidence in Primorsky region, depending on bio-climatic and environmental conditions. The authors used health statistics for the period from 2000 to 2014, F.12 class for congenital abnormalities in adolescents and children that were compared in geographical and temporal aspects with environmental factors of 33 settlements in Primorsky region. The environment is represented by nature and climate (6 factor modules) and sanitation (7 factor modules) blocks of factors. When formalizing the information database of the environment a specially developed 10-point assessment scale was used. Statistical processing of the information was carried out using Pearson's chi-squared test and multiple regression method from SSPS application program package.

RESULTS: The study found that over the 15-year period the level of congenital abnormalities in children increased by 27.5% and in adolescents – by 35.1%, and in 2014 it amounted to 1687.6 and 839.3 per 100 000 people, respectively. The predictive model shows a steady further growth of this pathology. The incidence has increased dramatically since 2000. This was due to the beginning of activities of medicogenetic service since 1998: the legal framework and information database were created, the flow of pregnant women was formed actively, and invasive prenatal diagnosis was introduced.

Incidence of congenital anomalies has a reliable statistical association (chi-square) with bioclimatic zones and ecological situation. The high level of pathology is observed in both teenagers and children in the critical environmental situation areas, where there are enterprises of coal, mining and chemical industry, ship repair, construction, engineering sites, and areas with intensive chemical use and improvement of agriculture. For the most part these are cities and districts of the region where more than a half of the major manufacturing plants of the 1st and 2nd hazard classes are located. Exceeding the maximum allowable concentrations (MAC) of harmful substances in the air, soil, and water in these areas

often reaches tenfold. It should be noted that in the territories with the critical environmental situation a relatively high level of malformations is observed in adolescents in the continental bioclimatic zone, and in children – on the coast, suggesting the influence of different climatic factors. Also a high level of the same congenital anomalies was revealed in children in bioclimatic zones of the coast and transition zones with the intense environmental situation.

According to the results of the regression analysis, the varying degrees of influence of ecological and hygienic factors on the incidence of congenital anomalies were determined. In children, up to 77.3% of the spread of pathology depends on the complex of parameters of the environment; the proportion of the influence of sanitary and hygienic indicators is 63.1%, and natural and climatic indicators - 14.2%. Such factors as the characteristics of the soil condition, the level of air pollution, chemical pollution and adverse physical factors in urban and rural settlements, transport load, the presence of hazard-class companies, and observance of sanitary protection zones are of the most significance. The influence of a complex of ecological and hygienic factors on the incidence of pathology in adolescents was 60.0%. The contribution of sanitary and hygienic parameters was 44.5%, and natural and climatic ones - 15.5%. Chemical pollution and adverse physical factors in urban and rural areas, the level of air pollution, traffic loads, and condition of the soil influence the most. Assessing the results of the analysis one should note that the incidence of congenital abnormalities in both children and adolescents depends largely on the same modular sanitary factors, but with varying degrees of influence. At the same time the natural and climatic block of factors has almost the same degree of influence in these age groups.

CONCLUSIONS: A significant increase of congenital anomalies in children and adolescents is registered in Primorsky Region, and the same is projected for the next 5 years.

– The incidence of congenital anomalies in the region depends on bioclimatic zones and ecological situation. The highest level of pathology is observed in children in the coastal bioclimatic zone, and in adolescents, in the continental bioclimatic zone in areas with critical environmental situation.

– Varied degree of influence on the level of congenital anomalies by a complex of sanitary and climatic factors is determined. The leading role (44.5–63.1%) belongs to sanitary and hygienic parameters of the life environment.

– The results obtained make it possible to develop a set of organizational, diagnostic and treatment, and preventive measures for the correction of health of the population.

Keywords: Congenital, malformations, anomalies, hereditary diseases, population, children, adolescents

References

[1] Baranov VS. Ecological genetics. 2003. No.1. pp 22-29. Russian
[2] Hereditary diseases control: Trans. from English. Report of WHO Scientific Group. WHO Technical Report Series. - M.: Medicine, 2007. No. 865. 134 p. Russian
[3] Bochkov N.P. Clinical genetics. M.: GEOTAR-MED. 2004. 480 p. Russian
[4] Forfar JO. Campbell AGM, McIntosh N, eds. Forfar and Arniel's textbook of pediatrics,4th/Ed. Edinburgh, Churchill livingstone. 2010. pp. 24-27.
[5] Rimoins DL, Connor MJ, Pyeritz RE. Emery and Rimoin's Principles and Practice of Medical Genetics. London, N.-Y., Toronto: Churchill Livingstone. 2012. 122 p.

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Patients in need of medicine information

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BACKGROUNDS: Reliable medicine information is important not only for physicians and pharmacists, but also for patients [6]. However, the results of studies implemented in some countries show that patients may have slightly different needs and preferences in using sources of information [1, 4, 5, 7]. The main objective of patient medicines information is assisting consumers to achieve safe and effective use of pharmaceuticals [2, 3].

OBJECTIVE: To identify patients' needs in medicine information and sources they use to receive it.

METHODS: We interviewed 1059 people who had visited community pharmacies in 10 regions of Armenia and Yerevan. Previously developed questionnaire was used for interviewing patients. Statistical analysis was conducted using SPSS program.

RESULTS: We found that consumers need medicine information. 68.9% of respondents often use pharmaceuticals only if necessary medicines information is available. The majority of them believe that it is important to have information about therapeutic indications of pharmaceuticals to be used (91.8%), their dosage and method of administration (91.1%), contraindications (82.4%), adverse reactions (81.9%) and the simultaneous use of multiple medicines (76.5%). 58.9% of consumers value information about medicine's price. More than 70% of patients often seek information from health professionals and use medicines package information leaflets (PIL), and more than 75% of respondents mainly trust the same sources. 71.5% of respondents read package leaflets, while 42.0% of consumers do this several times. Only 36.7% of respondents completely understand information in a leaflet.

CONCLUSIONS: Patients in Armenia need medicine information. They prefer to receive information from sources they trust.

Many patients do not understand the content of package information leaflets (PILs) due to barriers, which can be removed by introducing appropriate regulatory provisions for their content and readability.

Keywords: Patient information leaflet, medicine, information, patient, consumer

References

[1] Dickinson D, Raynor TDK, Kennedy JG, Bonaccorso S, Sturchio JL. What information do patients need about medicines? BMJ. 2003;327:861-64
[2] EFPIA Position on shortcomings of the Summary of Product Characteristics and the Package Leaflet, and Proposals to Resolve Them. Position paper. European Federation of Pharmaceutical Industries and Associations, Brussels, 2014, 5 p.
[3] FIP Statement of policy medicines information for patients. International Pharmaceutical Federation, The Netherlands, 2008, 4 p.

[4] Fuchs J., Hippius M., Schaefer M. A survey of package inserts use by patients. Hospital Pharmacy Europe 2005;7-8;29-31.
[5] Ho C.H., Ko Y., Tan M.L. Patients and sources of drug information in Singapore: Is the Internet replacing former sources? Ann Pharmacother 2009;43(4):732-39.
[6] Jeetu G., Girish T. Prescription Drug Labeling Medication Errors: A Big Deal for Pharmacists. J Young Pharm 2010; 2(1):107-111.
[7] Nair K., Dolovich L., Cassels A., McCormack J., Levine M., Gray J., Mann K., Burns S. What patients want to know about their medications. Canadian Family Physician 2002;1(48):104-10.

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CYP3A4 activity and haloperidol effects in alcohol addicts

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BACKGROUND: Haloperidol is one of the most commonly used typical antipsychotics [2]. It has a powerful antipsychotic activity blocking mesolimbic postsynaptic dopamine receptors. Unwanted adverse effects accompany the use of haloperidol. Therefore alcohol abusers' attitudes towards haloperidol are ambiguous and often negative, which sometimes limits it's use in patients with addictive disorders [3]. Cytosolic carbonyl reductase reduces haloperidol to reduced form, which has 10–20% of the activity of the parent molecule. It is further metabolized by CYP3A4 to a tetrahydropyridine and then conjugated by glucuronidation and sulphation. Reduced haloperidol is back-oxidized to haloperidol by CYP3A4 and CYP2D6. Haloperidol is N-dealkylated by CYP3A4 and CYP2D6 to 4-chlorophenyl-4-hydroxypiperidine and p-fluorobenzoyl propionic acid. The correlation between CYP2D6 and CYP3A4 activity and the rate of biotransformation of haloperidol was demonstrated in a number of studies on patients with schizophrenia [1, 2, 5]. At the same time other studies deny or disaffirm this correlation [4].

OBJECTIVE: To estimate the correlation between CYP3A4 isoenzyme activity and the efficacy and safety of haloperidol in patients with alcohol abuse during the exacerbation of the addiction.

METHODS: The study involved 15 men, alcohol abusers, in exacerbation of their addiction, who were hospitalized in Moscow Research and Practical Centre for Narcology of the Departament of Public Health. All 15 patients received haloperidol in tablets and injections. Determination of CYP3A4 activity was performed using high performance liquid chromatography with mass spectrometry (HPLC/ MS) by determination of endogenous substrate of this isoenzyme and its metabolite in urine - the ratio: cortisol/6-beta–hydroxycortisol. We used international psychometric scales to assess efficacy of haloperidol (the scale of determining the severity of addiction of The National Research Center on Addictions of the Ministry of Health Of Russia, Hamilton Anxiety Research Scale (HARS)). The safety of haloperidol was estimated by the UKU Side-Effect Rating Scale. Scales express the clinical picture of the abuse. The higher the score, the more pronounced the addiction is. Calculating the differences in scores of the scales allowed for clinical assessment of haloperidol effects. The larger the difference in scores was, the more pronounced were the changes in clinical picture of abuse, and the higher the efficacy of therapy was assumed. Statistical analysis of the results of the study was performed by non-parametric statistics by the program STATISTICA v10.0 («StatSoft Inc.», USA). The normality of sample distribution was estimated by Shapiro-Wilk's W-test, and the homogeneity of dispersion, that was estimated by Fisher's

T-test (in case of comparison of two samples). The differences were evaluated as significant in case of $p<0,05$ (statistic power >80%). To determine the correlation between the quantitative characteristics Spearman rank R coefficient was calculated. The value of correlation coefficient r from 0,3 to 0,7 ($p<0,05$) indicated positive moderate, but significant correlation between the characteristics, $r>0,7$ ($p<0,05$) – strong and significant correlation, negative value of r indicated inverse correlation.

RESULTS: Data analysis demonstrated a correlation between the activity of isoenzyme CYP3A4 and the scores of pathological addiction ($r_1=–0,36$), HARS ($r_2=–0,45$), UKU Side-Effect Rating Scale ($r_3 = –0.15$) in the entire group ($p<0.05$). In a group of patients, who received the higher doses of haloperidol (more than 7.5 mg per day in tablets or 5 mg per day in injections), the following results were received in the same groups of data: $r_1=–0.68$, $r_2=–0.71$, $r_3=–0.76$ ($p<0.05$).

CONCLUSION: The results demonstrate the correlation between CYP3A4 activities and the efficacy and safety of haloperidol in alcohol abusers during the exacerbation of the addiction. The inverse correlation indicates that the higher the activity of CYP3A4 is, the lower the efficacy of haloperidol is. Also it can be assumed that the presence of strong correlation between the activity of CYP3A4 and the efficacy of haloperidol in group of patients, who received higher doses of haloperidol, may indicate that CYP3A4 is involved in haloperidol metabolism when it is used at higher doses.

Limitations of the study: It should be noted that in this research the activity of CYP3A4 was determined using high performance liquid chromatography with mass spectrometry (HPLC/MS) by determination the ratio of cortisol/6-beta–hydroxycortisol for the fist time. To increase the level of our confidence in the results further studies with a larger number of people are necessary.

Keywords: Haloperidol, biotransformation, CYP3A4, ABCB1, side effects, alcohol abuse

Conflict of interest statement: None.

References

[1] Butwicka A1, Krystyna S, Retka W, Wolańczyk T. Neuroleptic malignant syndrome in an adolescent with CYP2D6 deficiency. Eur J Pediatr. 2014;173(12):1639-42. doi: 10.1007/s00431-013-2208-z. Epub 2013 Nov 20.
[2] Gasso P, Papagianni K, Bobadilla RF, Arnaiz JA, Bernardo M, Lafuente A. Relationship between CYP2D6 genotype and haloperidol pharmacokinetics and extrapyramidal symptoms in healthy volunteers. Pharmacogenomics. 2013;14(13):1551-63. doi: 10.2217/pgs.13.150
[3] Ju.P. Sivolap, Rational approaches to the use of antipsychotic drug treatment in practice. "Zdorovaja Ukraina" 7/1, 2008, p. 83-84 (in Russian).
[4] Nakamura A1, Mihara K, Ne moto K, Nagai G, Kagawa S, Suzuki T, Kondo T. Lack of correlation between the steady-state plasma concentrations of aripiprazole and haloperidol in Japanese patients with schizophrenia. Ther Drug Monit. 2014;36(6):815-8.
[5] Van der Weide K1, van der Weide J. The Influence of the CYP3A4*22 Polymorphism and CYP2D6 Polymorphisms on Serum Concentrations of Aripiprazole, Haloperidol.-

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Pharmacogenetic testing in population of South Ural

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BACKGROUND: Drug resistance is a phenomenon that has received serious attention in recent years in everyday medical practice. This may also be described as responsiveness or non-responsiveness to drugs, as patients respond partially to medical treatment or have no response at all [1]. The non-responsiveness to clopidogrel in cardiac patients of different populations is due to genetic variations in the cytochrome P450 (CYP) gene [2]. Carriers of at least one 'poor metabolizer allele' of CYP2C19 (either *2 or *3) have lower levels of the active metabolite of clopidogrel and have reduced platelet inhibition [3]. Furthermore, the significant inter-ethnic variability in the allelic frequencies of CYP2C19*2 has been associated with differential clopidogrel resistance [4]. Such mutations in this variant allele are responsible for the inability of the CYP enzyme to convert clopidogrel into its active metabolite, which may result in the increased risk of death, heart attack or stroke among patients who have undergone percutaneous coronary intervention (PCI) [5]. South Ural is a multinational region, a subject of the Russian Federation, where genetic variations have not been studied fully yet.

OBJECTIVE: To examine prevalence of mutant alleles in population of South Ural.

METHODS: We conducted pharmacogenetic testing for specific single nucleotide polymorphisms in 54 patients. The present research was conducted in the alleles CYP2C19*2 and CYP2C19*3. The data were processed using the program SPSS Statistics.

RESULTS: The mean age of patients was 58, 4 years (from 26 to 79 years). Among all patients 59.3% were male, 40.7% of female patients.

Among the studied patients in allele CYP2C19*2, the "wild" type GG was detected in 75,9% of patients, GA type in 22.2% and AA variant was detected in 1.9% of all patients. Allele CYP2C19*3 is often found among alleles with reduced function and also associated with resistance to clopidogrel. Functional drug response is observed in patients with type GG. All of the studied patients were carriers of this type. According to literature data the frequency of genotypes associated with resistance to clopidogrel in the Russian population is 11.4%, which is comparable with European ethnic groups [6].

CONCLUSIONS: It was revealed that 75,9% of patients were sensitive to clopidogrel, and for them this drug in its standard dosage will be effective, and 24,1% of patients were not sensitive, therefore, they would require replacement of clopidogrel with another drug.

Keywords: Clopidogrel, pharmacogenetic testing, CYP, single nucleotide polimorphism

Conflict of interest statement: None.

References

[1] Ding Z, Kim S, Dorsam RT, Jin J, Kunapuli SP. Inactivation of the human P2Y12 receptor by thiol reagents requires interaction with both extracellular cysteine residues, Cys17 and Cys270. Blood. 2003;101(10):3908-14. doi: http://dx.doi.org/10.1182/blood-2002-10-3027. Epub 2003 Jan 30.

[2] Sibbing, D., Stegherr, J., Latz, W., Koch, W., Mehilli, J., Dorrler, K., Morath, T., Schomig, A., Kastrati, A. and von Beckerath, N. (2008). Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J. 2009;30(8):916-22. doi: 10.1093/eurheartj/ehp041. Epub 2009 Feb 4.

[3] Ferreiro JL, Angiolillo DJ. Clopidogrel response variability: Current status and future directions. Thromb Haemost. 2009;102(1):7-14. doi: 10.1160/TH09-03-0185.

[4] Chan M. Clopidogrel pharmacogenetics of east, south and other Asian populations. European Heart Journal Supplements. 2012. 14(Supplement A), A41–A42. doi:10.1093/eurheartj/sur035

[5] Rehman KU, Akhtar T, Sabar MF, Tariq MA. Allele frequency distribution of CYP2C19*2 allelic variants associated with clopidogrel resistance in cardiac patients. Exp Ther Med. 2015;10(1):309-15. doi: 10.3892/etm.2015.2493 Epub 2015 May 14.

[6] Gaikovitch EA, Cascorbi I, Mrozikiewicz PM, Brockmöller J, Frötschl R, Köpke K, Gerloff T, Chernov JN, Roots I. Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population. Eur J Clin Pharmacol. 2003;59(4):303-12. doi: 10.1007/s00228-003-0606-2 Epub 2003 Jul 15.

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Clinical and electrophysiological aspects of tics in children

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BACKGROUND. Tics are diverse in nature inappropriate movements or vocalizations. They significantly degrade patients' quality of life, lead to social difficulties, and disturbance of learning especially during exacerbations. The prevalence of tics among children ranges from 4% to 24%, thus emphasizing the relevance of the problem.

OBJECTIVE: To study clinical and electrophysiological features of tics in children with development of new treatment methods.

METHODS: We conducted a comprehensive clinical and electrophysiological examination of 50 patients with tics, aged 5 to 15 years. The control group consisted of 20 healthy children. The research included a thorough study of the history, neurological examination, manual testing of skeletal muscles, psychological testing. Electrophysiological examination included a review of the functional state of corticospinal tract (CST) by the method of magnetic stimulation (MS), study of polysynaptic reflex excitability (PRE) according to a late component of the blink reflex (BR). Statistical analysis included parametric and nonparametric methods of data processing.

RESULTS. All children of the study group showed signs of minimal brain dysfunction (MBD), they had complicated antenatal and postnatal history (trauma, disease, occurring with intoxication). There was a trend towards the increase of MBD signs with worsening of tics. Manual diagnosis in patients identified functional blockade at different levels of the vertebral column, sacroiliac joints, we identified latent myofascial trigger points (MFTP) mainly in the cervical-collar zone, in the area of the paravertebral muscles, periosteal triggers in the area of the sacroiliac joints.

The research allowed determining decrease in propagation velocity of excitation (PVE) throughout CST in patients with tics. Correlation analysis revealed a negative correlation between the severity of tics and PVE ($r = -0.38$; $p < 0.001$).

When studying polysynaptic reflex excitability (PRE) a significant predominance of hyper-excited types of blink reflex (BR) (90% of cases) was revealed. However, in 10% of patients there was a moderate decrease in propagation velocity of excitation (PVE), which allowed us to identify two subgroups of patients with tics: I – low and moderate type of reflex responses; and II – high type of reflex responses. Collation of data of MS and BR revealed a significant decrease of PVE in patients of the subgroup I, which probably reflects a deeper disturbance of the neuro-motor apparatus. The presence of numerous myofascial trigger points (MFTP) in patients of the subgroup I with moderately low polysynaptic reflex excitability ($p < 0.05$) was characteristic.

CONCLUSIONS: The data show extraordinary sensitivity of neuromuscular system of children to various physiological and pathological stimuli, occurring in the body in the ontogenesis or diseases, and multifactorial origin of the pain syndrome in tics.

The results suggest that one of the main mechanisms of development of pathological process is dysfunction of descending inhibitory control. However, further clarification of the type of polysynaptic reflex excitability in a certain patient is needed, that will allow to develop individualized approach to the choice of therapeutic interventions.

Keywords: Tics, children, excitability, reflex, blink reflex

Conflict of interest statement: None.

Pharmacovigilance

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Safety and efficacy of valproic acid preparations

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BACKGROUND: Rising of the cost of drug therapy is one of the most notable negative tendencies of modern medicine. The main reasons for this trend are the increased costs for preclinical and clinical phases of drug development. Reproduction of drugs after cessation of patent protection is much less costly. Replacement of the original (reference) drug to generics would greatly reduce the cost of drug therapy. However, the use of generic drugs should provide maintaining quality of medication similar to achieved using the original drug. Thus, the original and generic medicines should be interchangeable and this factor largely determines the fate of the generics. In the Russian Federation the concept of drug interchangeability is entered by the Federal law of Russian Federation № 429-FZ from 22.12.2014. According to this law interchangeable drug is a drug with proven therapeutic equivalence or bioequivalence against the reference drug, having equivalent qualitative and quantitative composition, composition of active ingredients, the composition of excipients, same dosage form and route of administration. Especially the problem of interchangeability is particularly relevant for the drugs with a narrow range of therapeutic action, which include some anticonvulsants [1–3].

OBJECTIVE: In this regard the comparative analysis of indicators efficiency/risk using the data from the Federal database of adverse drug reaction in group of the patients treated with preparations of valproic acid is of interest [4].

METHODS: Assessment of the degree of certainty of causality between the development of adverse reactions and the use of the drugs of valproic acid in our research was assessed with Naranjo scale [5]. This method involves the use of the questionnaire focused on the obtaining concrete answers that are measured quantitatively in points. A certain number of points correspond to a certain degree of reliability.

The category of the degrees of reliability of the relationship "medicine - no" on a scale Naranjo as a result of answers to 10 questions are defined as:

the certain.....9 and more points
the probable.....5–8 points
the possible.....1–4 points
the doubtful.....0 and less points

After determining the degree of certainty of causality, spontaneous reports only having a high degree of reliability reports (definite, probable and possible) were exposed to the further analysis.

RESULTS: The Federal database of adverse drug reaction contains 753 spontaneous reports on the development of adverse reactions after the use of valproic acid preparations during the study period. Among 753 reports, 216 (29%) contained information about replacing one drug with another. The analysis of the action of drugs have shown that on the replacement of different drug forms of the original brand, adverse reactions occurred in 23 cases (14.6%), but on the replacement of the original drug on generic – in 135 (85,4%) cases. On the basis of clinical picture and assessment of severity of adverse reactions it was found that in 127 (77%) cases adverse reactions were serious. The criteria for seriousness of adverse reaction most often were clinically significant event and hospitalization or its prolongation.

Analysis of the distribution of adverse reactions on replacement of drug preparations showed that 122 (77%) of 158 spontaneous reports were due to the problems of replacing the original drug to generic.

CONCLUSIONS: Thus, replacement of the original preparation of valproic acid with generics should be considered as an independent risk factor for development of complications of drug therapy. In clinical practice, in case of successful seizure control substitutions of different preparations of valproic acid should be avoided.

Keywords: Antiepileptic drugs, valproic acid, safety, efficacy, interchangeability

Conflict of interest statement: None.

References

[1] Andermann F, Duh MS, Gosselin A. Paradis PE Compulsory generic switches of antiepileptic drugs: High switchback rates tobranded compounds compared with other drug classes. Epilepsia. 03/2007; 48(3):464-9. doi: 10.1111/j.1528-1167.2007.01007.

[2] Besag FMC. Is generic prescribing acceptable in epilepsy? Drug Safety. 2000;23(3):173-82. doi: 10.2165/00002018-200023030-00001

[3] Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drug? Seizure. 2006;15(3):165-76. doi:10.1016/j.seizure.2005.12.010

[4] Pasternac E, Alyautdin R, Romanov B. Transformation of views on the teratogenic effects of antiepileptic drugs. Safety&RiskofPharmacotherapy.2014;4:12-17Availablefrom:http://journals.regmed.ru/Content/File.aspx?id=3dc641cc-63c4-45f0-9674-75f87bf35ba6

[5] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154

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Monitoring drug safety in Astrakhan, Russia

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BACKGROUND: The problem of drug safety will never disappear as new drugs are delivered in increasing numbers. They have high biological activity and adverse drug reactions (ADR) [1]. Currently, adverse drug reactions are the fourth leading cause of death for patients.

There are databases of ADRs (Vigibase, Eudravigilance), but we know that ADR manifestations may vary in different countries and regions, due to the demographic, genetic characteristics of the population and the quality of manufactured drugs [2]. In this regard, the study of the ADR at the regional level is very relevant. We aimed to optimize the work on monitoring drug safety in Astrakhan region through pharmacoepidemiological research and development of computer database for analysis of information coming to the center for drug safety monitoring (CDSM).

OBJECTIVES:

1. To study the rates of ADR reporting and the structure in the Astrakhan region at the regional center for drug safety monitoring.
2. To analyze the outcomes of registered adverse drug reactions.
3. To determine the causality of adverse drug reactions.
4. To identify reports on the ineffectiveness of drugs.
5. To analyze the rates and structure of ADR reporting for drugs prescribed off-label.

METHODS: We studied spontaneous adverse event reporting. The adverse event reports received by the regional CDSM for the period of 2010 to 2014 was analyzed. The groups of drugs were categorized according by Anatomical Therapeutic Chemical classification system. The data were analyzed using Microsoft Office Excel. The likelihood of whether an ADR was actually due to the drugs was assessed with the Naranjo algorithm.

RESULTS: The analysis of the results showed that the establishment of the CDSM in September 2010, contributed to improvement of drug safety monitoring in health facilities of the region. Noteworthy was the increasing the number of adverse event reports in 2011 and 2012, compared with the beginning of the year 2010, when the CDSM was not yet functioning.

The decrease of adverse event reporting in 2013 and 2014 was due to the fact that doctors in the region had access to better ADR drug information. Along with the increasing number of adverse event reporting we also noted the increase in the number of health facilities that monitored drug safety. The number of health facilities that reported, doubled from 2010 to 2014. We observed the increase in the number of adverse event reports submitted by pharmaceutical companies. General anti-infective drugs for systemic use (class J) were the most common cause of all registered ADRs (44%). Drugs

for treatment of tuberculosis (group J04A) were the cause of adverse drug reactions in 34% of reports. ADRs associated with drugs used for treating diseases of cardiovascular system accounted for 16% of case-reports; drugs belonging to the group of Alimentary tract and metabolism (class A) and to the group of Nervous System (class A) were reported to cause ADRs in 10% of cases each. Type A adverse drug reactions, which are usually a consequence of a drug's primary pharmacological effect, were detected in 45% of cases. These reactions were often registered for drugs affecting cardiovascular system (class C), nervous system (class N), dlood and blood forming organs (class B). Type B ADRs were reported in 54% of cases. These were "idiosyncratic" reactions, which could not be predicted on the basis of the drug's main pharmacological action, were not dose-related and were severe [3]. The most frequent cause of type B adverse drug reactions was the General anti-infective medicines for systemic use (Class J). The fatality rate associated with ADRs was 0.3%. Type A adverse drug reactions resulted in death in 38% of cases. Type B ADR (anaphylactic shock) accounted for 62% of the patient's deaths. The Naranjo scale determined the causality of ADRs. The "definite" ADRs were detected in 14% of reports, "probable" – in 47%, and "possible" - in 39% of cases. The rate of reporting associated with ineffectiveness of drugs amounted to 1%. Most often the lack of therapeutic effect was reported in patients receiving drugs of class C (Cardiovascular system, 31% of all cases of inefficiency of drugs). These drugs were used in accordance with their official instructions for use. The proportion of ADR reports for drugs prescribed off-label was 1.4%.

CONCLUSIONS: The results substantiate the need to continue drug safety monitoring in the Astrakhan region. We plan to further improve the software for ADR analysis.

Keywords: Drug safety, monitoring, adverse drug reaction, regional reporting system, centre for drug safety monitoring

Conflict of interest statement: None.

References

[1] Zborovsky AB, Turenkov IN, Belousov UB. Side effects of drugs. Moscow: Medicine Information Agency Ltd; 2008.
[2] Kostyleva MN, Belousov UB, Gracianskaya AN, Postnikov SS. Safety assessment of drug therapy in clinical practice. Pharmacoeconomics. 2014;1:26-30.
[3] Ritter J, Lewis L, Mant T, Ferro A. A Textbook of Clinical Pharmacology and Therapeutics. London: Hodder Arnold; 2008.

Medical Law

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Fighting trafficking of falsified and substandard medicinal products in Russia

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BACKGROUND: The trafficking of falsified and substandard medicinal products is a global socio-economic problem, which poses a serious threat to economy and health of populations of most countries, including the Russian Federation.

OBJECTIVE: To identify the main achievements and challenges in the fight against trafficking of falsified and substandard medicinal products in the Russian Federation, to formulate possible solutions to these problems.

METHODS: The study of criminal cases and statistical information about the level of crime in the Russian Federation; legal analysis of regulatory legal acts in the sphere of criminal law and turnover of medicinal products; review of scientific and practical publications.

RESULTS: The problem of trafficking of falsified and substandard medicinal products in the Russian Federation was publicly discussed in the late 1990s – early 2000-ies, first in the media and special editions, later this phenomenon was the subject of extensive discussions at international conferences, in public authorities and public circles. However, the most significant results in tackling this problem were achieved only in the last 5 years.

Thus, in 2010, the Russian Federation first joined the annual international police operation under the code name Pangaea, held since 2008 on the initiative of Interpol and the Medicines and Healthcare products Regulatory Agency of the World Health Organization (MHRA WHO). From year to year, the special operation Pangea unites the efforts of many countries from different continents and aims to eliminate transnational criminal groups operating through a global network the Internet. In 2010, as a result of large-scale international inspections 1 200 Internet sites were revealed, through which the fake medicines were spread and 10,000 boxes of medicines were seized, making more than a million falsified tablets in the amount of 2.6 million USA dollars. In 2011, in a special operation Pangea IV was attended by 165 different organizations from 81 countries, including 72 customs, 30 regulators, 26 police and representatives of Interpol from 37 countries. Closed 13 495 illegal websites, seized about 8,000 packages of fake medicines, containing about 2.5 million doses. In 2015, the special operation Pangea VIII was held on the territory of 115 member States of Interpol. In the Russian Federation this operation was carried out jointly by the Ministry of internal Affairs, Federal customs service, the Federal Service on Surveillance in Healthcare of Russian Federation, the Federal Drug Control Service of the Russian Federation and their regional subdivisions. As a result of this operation 34 criminal cases were initiated in our country in connection with hard drugs, falsified and substandard medicinal products and biologically active additives under the guise of high-performance drugs. Special attention during the

operation was given to uncontrolled Internet sale of medicinal products and biologically active additives at a price, which was significantly higher than the actual costs, under the guise of highly effective means of treatment for various diseases. In General, in the Russian Federation 448 administrative offences were identified, which resulted in withdrawal of more than 268 thousand units of medicines from illegal circulation, worth over 9 million rubles; 40 thousand falsified and substandard preparations Contex and Durex for personal contraception were withdrawn. The mobile laboratory has conducted screening program of quality in respect of 294 samples of medicines. It identified 20 parties of dubious authenticity. A message about 264 Internet sites which sell medicines in violation of applicable Russian legislation was sent to the coordinating headquarters of the General Secretariat of Interpol. An official statement with Internet service providers on cessation of activities at these sites was issued [1].

On 26–28 October 2011, Moscow hosted an international high-level conference on counterfeiting of medicinal products, which was attended by more than 750 professionals in the field of law and pharmacy from different countries, including USA, China, countries of the European Council and the Commonwealth of Independent States. At the end of the conference the Convention on the counterfeiting of medicinal products and similar crimes involving threats to public health, was signed, which was called Medicrime [2]. The Convention was signed by representatives of Austria, Germany, Israel, Iceland, Italy, Cyprus, Portugal, Russian Federation, Finland, France, Ukraine, Switzerland. The Medicrime Convention is the first legal agreement in the field of criminal law aimed at criminalizing the trafficking of falsified and substandard medicinal products, as well as aimed at providing legal support for the investigation of these crimes at the international level. The positive side of the Convention of the Council of Europe Medicrime is that it is open for signature not only by member States of the Council of Europe and the European Union, but also by States that are not members of the Council of Europe, but participated in the elaboration of a Convention or have observer status with the Council of Europe. In addition, the Convention is open for signature by any other state at the invitation of the Committee of Ministers of the Council of Europe. The Convention introduces the responsibility for the production, storage and distribution of falsified medicinal products, active substances, excipients, components, materials and supplies; the use of falsified documents related to the trafficking of medicinal products (Articles 5, 6, 7). This legal act regulates the cooperation between the health authorities, customs, police and other competent authorities at international and national level (Articles 17, 21, 22).

One of the results of the legal implementation of the rules of the Convention Medicrime in the Russian legislation was the adoption of the Federal law of the Russian Federation dated 31.12.2014 No. 532-FZ On amendments to certain legislative acts of the Russian Federation on countering the trafficking of falsified, counterfeit, substandard and unregistered medicines, medicinal devices and falsified biologically active additives [3]. The law came into force on 23 January 2015. In accordance with the Federal Law of the Russian Federation Criminal Code is supplemented by three new articles: Article 235.1. Illegal manufacture of medicines and medicinal devices; article 238.1. Circulation of falsified, substandard and unregistered medicines, medicinal devices and trafficking in falsified biologically active additives; article 327.2. Forgery of documents on medicines or medicinal devices or the packaging of medicines or medicinal devices [4].

Although there are some deficiencies in the wording of these penal regulations, we believe their introduction in the Criminal Code is a serious step forward by the state to neutralize the trafficking of falsified and substandard medicinal products, and consequently to ensure the safety of the nation's health and economic security of the country. The inclusion of these special articles in the Criminal Code will allow to analyze statistical information on their practical application by the authorities, to investigate crimes, to fully implement the monitoring, prediction and prevention of these socially dangerous acts. It will contribute to the development and implementation of effective management decisions on the identification and investigation of crimes of this type.

In recent years, in the framework of the joint preventive measures to combat the circulation of

falsified and substandard medicinal products there has been some constructive interaction between law enforcement and regulatory authorities, primarily by the bodies of internal Affairs and units of the Federal Service on Surveillance in Healthcare of Russian Federation. During 2010–2013 researches in the field of Economics, International and Criminal Law, Criminology, Criminalistics, Operatively-search activity, devoted to the development of measures to neutralize trafficking of falsified and substandard medicinal products, were developed as reserved dissertations. The legislation in the sphere of protection of public health and the turnover of medicines was updated.

Thus, trafficking of falsified and substandard medicinal products in the Russian Federation at present is not an appeal and not a theory, but there is a real activity of specialists in the field of law and pharmacy, with a certain legal framework, scientific and methodological support.

However, this problem is not yet solved. The Indicator of withdrawn from circulation of falsified and substandard drugs remains high. In Russia by the end of 2014, 1 109 batches of substandard, falsified and counterfeit medicines were detected and withdrawn from circulation. The volume of state quality control of medicines coming into circulation accounted for 16,3% [5]. A serious danger is the increased level of falsification of pharmaceutical substances, 80% of which is imported to the Russian Federation on indirect contracts from China and India without proper control at customs posts.

The study of criminal cases and statistics about the trafficking of falsified and substandard medicinal products in the Russian Federation leads to the conclusion that this crime is of a latent character. Every year about 50 crimes are detected, for only 30–35 of them criminal cases are initiated, and only 15–20 of the investigated criminal cases are submitted to court. This indicates serious problems in proving the guilt of the perpetrators of these crimes and bringing them to justice. The fight against this crime requires long and reliable operational development of criminal groups, qualified investigation and trial. The special knowledge in the field of circulation of medicinal products is required at all stages, however, relevant educational programs to date have not been developed [6].

Trafficking of dangerous medicines over the Internet and the media remains widespread in the Russian Federation. Biologically active additives are sold uncontrollably outside of pharmacies. The scale and danger of these crimes is erroneously determined on the basis of market value of the seized medicines, and not on the basis of their type of action and dosage, the presence of direct threat of harm to life and health due to the content of harmful substances. Obviously, a spread of just a few packages of falsified or substandard medicines, which contain dangerous ingredients, or contain no active substances, can have irreversible impact for health of people.

CONCLUSIONS: Detection, suppression, investigation and prevention of trafficking of falsified and substandard medicinal products should be systematic and not periodic in nature. It is necessary to organize training, close cooperation and continuous exchange of experience between specialists in the field of criminal law and pharmacy in the fight against this criminal phenomenon.

Law enforcement and regulatory agencies need to adopt joint normative legal acts, regulating their functions and powers in joint fight against trafficking of falsified and substandard medicinal products.

The use of an official position in the crimes related to trafficking of counterfeit and substandard medicinal products should be considered as an aggravating circumstance when considering qualification of those socially dangerous acts.

It is necessary to develop a set of measures to prosecute Internet service providers, hosting and serving web sites, through which they operate the illicit trade of medicinal products on the Internet.

We should develop a mechanism of accountability of media for advertising and distribution of obviously false information about medicinal products.

It is advisable to tighten control over the circulation of biologically active additives, prohibit their sale outside pharmacies.

It is necessary to revise the legal framework and to tighten control over the conduct of clinical trials of medicines and the legality of their registration.

Keywords: Trafficking, falsified, substandard, medicinal products, enforcement, legal framework, international law, convention

Conflict of interest statement: None.

References

[1] Employees of Interpol Russian Interior Ministry took part in an international police operation Pangea, [Internet] (accessed 2015 June 25) Available from: https://mvd.ru/news/item/3587248/

[2] Council of Europe Convention on the counterfeiting of medicinal products and similar crimes involving threats to public health. – Moscow, 28.X.2011.

[3] On Amendments to Certain Legislative Acts of the Russian Federation with regard to countering trafficking in counterfeit, counterfeit, substandard and unregistered medicines, medicinal products and counterfeit dietary supplements: Federal Law of the Russian Federation dated 31.12.2014 No. 532-FZ. Rossiyskaya Gazeta. January 12, 2015. No. 6572.

[4] The Criminal Code of the Russian Federation of 13.06.1996 No. 63-FZ, taking into account changes on, 2015 July 13.

[5] M.A. Murashko. The work Roszdravnadzor and its territorial bodies in 2014 (based on the final board) Vestnik Roszdravnadzor No. 2 (2015), 8-9.

[6] N.F. Faizrakhmanov, the investigation into the trafficking of falsified and substandard medicines, biologically active additives, Moscow (2013), 4.

Essential Medicines, Clinical Guidelines and Rational Use of Medicines

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Essential medicines for children in Armenia

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BACKGROUND: Drug therapy plays a key role in pediatrics. Effective treatment in pediatric practice means that medicines should be both effective and safe for children. However, there is not enough data on effectiveness and safety of medicines for children due to small number of clinical trials [1]. Access to medicines for children remains a serious problem worldwide [2]. The World Health Organization (WHO) has significantly increased the efforts in the field of pediatric pharmaceuticals in order to improve the situation [4]. In 2007, the World Health Organization (WHO) Model List of Essential Medicines for Children (EMLc) was firstly developed. Although WHO promotes access to essential medicines for children in countries by encouraging inclusion of these medicines in national essential medicines lists (EMLs) and treatment guidelines, many essential medicines are not covered by (EMLs) in some countries. The results of a study performed in 14 countries has shown that of 20 surveyed medicines the proportion included in national EMLs ranged from 50% to 90% and some medicines of the EML were not included in local standard treatment guidelines [3].

OBJECTIVES: To examine the current situation with access to essential medicines for children in the Republic of Armenia (RA).

METHODS: The Armenian Essential Medicines Lists (AEML) of 2007 and 2013, as well as the Lists of medicines registered in Armenia have been analyzed (2011 – 2013). The following indicators have been calculated: the percentage of medicines from the WHO EMLc, which were included on the current AEML, the percentage of medicines from the WHO EMLc which were registered in Armenia and the percentage of medicines from the WHO EMLc which were included in approved clinical guidelines. Also, recommendations on prescribing of medicines for pneumonia, included in Armenian clinical guidelines, were analyzed.

RESULTS: The analysis of the use of pharmaceuticals from the WHO Model List of Essential Medicine for Children (WHO EMLc) by medicines supply system in the Armenia has revealed that in 2013 only 57.7% of all the medicines from WHO EMLc were included on the National List of Essential Medicines of RA (AEML) and only 68.5% were registered. The results of studies carried out in 2011, 2012, 2013 showed that the situation in regard to the coverage of medicines from the WHO EMLc (without taking into account drug formulations and strengths) by AEML and clinical guidelines used in RA has not changed considerably during that period of time, while the percentage of essential medicines for children recommended by WHO, which were registered in Armenia and available in the pharmaceutical market, slightly increased.

Analysis of recommendations on prescribing medicines for pneumonia treatment, included in clinical guidelines used in Armenia, has revealed that these recommendations slightly differ in terms of recommended medicines and other treatment details. Accordingly, approval and use of a single set of criteria for selecting medicines to be included into pediatric clinical guidelines should be considered as an effective approach for optimizing supply of medicines for children.

CONCLUSIONS: Access to essential medicines for children in Armenia is unsatisfactory. Essential medicines for children recommended by the WHO are only partially covered by the medicines supply system for children in Armenia. Development of the List of Essential Medicines for children in Armenia is an approach to solve this problem. Currently actions are being taken in this direction. It is also considered appropriate to develop national clinical guidelines on the most common childhood diseases in Armenia.

Keywords: Access to medicines, essential medicines, children, clinical guidelines, Armenia

References

[1] Finney E. Children's medicines: A situational analysis. World Health Organization, Geneva, 2011.
[2] Ivanovska V., Mantel-Teeuwisse Aukje K., Dijk L.Van. Background Paper 7.1 Priority Medicines for Children. WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht, the Nitherlands, 2013.
[3] Robertson J., Forte G., Trapsida J.-M., Hill S. What essential medicines for children are on the shelf? Bull World Health Organization. 2009;87:231-37.
[4] WHO Better medicines for children. Sixtieth World Health Assembly, Geneva, 2007.

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Evidence-based clinical guidelines in Kyrgyz Republic

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BACKGROUND: Improving quality of care in many countries is one of the priorities of health systems. At the same time one of the most important methods of improving quality of care is the widespread use of methods and principles of evidence-based medicine (EBM) [1]. The implementation of EBM in public health practice provides for the optimization of quality of care in terms of safety, efficacy and cost, one way of which is the use of clinical guidelines. Clinical guidelines developed with the use of EBM, provide an opportunity to use the latest and accurate information to optimize or neutralize impact on physician decision-making of subjective factors such as intuition, expertise, opinion of respected colleagues, recommendations of popular manuals and handbooks, etc.

OBJECTIVE: To assess and analyze the developed clinical guidelines (CG) and protocols (CP) in the Kyrgyz Republic in the period from 2008 to 2014 and evaluate their implementation in practical healthcare.

METHODS: Retrospective analysis of the developed clinical guidelines and protocols according to the approved methodology, interviewing leaders, questioning doctors and patients for their implementation. All participants gave informed consent for voluntary participation in the study.

RESULTS: Within the framework of the National Program "Manas Taalimi" "Strategy for development of evidence-based medicine in the Kyrgyz Republic for 2006–2010" (MOH Order №490 from 09.04.06) was developed and approved for use. Its main purpose was to create a sustainable system of development, deployment and monitoring of the CG and CP and further promotion of EBM into practical health care, education and science. As a result, a number of documents ("Expert Council for assessing the quality of clinical guidelines/protocols", "AGREE instrument to assess the methodological content of clinical guidelines" [2], "The methodology of development and adaptation of clinical guidelines based on evidence-based medicine") were approved by the Order of the Ministry of Health from 31.12.2008 №704.

This methodology was based on the international guideline SIGN-50 [3], as part of the strategy, it was decided to adapt clinical guidelines of the advanced countries of the world to the organizational characteristics of health care in the Kyrgyz Republic. According to the adopted methodology, the development of clinical guidelines should include the following steps: choose a theme, create a multidisciplinary group to conduct a search of existing clinical guidelines and assess their quality, if necessary, conduct an additional search of evidence, make recommendations and draw up the text of clinical guidelines, conduct peer review and consultations, approve clinical guidelines in the pilot, approve the clinical management of the Ministry of Health, publish and distribute, put into practice, monitor the effectiveness of implementation, provide for the revision and updating of clinical guidelines as new credible information appears. In the future, these CGs will be considered as a basis for the

development of the CP in accordance with the possibilities of health care organizations of the country. Figuratively speaking, the CG answers the question - "What can be done in an ideal situation? ', And CP -" What should be done in a country?".

The Ministry of Health over the period 2008–2014 years approved 41 CGs and 118 CPs for common diseases. It should be noted that only 31.7% of them were represented by the corresponding CGs. Among the approved CPs only 15.3% were based on the corresponding CGs. All of the CGs and CPs (100%) identified experts who prepared the documents and to whom they are addressed. The search strategy information was available only in 24.3% of cases, and only 18.1% used the criteria for selection of international guidelines, which were found in the CGs. 100% of the CGs and CPs indicated no conflict of interest of their developers, but it should be noted that 89% of the CG and CP were developed with the financial assistance of donor organizations supporting the Kyrgyz health reform. The degree of evidence of the recommendations was presented in 100% of the documents, but grading scales were different: in one CG manual grading was used with 3 levels of evidence (A, B, C), in the other – 4 levels (A, B, C, D), and in the third - tier 5-6 (I, II, III, IV, V), which is not the approved methodology, which was based on gradation - A, B, C, D. In the process of approval of CGs and CPs, 100% did not specify points of methodological quality evaluation.

To assess the implementation of approved CG in the practice (training, availability of the CG and CP for each doctor, informing patients about the CG and CP, monitoring use) we interviewed the leaders of health care organizations (20), surveyed 200 doctors and 100 patients. Only 10% of leaders said that they participated in the training on the CG and CP. 5% of them confirmed that every doctor had the corresponding copies of CGs and CPs, 100% of the leaders conduct internal audits on the use of the CG and CP, in 95% of cases the developed CGs and CPs do not take into account local health systems conditions (drugs, equipments etc.). 100% of respondents followed the CGs and CPs, as penalties were introduces by the Ministry of Health, Health Insurance Fund for violation of these recommendations. 25% of respondents reported improved clinical outcomes. To the question "How to improve the practice of medicine with the use of CGs and CPs?" 100% of the managers answered that they needed trainings: trainings for physicians, trainings for the developers of these documents. The survey of doctors showed that only 5% of them were trained in the use of CGs and CPs, 100% of them had the copies of CGs and CPs, 100% of doctors answered that the CGs and CPs not always were suitable for their practice. Questioning patients revealed the following: 100% of them never heard of the CGs and CPs, 2% of patients noted some improvement in healthcare delivery, and 20% of patients were referred to private laboratories for diagnostic tests, and 100% of the patients-respondents bought their drugs for their own pocket money.

CONCLUSIONS: It is very important to ensure equal opportunities in access to medical interventions designed accordingly to the CGs and CPs at all health facilities that will prevent discrimination, depending on territorial distribution, administrative subordination, and other factors in the provision of health care. Implementation of CG and CP recommendations depends not only on the level of health care, knowledge and judgment of a clinician, but also on affordability of a particular diagnostic or therapeutic technologies for a patient. Cases when effective services are not unaffordable for patients should be considered from ethical perspective.

Keywords: Evidence-base guidelines, Kyrgyz Republic, clinical guidelines, clinical protocols, interviewing, survey

References

[1] VV Vlasov The modern process of standardization in the Russian medicine // Int. Journal of Medical Practice. - 2000. - №2. - P. 5-12.1.
[2] AGREE Instrument. The Agree Collaboration. [Internet] 2003 [cited 2003]. Available from: www.agreecollaboration.org.
[3] SIGN 50: A guideline developer's handbook. Scottish Intercollegiate Guidelines Network. - 2001.

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Rational use of medicines – Indian perspective!

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BACKGROUND: India, the largest democracy in the world, is with a federal structure of 29 states and 7 union territories. With a population of more than 1.2 billion, resource is always a constraint and so is in the health system too. In the federal structure, providing healthcare is largely the responsibility of state governments. Medicines are important component of health care delivery system and quality care is dependent on the availability and proper use of quality medicines. In spite of being known as pharmacy of the third world, poor access to medicines in the country is always a serious concern. Realizing the need of quality use of medicines, several initiatives have been initiated.

RESULTS: As early as 1994, seeds of rational use of medicines were sown in the country with two initiatives: establishment of a civil society, Delhi Society for Promoting Rational Use of Drugs (DSPURD) and establishment of government agency in Tamil Nadu, a southern state, called Tamil Medical Services Corporation Limited (TNMSCL). DSPUD was in official association with World Health Organization Country Office for implementing essential medicine programme in the country for two biennia. In addition to organizing sensitising and training programme for healthcare professionals throughout the country, it looked after the procurement and appropriate use of medicines in Delhi government health facilities. TNMSCL has made innovations in medicine management including procurement directly from manufacturers as a part of pooled procurement, establishing warehouses with modern storage facilities and Information Technology enabled management of whole process. TNMSCL Model is now replicated in almost the entire country and even in some small other countries as it is successful in improving access to medicines.

The National Government and the State Governments have developed strategies to promote rational use of medicines as a part of improving access and quality care in public health facilities. National Government developed policies and regulations for combating antimicrobial resistance, controlling the prices of medicines, establishing generic medicines stores and advocating for the need for improvement of medicine logistics at state level and prescription auditing system. There is wide variation in medicine procurement and management system among the states. Spending on medicines ranges from as small as 2% of health budget to as high as 17%. The procurement system varies from individual facilities to partial pooled procurement to complete centralised system.

There are attempts of developing essential medicine lists, standard treatment guidelines and costing of treatment of common illnesses. Except for the few states, essential medicine list remains an ornamental showpiece. However, with apex court's intervention, the prices are now controlled for all 348 medicines listed in national list. The pharmaceutical companies continue to violate price regulations either through making the medicines at different strengths or new fixed dose combinations (FDCs). Perhaps the largest number of FDCs and many of them with no valid justification are available in the country. Decisions

on compulsory licensing have made the new anticancer medicines affordable. Other countries have also benefited from this decision.

CONCLUSIONS: While some progress has been made for appropriate use of medicines in public health facilities, there are little efforts in private sectors and at community levels. Availability of prescription medicines without much control and free drug advertising are other concerns. Like all other countries irrational use of medicines continues to be of concern in India despite of several attempts of improving use of medicines both in the health system as well as in community. But efforts continue to be made for improving the use of medicines!

Keywords: Rational use of medicines, health system, improving use of medicines, medicine list

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Furthering benefit/risk ratio and cost effectiveness of anticancer drugs

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BACKGROUND: In Russia, the incidence of melanoma is increasing steadily. The approved standard of specialized medical care for melanoma of the skin defined the range of drugs, recommended for the provision of quality health care. However, it appears that the most effective innovative and safe medicines are at the same time the most expensive drugs. The most important is the assessment of drug use, taking into account their relative efficacy, safety (risk/benefit) and cost (economic efficiency), which may help to create the conditions for controlling their use. Based on this analysis, it is necessary to introduce drugs on the lists of drugs within the framework of the provision of state guarantees of free medical care to citizens (patients).

OBJECTIVE: To analyze the drug use according to the standard of specialized medical care for melanoma of the skin, to perform information retrieval in specialized libraries and databases Cochrane, Pubmed, Medline, as well as in the database of the state register of medicines (GRLS) of Russian Ministry of Health.

METHODS: The nomenclature of drugs was determined according to the standards of specialized medical care for 2006 and 2012, to the data of GRLS; information searches were performed in specialized libraries and databases Cochrane, Pubmed, Medline.

RESULTS: Analysis of anticancer drugs for melanoma of the skin consisted of determining of nomenclature of drugs, included in the standard of specialized medicine care. The standard of specialized medicine care for patients with malignant melanoma of the skin (with specialized assistance) (Order dated December 6, 2006 № 828) includes the following anticancer drugs: dacarbazine (alkylating agents), vinblastine (antineoplastic agent - an alkaloid), cisplatin (platinum), lomustine (nitrosoureas), bleomycin (antitumor agent, an antibiotic) [1]. The standard of specialized medical care in melanoma skin generalization or recurrent disease (chemotherapy) (Order of November 7, 2012 № 604n) includes the following anticancer drugs: lomustine and fotemustine (nitrosoureas), dacarbazine and temozolomide (alkylating agents), cisplatin (platinum) [2]. So, the standard of specialized medical care for for melanoma of the skin by 2012 compared with the standard of care by 2006 includes temozolomide and fotomustin and excludes vinblastine and bleomycin. Based on the database GRLS of Russian Ministry of Health Care [3], as well as information retrieval in databases of Cochrane, Pubmed, Medline the efficacy and safety of melanoma of the skin have proven innovative products, in particular, such as vemurafenib (Zelboraf) dobrafenib (Tafinlar) and trametinib (Mekinist) that are already registered in Russia. At the stage of the clinical study are targeted drugs, such as GSK1120212, AMG 678, pembrolizumab, ipilimumab, tremilimumab, nivolumab and etc. The inclusion or exclusion of data from the restrictive

drug lists, such as lists of "Vital and essential medicines", "Drugs for certain categories of citizens", the "Minimum range", according to the Russian Government Decree №871 of 28.08.2014 [4] is carried out after the risk/benefit ratio and cost effectiveness assessment to increase their availability. The availability of high-quality, effective and safe drugs for medical use within the reduced budget, taking into account the formation of a rational and balanced system of health care is the main task of the strategy of the drug provision of the population of Russia for the period till 2025 [5].

CONCLUSIONS: The most rational use of limited resources and cost containment within the framework of state regulation refers to modern trends in the health care of the Russian Federation. There is a need to develop targets aimed at all subjects of the pharmaceutical market, to increase the availability of innovative drugs for melanoma of the skin treatment. This strategy should be based on evidence and assessments of the efficacy, safety and economic viability of anticancer drugs.

Keywords: Anticancer drugs, standard, medical care, melanoma, benefit/risk ratio, cost effectiveness

Conflict of interest statement: None.

References

[1] "On approval of the standard of care to patients with malignant melanoma of the skin (with specialized assistance)". Ministry of Health and Social Development of the Russian Federation, 2006 Dec 6, Order № 828

[2] "On approval of the standard of specialized medical care for melanoma of the skin, and the generalization of relapse (chemotherapy)". Ministry of Health of the Russian Federation, 2012 Nov 7, Order № 604n

[3] State Register of Medicinal Products [Internet] – Available from: http://grls.rosminzdrav.ru

[4] "On approval of the formation of lists of drugs for medical use and minimal assortment of drugs needed for medical care". The Government of the Russian Federation, 2014 Aug 28. Government Decree №871

[5] "Strategy of the drug provision of the population of the Russian Federation until 2025, The Ministry of Health, 2013 February 13, Order of № 66.

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Developing drug formularies for the "National Medical Holding" JSC

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BACKGROUND: One of the main problems of drug provision of multidisciplinary hospitals is the necessity to improve the efficiency of budget spending. Despite the efforts undertaken in Kazakhstan for improving the mechanism of drug distribution (creation of the Kazakhstan National Formulary, Unified National Health System, the handbook of medicines (drugs) costs in the electronic register of inpatients (ERI), having a single distributor), the number of unresolved issues still remain.

"National Medical Holding" JSC (NMH) was established in 2008 and unites 6 innovational healthcare facilities with up to 1431 beds (700 children and 731 adults), located in the medical cluster – which are "National Research Center for Maternal and Child Health" JSC (NRCMC), "Republic Children's Rehabilitation Center" JSC (RCRC), "Republican Diagnostic Center" JSC (RDC), "National Centre for Neurosurgery" JSC (NCN), "National Research Center for Oncology and Transplantation" JSC (NRCOT) and "National Research Cardiac Surgery Center" JSC (NRCSC). The main purpose of NMH is to create an internationally competitive "Hospital of the Future", which will provide the citizens of Kazakhstan and others with a wide range of medical services based on advanced medical technology, modern hospital management, international quality and safety standards. These services include emergency care, outpatient diagnostic services, obstetrics and gynecology, neonatal care, internal medicine, neurosurgery, cardiac surgery, transplantation, cancer care for children and adults, as well as rehabilitation treatment.

OBJECTIVE: To create a program of development of a drug formulary of NMH and its subsidiaries.

METHODS: In order to create drug formularies of NMH, analytical, software and statistical methods were used.

AII subsidiary organizations of NMH (5 out of 6) except for the NRCOT have been accredited by Joint Commission International (JCI) standards, which ensure the safety of patients and clinical staff, by improving the technological infrastructure, management systems, production environments, and developing program for medications management and use (MMU), etc.

MMU is the Chapter 7 of the 5th edition of the standard JCI [1] which is an up-to-date recognized international standard for hospital drug supply and includes 7 points of medication management lifecycle for inpatient hospitals: drug management and organization; selection and procurement; storage; prescription; preparation and distribution; administering medications; monitoring.

Due to the developed MMU program of subsidiary organizations the drug provision system was rationalized, starting from defining the individual therapy of a patient and ending with the drug procurement strategy. The practical activity was introduced to the use of drugs committeees with reliable evidence-based performance with obligatory consideration of cost-benefit analysis for each diagnosis-related group.

RESULTS: Pre-collected applications for drugs for the year 2015 were submitted in a uniform format in accordance with the structure of the Republican form of the drug [2]. In view of the evidence-base physicians-clinical pharmacologists performed discussions and review of 851 drugs included on the uniform format of the list. Totally 51 (6%) positions were excluded from the list; it was suggested that the format of the application for Paracetamol and Ibuprofen in injectable form be revised; the committee revised the sections on the list for "Antianaemia drugs", iron preparations and methods of prevention of venous thromboembolism with oral anticoagulants.

On the basis of this work, the new format, consisting of 449 international nonproprietary names was developed, representing 795 positions with pediatric formulations. In view of the exisitng data and the move to bring to the common standards and uniformity prices of drugs purchased for 2016, the NMH program of clinical pharmacology content with on-line and open access to physicians was created. Within 60 days the DSCHC work was carried out with consultations, selection, definition of requirements of generic and therapeutic substitution.

CONCLUSIONS: Summing up, drug applications for 2016 with dosage forms include 802 positions and the total bid in monetary terms was by 4,7% lower than in 2015.

For the establishment of NMH rational and balanced system of medicine provision to patients and in order to increase availability of quality, safe and effective drugs, we need to have an open and transparent program of the MMU, developed in accordance with the standards of JCI, with the NMH drug formulary, indicating the reference price values of the lower units (tablet, capsule, ampoule, vial, etc.), including the drug lists for a single distributor.

To improve drug supply of the NMH DSCHC we have to further cooperation with clinical pharmacologists for the rational use of medicines, guided by the principles of evidence-based medicine.

Keywords: drug formularies, drug safety, efficacy, availability, rational drug use, monitoring

Conflict of interest statement: None.

References

[1] Joint Commission International Accreditation Standards for Hospitals, Fifth Edition. Oakbrook Terace, 2013 Sep, ISBN: 978-1-59940-787-6, P.314

[2] On approval of the republican form of the drug (rev. 12.29.2014) Ministry of Health of the Republic of Kazakhstan dated September 9, 2011 Order № 593

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Adherence to EBM guidelines in clinical practice

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BACKGROUND: Adequate and rational pharmacotherapy is an important element of rehabilitation of patients with myocardial infarction. Orders of the Ministry of Health of the Russian Federation, domestic and international guidelines, and scientific publications - all contain a complete algorithm for rational pharmacotherapy [1, 2]. These documents are based on the principles of evidence-based medicine (EBM) and help practicing physicians to carry out individualized and rational pharmacotherapy. However, clinical studies have shown low adherence of physicians to clinical guidelines. In the Russian Federation the death rate from cardiovascular diseases is higher than in developed countries. Thus, studies of the causes of high cardiovascular mortality are needed.

OBJECTIVE: To assess adherence of practicing physicians to principles of evidence-based medicine in treating patients after myocardial infarction at the stage of rehabilitation.

METHODS: A retrospective analysis of 157 cases of patients in rehabilitation after myocardial infarction for the years 2006 and 2009 was undertaken.

We analyzed the list of drugs, prescribed to patients during the period of rehabilitation, drug combinations, regimens and pharmacoepidemiological parameters. We used the following rehabilitation criteria: blood pressure control, smoking cessation, and weight control. Recommendations of controlled physical activities have also been studied. Patient care was compared with the guideline recommendations. Statistical analysis was performed using the OLAP system.

RESULTS: 65 patients with myocardial infarction received rehabilitation therapy in 2006, and 92 - in 2009. It was found, that in 2006 physicians prescribed an average of 4.5 drugs per patient, and in 2009 - 4.6 drugs per patient. The average number of cardiovascular drugs (category C of ATC classification) per patient was 2.9 in 2006, and 2.6 – in 2009. Polypharmacy was found in half of the patients.

In terms of evidence-based medicine, an important element in the rehabilitation of patients is smoking cessation and normalization of body weight. Nicotine replacement therapy and prescriptions of drugs for weight loss is one of the strategies to achieve goals. According to our study, drugs for smoking cessation and overweight were not prescribed at all. In terms of evidence-based medicine, the use of beta-blockers and ACE inhibitors for a long time by all patients is an important element of secondary prevention.

The frequency of prescribing of beta-blockers was 86.1% and 91.1 %% in 2006 and 2009 respectively. The frequency of prescribing of subgroup C09 "Agents acting on the renin-angiotensin system (RAAS)" was 67.7% and 44.4% in 2006 and 2009 respectively. Beta-blockers had the highest frequency of use, while the subgroup RAAS drugs were second to them.

We found that the following recommendations of clinical guidelines, based on the principles of evidence-based medicine, were not followed. We found low rates of ACE inhibitors prescribing. The structure of prescribed ACE inhibitors varied in 2006 and 2009. In 2006, 58.4% of all prescriptions were for enalapril. In 2009 enalapril use decreased to 30%, while prescribing of lisinopril increased from 0 in 2006 to 13.3%. Among angiotensin II antagonists (C09C) only losartan was used in 3.1% and 1.1% of cases in 2006 and 2009, respectively. Fixed drug combinations were not used at all.

The proportion of patients who had hypertension was 73.9% and 61.9 %% in 2006 and 2009, respectively. The rate of Antihypertensive use (C02), namely Guanfacine and Moxonidine was less than 2% in both 2006 and 2009.

In accordance with evidence-based principles the strategy for prevention of recurrent myocardial infarction with prescription of lipid-lowering drugs was used. Lipid-lowering drugs were prescribed to 13.8% of patients in 2006 and to 82.2% of patients in 2009. Doctors used atorvastatin and simvastatin only from the list of drugs of this group. We found that in clinical practice physicians used drugs, not supported by evidence, in particular trimetazidine was frequently used. Antiarrhythmic drugs were not prescribed at all, while part of the patients had arrhythmias. Standards of rehabilitation of patients with myocardial infarction do not contain a section on pharmacotherapy and could not be used for quality assessment.

CONCLUSIONS: Pharmacotherapy of patients aimed at secondary prevention of myocardial infarction did not fully conform to the principles of evidence-based medicine. Standards for rehabilitation after myocardial infarction require revision based on existing clinical guidelines and evidence-based medicine.

Keywords: Adhearance, guidelines, myocardial infarction, rehabilitation

References

[1] Russian Society of Cardiology. Diagnosis and treatment of patients with acute myocardial infarction with ST segment elevation on the electrocardiogram. Cardiovascular Therapy and Prevention. 2007; 6(8) App 1, 146 p.

[2] The Ministry of Health and Social Development of the Russian Federation. Order № 221:“Standard health - resort care for patients with coronary heart disease.” 2004 Nov 22

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Timing of treatment initiation in West's syndrome

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BACKGROUND: Infantile spasms (called the West's Syndrome) represent a severe epileptic syndrome which is characterized by a peculiar type of epileptic seizures, spasms, and by electroencephalographic (EEG) abnormalities often called hypsarrhythmia [1]. Infantile spasms are usually resistant to conventional antiepileptic drugs (AEDs) and adrenocorticotrophic hormone (the synthetic analog - tetracosactide) has been the preferred treatment since 1958. The evidence for other antiepileptic drugs is extremely limited compared with vigabatrin. Most recent studies deal only with short-term drug effects and fail to use clinically meaningful outcome measures. Furthermore, attention needs to be given to dropout rates in the studies, because some studies include a majority of patients with primarily favourable outcome [2]. Effective treatment is now defined as complete cessation of the spasms plus abolition of hypsarrhythmia ('all-or-none response') [3]. So far there has been no consensus on dosage or duration of therapy, influence of early initiation of treatment on the outcomes of West syndrome therapy.

OBJECTIVE: To assess if the timing of treatment initiation (early or late) influences the outcomes of West syndrome therapy.

METHODS: We conducted a retrospective observational study at the Kazan Municipal children's hospital № 8 among children with West syndrome. When treatment with tetracosactide (synacthen depot) or antiepileptic drugs was initiated within 1 month after the onset of seizures we defined it as "early treatment initiation". If this therapy was started after 1 month of the onset of seizures, we defined it as "late treatment initiation". We used was the number of seizure-free patients after 2 months, 6 months and 1 year from the start of the treatment as the favorable outcome measure. We calculated risk ratios (RR) for favorable outcomes and their confidence intervals (CI) using RevMan 5.3 Software, comparing outcomes of early and late treatments.

RESULTS: We analyzed medical records of 150 children with infantile spasms. The diagnosis of West syndrome was confirmed by video-EEG-monitoring findings and by clinical examinations. Gender distribution of patients with West syndrome was with some predominance of boys: 93 boys (62%) and 57 girls (38%), which corresponded to the published literature data. The duration of follow-up was at least 3.5 years. The mean age of patients at the time of analysis was 6 years, from 4 years (min) to 14 years 5 months (max). We divided all of the children into four groups:

Group IA - early treatment initiation – included children who were started on tetracosactide within 1 month from the onset of seizures (30 patients).

Group IB - late treatment initiation – included children who were started on tetracosactide after 1 month of the onset of seizures (60 patients).

Group IIA - early treatment initiation – included children who were started on antiepileptic drugs as mono- or polytherapy within 1 month from the onset of seizures (22 patients).
Group IIB - late treatment initiation – included children who were started on antiepileptic drugs after 1 month of the onset of seizures (38 patients).

Children in all groups were similar with respect to age, sex, severity of the disease. Effectiveness of tetracosactide in the group IA and in the group IB at 2 months, 6 months and 1 year of follow up (from the beginning of treatment) was comparable: RR= 1.00; 95% CI [0.79, 1.27]; P=1,00; RR= 0.96; 95% CI [0.74, 1.24]; P=0,74; RR= 1.00; 95% CI [0.75, 1.33]; P=1,00; respectively

Comparative analysis of the effectiveness of treatment with antiepileptic drugs (without tetracosactide) at 2 months, 6 months and 1 year of follow up (from the initiation of treatment) demonstrated that the number of patients achieving clinical remission was higher in the group IIA, in which the therapy was started within 1 month of the onset of the disease versus the "late treatment initiation" group IIB: RR= 2.76; 95% CI [1.03, 7.41]; P=0,04; RR= 1.62; 95% CI [1.01, 2.59]; P=0,04; RR= 1.37; 95% CI [1.02, 1.84]; P=0,04; respectively.

CONCLUSIONS: The timing of initiation of tetracosactide therapy did not influence the outcomes of West syndrome therapy. The early initiation of treatment with antiepileptic drugs (but without tetracosactide) resulted in a greater number of patients achieving remission, compared with late treatment initiation.

Keywords: West's syndrome, tetracosactide

Conflict of interest statement: Authors declare that there is no conflict of interest.

References

[1] Hancock E, Osborne J, Edwards S. Treatment of infantile spasms. Cochrane Database of Systematic Reviews [Internet] 2013 [cited 2013 JUN 5]. Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001770/frame.html

[2] Mackay, M.T., Weiss, S.K., Adams-Webber, T., Ashwal, S., Stephens, D., Ballaban-Gill, K. et al, Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004;62:1668–1681.

[3] Riikonen R. Recent advances in the pharmacotherapy of infantile spasms. CNS Drugs. 2014 Apr;28(4):279-90. doi: 10.1007/s40263-014-0139-5

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Antibiotics for skin and soft tissues infections in type 2 diabetes mellitus

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BACKGROUND. Type 2 diabetes mellitus is a chronic pathology characterized by high prevalence, high morbidity and mortality. According to the data of the Ministry of Health of Volgograd region the number of patients with type 2 diabetes was 68,227 people on 01.01.2014. Medical and social significance of type 2 diabetes mellitus is determined by its complications. Skin and soft tissue infections (SSTIs) in patients with type 2 diabetes are among the main factors of hospitalization and mortality [1]. Diabetic foot syndrome is found in 30–80% of patients [2].

OBJECTIVE: Pharmacoepidemiological analysis of the structure of skin and soft tissues infections in patients with type 2 diabetes, taking into account data on pathogens, parameters of their sensitivity, analysis of prescribed medicines and evaluation of their compliance with current clinical guidelines and standards.

METHODS: A retrospective descriptive cross-sectional pharmacoepidemiological study using randomization by random numbers. The sample consisted of 253 medical records of patients with SSTIs and type 2 diabetes. These were patients admitted to the surgical departments of hospitals of the city of Volgograd for the period from January 2011 to December 2014. Gender structure was the following: 51.4% - women, 48.6% - men. The average age of patients was 64.5 years. The average number of hospital days was 19,5 ± 14,9.

RESULTS: Diabetic foot syndrome was found in 81.3% of cases (*n*-204). The most common forms of diabetic foot syndrome were the following: gangrene of the lower extremities - 28% (*n*-58), ulcers of the skin - 26% (*n*-53), mixed forms of SSTIs - 18% (*n*-37). Surgical manipulations were performed in 39.1% of cases (*n*-99), including amputations in 65.7% (*n*-65) of cases. The blood glucose level on admission was studied in 97.6% (*n*-247), at discharge – in 89% (*n*-225). Urine analysis on admission was performed in 66.4% of patients (*n*-168), at discharge – in 51% of patients (*n*-129). The glycemic profile was studied in 81.4% of patients (n-206). Bacteriological sowing was carried out in 19% (*n*-48) of cases: blood - 4,2% (*n*-2), urine - 6,2% (*n*-3) (the growth of microorganisms was not detected in 100%); bacteriological sowing from the wound - in 89.6% (*n*-43), the growth of microorganisms were identified in 95.7% (*n*-44). Most common pathogens were: *St. aureus* - 28%, *E. coli* - 19%, *St. epidermidis* - 14%. Antibacterial medications were prescribed in 86% (*n*-216). These were: cephalosporin of the III generation - ceftriaxone (49.4%), other synthetic antibacterials - metronidazole (21%), fluoroquinolone - ciprofloxacin (7.5%). The highest levels of bacterial resistance of SSTIs pathogens were found to beta-lactam antibiotics (amoxicillin/clavulanic acid, ceftriaxone, and ampicillin), rifampin, and gentamicin. The highest levels of sensitivity of SSTIs pathogens were observed to levofloxacin, to vancomycin and meropenem.

CONCLUSIONS: There is a vicious circle in patients with type 2 diabetes: the infectious process leads to decompensation of carbohydrate metabolism parameters; in turn, hyperglycemia leads to increase of severity of SSTIs. Normalization of glucose levels promotes prompt relief of symptoms of infection and bacterial eradication, rational treatment of infection contributes to rapid correction of glucose level. Therefore, an essential element of comprehensive treatment of this group of patients should be rational antibiotic therapy; the choice of medication should be based on the severity of the disease and potential etiologic agents [3]. The analysis of the degree of conformity of the pharmacotherapy to existing standards is a way to optimize the treatment of the given group of patients [4].

Keywords: Pharmacoepidemiology, antibiotic, infection, skin and soft tissues, diabetes mellitus, type 2 diabetes

References

[1] Butranova OI, Ryazanova AY. "Drug therapy of skin infections and soft tissue" Bulletin of the Drug: 2011 No.1(41): 27-35. Russian Available from: http://www.volgmed.ru/uploads/journals/articles/1348140788-drugs-bulletin-2011-1-1550.pdf

[2] Savel'ev V. S. et al. Khirurgicheskie infektsii kozhi i myagkikh tkaney. Rossiyskie natsional'nye rekomendatsii [Surgical infections of skin and soft tissues]. Moscow, 2009, p. 90. Russian

[3] Rajender Agarwal and David N. Schwartz. Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review. Clin Infect Dis. (2011)53(4):379-87 doi:10.1093/cid/cir408

[4] V. I. Petrov, N. V. Rogova, D. O. Mikhailova. Pharmacoeconomic analysis of the efficacy of complex therapy in patients with diabetes mellitus type 2. Journal of VolgSMU: 2010 No. 1(33):28-32. Russian Available from: http://www.volgmed.ru/uploads/journals/articles/1327297835-vestnik-2010-1-683.pdf

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Towards the rational use of medicines

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BACKGROUND: Rational use of medicines remains to be one of the most challenging problems in health systems worldwide [1, 2]. ABC/VEN-analysis has been recommended for use by the World Health Organization (WHO) and has been used in health care practice globally since 1981. It represents the simple and effective method of analysis of medicine expenditures, identifying priority groups of medicines, the use of which, when improved, may provide the greatest clinical and economic impact. ABC analysis provides an accurate and objective picture of budget expenditures on medicines. VEN-analysis helps to prioritize between various medicines in their selection for procurement and use within a drug supply system [3–5].

OBJECTIVE: To assess the impact of introduction of evidence-based principles in the practice of medicine procurement and use on budget expenditures on medicines of a multidisciplinary health facility for the period of four years (2011–2014).

METHODS: ABC/VEN analysis was carried out in a multidisciplinary health facility with over 1000 beds (an average number of beds for three years), which is responsible for provision of care to the population of about 1.4 million people. The analysis was carried out on the basis of information on medicine expenditures for 4 years: 2011 (1st year), 2012 (2nd year), 2013 (3rd year) and 2014 (4th year). When assigning VEN categories of medicines we used expert method: assignment of categories was carried out by clinical pharmacologists after reviewing all available evidence on effectiveness, safety and cost-effectiveness compared to other drugs in this group. In 2013, we implemented educational intervention, including detailed discussion of the results of the ABC/VEN-analysis for the years 2011-2012 from the standpoint of evidence-based pharmacology and recommendations for medicine procurement. In 2014, we delivered training workshop for the heads of clinical departments on evidence-based principles in clinical pharmacology and rational use of medicines.

RESULTS: Medicines expenditures of the studied health facility for the year 2014 were less than for the year 2013, which was the important decrease reversing the trend of increasing medicines expenditures of the last three years: 2011 - 59,868,963 roubles; 2012 - 85,324,084 roubles, 2013 - 107 303 390 roubles, and 2014 - 74,416,692 roubles. The number of International Non-proprietary Names (INN) of medicines used in 2014 was 519, which was the highest number for the four years of the study: 2011 – 429 INN, 2012 – 432 INN, 2013 – 513 INN, and 2014 – 519 INN. Nearly 40% of the funds spent in 2014 on medicines have been used for Vital medicines: 2011 - 26%, 2012 - 39%, 2013 - 25%. Expenditures on Non-essential medicines in 2014 were about the same as in previous years - 14% of total medicine expenditures: 2011 - 16%, 2012 - 13%, 2013 - 15%. However in absolute numbers (roubles) expenditures on non-essential medicines decreased compared to the years 2013 and 2012: 2011 – 9,428,135 roubles, 2012 – 11,129,388 roubles, 2013 – 15,578,325 roubles, 2014 – 10,616,023 roubles.

Expenditures on solutions for infusion (sodium chloride, Ringer's solution, dextran, glucose, hydroxyethyl starch) decreased as compared to the year 2013, but still remained high, thus indicating on the abuse of parenteral methods of drug administration. The portion of expenditures on isotonic sodium chloride solution and hydroxyethyl starch in 2014 decreased compared to the year 2013. We found a positive trend in the structure of expenditures on antibacterial agents: in 2014 expenditures on fluoroquinolones decreased nearly fivefold compared to 2013, expenditures on cephalosporins also decreased, but not so dramatically. However, there was a significant increase in expenditures on carbapenems, more than twofold compared with the year 2013. In 2014 we noted a twofold decrease in expenditures on medicines affecting blood, including antithrombotic agents, hemostatics and antianemic medicines, as compared to the values of the year 2013. In 2014 there was also a decrease in expenditures of cardio-vascular medicines, medicines affecting nervous system, alimentary tract and metabolism.

CONCLUSIONS: Introduction of evidence-based principles through educational interventions at a multidisciplinary health facility resulted in a number of changes towards more rational medicine use. Regular educational interventions for practicing physicians and heads of clinical departments of health facilities that promote rational prescribing are needed.

Keywords: Rational use of medicines, ABC VEN analysis, multidisciplinary, health facility

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References

[1] Laing RO, Hogerzeil HV, Ross-Degnan D. Ten Recommendations to Improve Use of Medicines in Developing Countries. Degnan Health Policy Plan. 2001;16(1):13-20.
[2] Medicines: Rational Use of Medicines, WHO, 2010. Fact sheet N°338.
[3] Ziganshina LE, Niyazov RR, Titarenko AF. Metodicheskie rekomendatsii po provedeniyu kliniko-farmakologicheskogo analiza (AVS-analiz, VEN-analiz, farmako-epidemiologicheskiy metod, dopolnitelnoe lekarstvennoe obespechenie, chastotnyiy analiz)[Guidelines for the clinical and pharmacological analysis (ABC analysis, VEN-analysis, pharmaco-epidemiological method, additional drug coverage, frequency analysis)] [A manual for physicians]. Kazan: Kazanskaya GMA; 2008. 32 p. Russian
[4] Management Sciences for Health in collaboration with WHO. Managing drug supply: The selection, procurement, distribution and use of pharmaceuticals. 2nd ed. Bloomfield, CT: Kumarian Press Inc.; 1997. 830 p.
[5] Roughead L. Evaluation Australia's National Strategy for Quality Use of Medicines: results of indicator measurements 1992-2003[conference abstract]. Improving use of medicines: Abstracts of second international conference. Thailand. 2004. - P. 50.

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Regional specifics of microbial landscape in outpatients with lower respiratory tract infections

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BACKGROUND: The last years have witnessed progressive growth of antimicrobial resistance (AMR) both in hospital-acquired and community-acquired respiratory infections. Regional guidelines (2006) presented standard approaches to pharmacotherapy and provided an important contribution to improvement of antimicrobial therapy at healthcare facilities of both the City of Stavropol and the Stavropol Region. At the same time, recent years have witnessed substantial changes in sensitivity to antimicrobials; besides, newer antibiotics have become available now. This substantiates the need for update of the regional guidelines [1].

OBJECTIVE: To determine the issues related to standardization of antibiotic therapy of lower respiratory tract (LRT) infections at an outpatient setting; to assess regional changes (2007–2012) in the spectrum of pathogens causing LRT diseases in patients of the regional healthcare facilities in view of their age and the diagnosis as compared with the years of 2003–2006.

METHODS: In 2007–2012, we examined sputum microbiology of patients with LRT infections at the bacteriological laboratory of the Centre for Clinical Pharmacology and Pharmacotherapy (Stavropol, Russia), following the methodology guidelines [2]. The comparison was carried out with the results of the microbiological examination of 7051 sputum samples (held in 2003–2006). Statistical analysis was carried out using arithmetic means, standard errors, and Student's t test involving a software package STATISTICA 6.0.

RESULTS: In the outpatient practice, half of the patients with LRT infections were identified to have *Str. Pneumoniae*. The sputum of every fifth examined patient allowed isolating *Enterobacteriaceae* family members such as *Klebsiella spp.* (*Klebsiella pneumoniae* in most cases), *Serratia spp.*, *E. coli*, *and Enterobacter spp.* It is essential to note that almost a quarter of the patients were found to have *M. pneumoniae. C. Pneumonia* was detected quite often as well (19%). *Str. pneumoniae, M. pneumoniae,* and *C. pneumoniae* were found in virtually 80% of all the cases of community-acquired pneumonia in adults. *H. influenzae* and *M. pneumoniae* were 2-3 times more often isolated from the sputum of patients with chronic obstructive pulmonary disease (COPD) and chronic non-obstructive bronchitis.

Along with an increase in the patients' age, regardless of the diagnosis, the proportion of pneumococci, *Haemophilus influenzae* and various members of the *Enterobacteriaceae* family went up, while the share of mycoplasmas went down. However, even in patients over 60 years of age *M. pneumoniae* accounted for a significant share in the overall spectrum of pathogens, which indicates the need for microbiological monitoring, especially as far as COPD is concerned.

In contrast to the previous years, only 35% of the patients (previously 60%) underwent bacteriological examination ($p<0.05$) while receiving antibiotic therapy. Significant prevalence of mycoplasmas in the structure of the isolated microorganisms was found in patients who had been previously treated with β-lactam antibiotics.

Associations of pathogens were detected in 14% of cases, which is half the rate found 2-3 years ago. The associations were found to reveal more frequent presence of *H. influenzae* in patients with acute exacerbation of chronic non-obstructive bronchitis, and *Enterobacteriaceae* – in patients with COPD and pneumonia. The recent years have shown that, combined with other microorganisms, there can be detected pneumococci ($p<0.05$), *H. influenzae*, as well *M. pneumoniae,* while there have been fewer cases of enterococci and enterobacteria; as for non-filterable bacteria, they have been never detected again ($p<0.05$).

Strains of *H. influenzae* maintained high sensitivity to aminopenicillins, including the protected ones. The antibiotic resistance possessed by *Str. pneumoniae* to aminopenicillins doubled (12.4% strains vs. 6.4% 3 years ago, $p<0.05$). The resistance to Co-trimoxazole and Ofloxacin was 27.9% and to macrolides it was 17.9%. Various representatives of the *Enterobacteriaceae* family maintained high sensitivity to aminopenicillins, second and third generation cephalosporins, fluoroquinolones.

Of the 20 *M. pneumoniae* strains that were tested, 8 (40%) displayed resistance to one or more antimicrobials. The highest numbers of cases with resistance were detected to Ciprofloxacin (25%) and Erythromycin (20%). 10% strains of mycoplasma showed resistance to Doxycycline and Ofloxacin, while only 5% of mycoplasmas were identified as having non-sensitivity to Clarithromycin and Azithromycin.

CONCLUSIONS: The results of the research carried out in the recent years in comparison with the data of the previous years, call for reviewing of the standard approaches to the choice of antimicrobial agents in respiratory tract infections. In order to improve the standard of care, the choice of medicines should be based on a number of factors, namely the age, the severity of the respective pathological condition, previous antimicrobial use, and the level of care.

Keywords: Antimicrobial resistance, respiratory tract infections, antimicrobial agents

Conflict of interest statement: The Center For Clinical Pharmacology And Pharmacotherapy (Stavropol, Russia) has offered free access to the data obtained through the microbiological examination of sputum samples in cases of respiratory tract infections.

References

[1] Baturin VA, Shchetinin EV, Baturina MV, Demidenko IF, Kunitcyna EA, Afanasev NE, Pozdniakova OI, Malykhin FT. Ratcionalnaia antibakterialnaia terapiia pri vnebolnichnykh respiratornykh infektciiakh v ambulatornoi praktike [Rational antibiotic therapy in community-acquired respiratory infections in ambulatory practice] [guidance manual]. Stavropol: Publ. StGMU; 2015. Russian

[2] Federal Centre for Sanitary Inspection Ministry of Health of the Russian Federation, Guidelines for Susceptibility Testing of Microorganisms N 4.2.1890-04 [Regulatory and technical documents], 2004 Mar 03, Clinical Microbiology and Antimicrobial Chemotherapy, pp. 306-359.

Molecular Mechanisms Contributing to the Evidence-Base

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Towards effective and stable probiotics

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BACKGROUND: Probiotics are live microorganisms, generally either lactobacilli or bifidobacteria, which when administered in adequate amounts confer a health benefit to the host [1]. Due to the growing evidence of health benefits associated with their use, probiotics are of increasing interest and represent now a significant growth area in the functional foods industry [2]. However, to be effective, orally administered probiotics should survive preparation of dosage forms and passage through acidic environment of the gastrointestinal tract (GIT). Reaching the intestine, these microorganisms should be able to establish themselves, remain viable and perform their beneficial actions. In this context, oral formulations have to protect probiotic bacteria from gastric acidity and delay their release in the small intestine in order to allow their complete release in the colon.

OBJECTIVE: To evaluate effects of starch formulations of lactobacilli on their survival in gastric environment and probiotic properties.

METHODS: Nineteen *Lactobacillus* strains belonging to the species *L. fermentum* (14 strains), *L. plantarum* (4 strains), and *L. rhamnosus* (1 strain), were isolated from dairy products and probiotics, and were used in this study. Lactobacilli were cultured in de Man, Rogosa, Sharpe (MRS) broth (Merck, Germany) under microaerobic conditions at 37°C.

Amylolytic activity of lactobacilli, cultured for 3–5 days on MRS agar supplemented with 1% soluble potato starch (SPS), was determined with iodine reagent (0.01 M I_2-KI solution).

Loading in starch was performed with *L. plantarum* 8PA3 bacteria ("Dry lactobacterin", Perm, Russia), which were resuspended to the concentration 10^{10} cells/mL in 10 mL of 0.85% NaCl solution and added to 90 mL of 2.5% SPS solution. Resulting mixture was frozen at –18°C and then lyophilized (Martin Christ Alpha 1-2 LDplus, Germany).

Atomic force microscopy (AFM) images of formulated *L. plantarum* 8PA3 cells were acquired in air by a Solver P47H atomic force microscope (NT-MDT, Moscow, Russia).

Starch swelling and dissolution was studied in simulated colonic fluid (SCF), prepared according to [3] and in distilled water (pH = 6.0) as control. Amylase from *Aspergillus oryzae* (A8220, Sigma) was added to the solutions to study the influence of amylase. The formulation form was examined visually during 14 h incubation time.

Fluorescence microscopy images were obtained with a Leica DM6000B (Germany) fluorescent microscope using Leica FW4000 software.

L. plantarum 8PA3 loaded in SPS were placed either in HCl solution (pH 2), or in 2% oxgall bile solution, or in 0.85% NaCl solution. Viability was tested after 2, 4 and 6 h incubation at 37°C by plating diluted aliquots onto MRS agar with subsequent counting of bacterial colony forming units

(CFU). In addition, viability was determined using LIVE/DEAD *Bac*Light bacterial viability kit L-7012 (Molecular Probes, Invitrogen) as described elsewhere [4]. Fluorescence in the stained samples was estimated with BD FACS Canto II (USA) flow cytometer or fluorescent microscope.

Nitric oxide (NO) production was assessed with DAF-FM DA and DAA fluorescent dyes as described earlier [4]. Each experiment was performed in triplicate.

RESULTS: In the present study we studied the probiotic composition comprising of SPS and bacteria *L. plantarum* 8PA3. We used AFM to confirm effective fixation of the cells to carbohydrate. The compositions were found to swell quickly (~5 min) in aqueous solutions either containing amylase, or not. Tested starch formulations disintegrated during the first 5-10 min of incubation in amylase solutions whereas in amylase-free probes dissolution was less intensive (after ~30 min). Amylolysis of starch excipients was less pronounced in aqueous amylase solution than in SCF, supplemented with amylase. None of 19 studied *Lactobacillus* strains hydrolyzed SPS when growing on MRS agar supplemented with it. The amount of viable *L. plantarum* 8PA3 cells formulated with SPS was high and did not change when stored for 6 months at 4°C. The bacterial viability tests also demonstrated that after 6 h treatment with 2% bile or HCl (pH 2) *L. plantarum* 8PA3 exhibited increased sensitivity (viability 14% and 0.4%, respectively). However, in similar conditions no significant differences were noticed between bacterial viability obtained for formulated with starch and non-formulated bacteria. Furthermore, we showed that loading into SPS had no effect on bacterial production of nitric oxide (NO) – a pluripotent regulatory molecule in human organism.

CONCLUSIONS: Overall, the results strongly support that formulation with polymeric matrices on the basis of SPS represent an appealing technology of probiotics production. It provides slow release of bacteria in target environment and does not alter their viability and NO biosynthesis. However, SPS excipient does not preserve the bacteria from harsh conditions of upper GIT. Therefore, we conclude that for oral administration the composition should be loaded in acid-resistant capsules.

Keywords: Probiotic, polymeric matrix, composition, soluble potato starch

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References

[1] FAO/WHO. Report on Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. 2001 Oct. Available from: ftp://ftp.fao.org/es/esn/food/probio_report_en.pdf

[2] Kanmani P, Satish Kumar R, Yuvaraj N, Paari KA, Pattukumar V, Arul V. Probiotics and its functionally valuable products - A review. Crit Rev Food Sci Nutr. 2013;53(6):641-58. doi: 10.1080/10408398.2011.553752

[3] Chen L, Li X, Pang Y, Lin L, Zhang X, Yu L. Resistant starch as a carrier for oral colon-targeting drug matrix system. J Mater Sci Mater Med. 2007 Nov;18(11):2199-203. Epub 2007 Aug 1. doi: 10.1007/s10856-007-3009-6

[4] Yarullina DR, Beuerlein K, Silkin NI, Ilinskaya ON. Nitric oxide production in probiotic *Lactobacillus plantarum*: Revision of the origin. JMRR. 2015;1(1):5-14.

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Anti-inflammatory and anti-oxidant properties: Is there a link?

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BACKGROUND: It is believed that the anti-inflammatory activity of medicines is closely related to their antioxidant activity. However, in clinical practice rigorous evidence-based medicine approach fails to reveal important effects of antioxidants on patient important outcomes in inflammatory disorders, as has been shown by a number of Cochrane reviews [1–3].

OBJECTIVE: To evaluate anti-inflammatory and antioxidant effects of newly developed pharmacological agents: dimephosphone and its structural analogues ephorane and mephoprane, and xymedon, in comparison with prednisolone and etidronate in experimental animal model of adjuvant arthritis.

METHODS: Experiments were conducted in 64 white mongrel rats of both sexes weighing 180–200 g, which were divided into 8 groups 8 rats each (4 males and 4 females each), kept under standard vivarium conditions with certified feeding ration (kombikorm). The study was approved by the local ethics committee. We induced adjuvant arthritis by administration under the plantar aponeurosis of the left hind paw of 0.1 ml of Freund's adjuvant (Sigma) in rats of 7 study groups. The groups were as follows: 1st group - intact animals (control); 2nd group – animals to whom the solvent (distilled water) was administered with intra-gastric tube in corresponding volume (control of the model); 3rd – 8th study groups, in which animals were administered with study agents each at a dose of 1 mmol/kg body weight: dimephosphone, ephorane, mephoprane, xymedon, etindronate and prednisolone. The intensity of the modeled arthritis was determined by measurements of paw volumes with plethysmometer (UgoBasile). We calculated the difference in rat paw volume before the administration (baseline) and after administration of Freund's adjuvant at 3, 7, 11, 15, 20, 27, 31, 38, 41 days. The development of secondary arthritis was documented by the increase in volume of both hind and fore paws and tails. On the 41st day of the experiment the animals were sacrificed under light ether anesthesia and exsanguinated. The blood was used to determine the activity of catalase and peroxidase, the content of the total, reduced and oxidized glutathione, the level of ceruloplasmin, conjugated dienes of unsaturated fatty acids (DC), TBA-interacting products (MDA), and the total antioxidant activity of serum (AOA). The results were processed statistically using the Student's *t*-test.

RESULTS: The primary reaction to the Freund's adjuvant in a form of swelling of the ankle joint of the left hind paw was observed at 24 hours after its injection. External clinical manifestations of the modeled disease were more pronounced on the third day: local inflammatory reaction (redness, swelling, ulceration) was seen in all the animals at the injection site with the increase of the paw volume. On the 11th day of the experiment 20% of the animals developed secondary arthritis. The study agents

dimephosphone, ephorane, and prednisone exerted anti-inflammatory effect decreasing the volume of left hind paws by 45%, 46% и 27% respectively on the 40th day of experiment. Mephoprane did not affect the primary inflammatory response to the Freund's adjuvant (rats' left hind paws), however it reduced the volume of the contralateral right paw (secondary arthritis) by 90% on the 20th day of the experiement. This ant-inflammatory effect was accompanied by documented antioxidant activity in case of dimephosphone, ephorane, prednisolone, but not mephoprane. Dimephosphone reduced the levels of lipid peroxidation products in rats blood by 46% (DC) and by 25% (MDA). Ephorane also reduced the levels of lipid peroxidation products in the blood by 46% (DC) and by 25% (MDA), increasing the level of glutathione by nearly half, both the total and the reduced form. Prednisolone reduced the level of lipid peroxidation products in blood by 61% (DC), but not the TBA-interacting products. Mefopran did not affect the blood level of lipid peroxidation products. Xymedon and etidronate showed no anti-inflammatory effect. Xymedon demonstrated anti-oxidant properties, decreasing the blood levels of lipid peroxidation products, while etidronate seemed to behave in pro-oxidant mode, increasing the blood levels of lipid peroxidation products.

CONCLUSIONS: The effects of studied agents on the intensity of inflammation and lipid peroxidation were inconsistent. The results of the study did not show a clear link between anti-inflammatory and anti-oxidant activity. Further research in potential anti-inflammatory activity of new drugs exhibiting antioxidant properties needs to be done before recommending their use in clinical practice.

Keywords: Anti-inflammatory, anti-oxidant, rat paw oedema, arthritis

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References

[1] Andrés M, Sivera F, Falzon L, Buchbinder R, Carmona L. Dietary supplements for chronic gout. Cochrane Database of Systematic Reviews. 2014, Issue 10. Art. No.: CD010156. DOI: 10.1002/14651858.CD010156.pub2

[2] Ciofu O, Lykkesfeldt J. Antioxidant supplementation for lung disease in cystic fibrosis. Cochrane Database of Systematic Reviews. 2014, Issue 8. Art. No.: CD007020. DOI: 10.1002/14651858.CD007020.pub3

[3] Szakmany T, Hauser B, Radermacher P. N-acetylcysteine for sepsis and systemic inflammatory response in adults. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006616. DOI: 10.1002/14651858.CD006616.pub2

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6-Methyluracil derivatives as acetylcholinesterase inhibitors for treatment of Alzheimer's disease

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BACKGROUND: Alzheimer's disease (AD) is the major age-related progressive neurodegenerative disorder. The brain of AD patients suffers from loss of cholinergic neurons and decreased number of synapses [1]. AD is caused by an imbalance between Aβ production and clearance, resulting in increased amount of Aβ in various forms [2]. Reduction of Aβ production and increasing clearance of Aβ pathogenic forms are key targets in the development of potential therapeutic agents for AD treatment. Unfortunately, only nosotropic approaches for treatment of AD are currently effective in humans. These approaches mainly focus on the inhibition of brain acetyl-cholinesterase (AChE) to increase lifetime of cerebral acetylcholine [3]. It is important to emphasize that AChE itself promotes the formation of Aβ fibrils in vitro and Aβ plaques in the cerebral cortex of transgenic mouse models of AD [4]. This property of AChE results from interaction between Aβ and the peripheral anionic site of the enzyme (PAS) [5]. Dual binding site inhibitors of both catalytic active site (CAS) and PAS can simultaneously improve cognition and slow down the rate of Aβ-induced neural degeneration. Unfortunately, the assortment of AChE PAS ligands is still extremely limited.

OBJECTIVE: To study putative advantages of AChE non-charged PAS inhibitors based on 6-methyluracil derivatives for the treatment of Alzheimer's disease.

METHODS:

***In vitro* studies.** Concentration of drug producing 50% of AChE/BuChE activity inhibition (IC50) was measured using the method of Ellman et al. [6]. Toxicological experiments were performed using IP injection of the different compounds in mice. LD50, dose (in mg/kg) causing lethal effects in 50% of animals was taken as a criterion of toxicity [7]. The ability of compound to block in vitro AChE-induced Aβ1−40 aggregation was studied using a thioflavin T (ThT) fluorescent probe [8].

***In vivo* biological assays.** For in vivo blood–brain barrier permeation assay brains were removed 30 min after IP injection of LD50 dose of tested compound injection. The inhibitory potency was measured using the method of Ellman.

Scopolamine and transgenic models of AD were used to evaluate the influence of compound 35 on spatial memory performance.Water solution of scopolamine was injected to mice (ip) 20 minutes before starting memory test during 14 days [9]. Mice were assigned to 7 groups, including 4 groups receiving injection (ip) of compound in different dosages, donepezil-treated mice (donepezil is conventionally used to treat Alzheimer's disease), positive and negative control groups. Double transgenic (APP/PS1) mice expressing a chimeric mouse/human amyloid precursor protein and a mutant of human presenilin-1 [10] were assigned to 4 groups, including transgenic animals injected (ip) with compound 35 or donepezil solution, positive (transgenes injected with water) and negative (wild-type mice) controls.

To evaluate spatial memory performance, mice were trained on a reward alternation task using a conventional T-maze [11]. The criterion for a mouse having learned the rewarded alternation task was 3 consecutive days of at least 5 correct responses out of the 6 free trials.

For β-amyloid peptide load was evaluated quantitatively as a number and summary area of Thioflavine S fluorescent spots in cerebral cortex and hippocampal images using Image J program. Statistical analyses were performed using the Mann-Whitney test.

RESULTS: We evaluated the acute toxicity of the most active compounds. The most potent AChE inhibitor compound 35 (IC50 (AChE) = 5±0.5 nM) exhibited the lowest LD50 values (51 mg/kg) and inhibited brain AChE by more than 71±1%. Compound 35 at 10 nM, exhibited a significant (35±9%) inhibitory activity toward human AChE-induced Aβ aggregation.

Scopolamine injection induced significant decrease in correct choice percentage in T-maze, as well as decrease in percentage of mice reaching criterion for learning the task by day 14. This memory deficit was relieved to some extent either by compound 35 (5 mg/kg) or donepezil (reference compound) treatment (0.75 mg/kg). Interestingly, higher doses of compound 35 (10 and 15 mg/kg) produced less therapeutic effect on spatial memory deficit.

Group of APP/PS1 mice showed 3 times lower percentage of reaching behavioral criterion and lower percentage of correct choice in T-maze alternation task comparing to WT mice, whereas compound 35 (5 mg/kg) or Donepezil treatment effectively improved these parameters in APP/PS1 mice.

Compound 35 treatment (5 mg/kg) during 14 days significantly reduced percentage of summary area and number of β-amyloid peptide (βAP) deposits visualized in sections of cerebral cortex, dentate gyrus, and hippocampal CA3 area in APP/PS1 mice. The most prominent reduction of βAP load by compound 35 treatment was found in CA3 area and cerebral cortex. Meanwhile, Donepezil treatment (1 mg/kg) during 14 days significantly reduced βAP load in cerebral cortex but not in dentate gyrus and CA3 area.

CONCLUSIONS: Experiments showed that the most potent AChE inhibitor compound 35 (6-methyluracil derivative) permeated the blood-brain barrier, improved working memory in the APP/PS1 transgenic mice and significantly reduced the number and area of Aβ plaques in the brain. Thus, compound 35 is a promising candidate as a bi-functional inhibitor of AChE for treatment of AD.

Keywords: Alzheimer's disease, acetyl-cholinesterase inhibitors, methyluracil derivatives

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References

[1] Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet. 1976;2(8000):1403. doi: http://dx.doi.org/10.1016/S0140-6736(76)91936-X
[2] Cummings JL. Alzheimer's disease. N. Engl. J. Med. 2004; 351: 56-67. doi: 10.1056/NEJMra040223
[3] Citron M. Alzheimer's disease: Strategies for disease modification. Nat Rev Drug Discov. 2010;9(5):387-98. doi: 10.1038/nrd2896

[4] Inestrosa NC1, Dinamarca MC, Alvarez A. Amyloid-cholinesterase interactions. Implications for Alzheimer's disease. FEBS J. 2008;275(4):625-32. doi: 10.1111/j.1742-4658.2007.06238.x. Epub 2008 Jan 17.
[5] De Ferrari GV, Canales MA, Shin I, Weiner LM, Silman I, Inestrosa NC. A structural motif of acetylcholinesterase that promotes amyloid beta-peptide fibril formation. Biochemistry. 2001;40(35):10447-57. doi: 10.1021/bi0101392
[6] Ellman GL, Courtney KD, Andres V Jr, Feather-stone RM. A new and rapid colometric determination of acetylcholinesterase activity. Biochem Pharmacol. 1961;7:88-95.
[7] Weiss ES. An abridged table of probits for use in the graphic solution of the dosage-effect curve. Am J Public Health Nations Health. 1948;38(1 Pt 1): 22-4.
[8] Viayna E., Sola I., Bartolini M., Simone A. De, Tapia-Rojas C., Serrano F.G., Sabaté R., Juárez-Jiménez J., Pérez B., Luque F.J., Andrisano V., Clos M.V., Inestrosa N.C., Muñoz-Torrero D. Synthesis and multitarget biological profiling of a novel family of rhein derivatives as disease-modifying anti-Alzheimer agents. J Med Chem. 2014;57(6):2549-67. doi: 10.1021/jm401824w. Epub 2014 Mar 10
[9] Smith G. Animal models of Alzheimer's disease: experimental cholinergic denervation. Brain Res. 1988;472(2):103-18.
[10] Savonenko A., Xu G.M., Melnikova T., Morton J.L., Gonzales V., Wong M.P., Price D.L., Tang F., Markowska A.L., Borchelt D.R. Episodic-like memory deficits in the APPswe/PS1dE9 mouse model of Alzheimer's disease: relationships to beta-amyloid deposition and neurotransmitter abnormalities. Neurobiol Dis. 2005;18(3):602-17. doi: 10.1016/j.nbd.2004.10.022
[11] Deacon RM, Rawlins JN. T-maze alternation in the rodent. Nat Protoc. 2006;1(1):7-12. doi:10.1038/nprot.2006.2

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Macrocyclic derivatives of 6-methyluracil: New ligands of the peripheral anionic site of acetylcholinesterase

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BACKGROUND: Acetylcholinesterase (AChE) inhibitors are widely used in medicine for pharmacological correction of cholinergic neurotransmission pathologies such as myasthenia gravis (MG) and Alzheimer's disease [1, 2]. The efficacy of anti-AChE drugs is based on their ability to potentiate the effects of acetylcholine (ACh) due to a decrease in the rate of AChE-catalyzed hydrolysis of ACh. Crystallographic studies showed that the active site of AChE is located at the bottom of a deep gorge [3]. It was shown that, in addition to its catalytic center, AChE has other sites that are crucial for the proper functioning of the enzyme. In particular, the so-called peripheral anionic site (PAS) located at the entrance of the active site gorge is responsible for: 1) allosteric modulation of the catalytic center; 2) enzyme inhibition at high substrate concentration; 3) and non-catalytic functions such as enhancement of cell adhesion and neurite outgrowth.

OBJECTIVE: Especially interesting is the relationship between the PAS and pathological beta-amyloid deposition. This led to a new hypothesis for rational design of more effective anti-Alzheimer drugs [4].

METHODS: Concentration of drug producing 50% of AChE activity inhibition (IC50) was measured using the method of Ellman et al. [5]. Toxicological experiments were performed using IP injection of the different compounds in mice. LD50, dose (in mg/kg) causing lethal effects in 50% of animals was taken as a criterion of toxicity [6]. Molecular docking was performed with Autodock 4.2.6 software.

RESULTS: We described previously a new class of selective mammalian AChE *vs.* butyrylcholinesterase (BChE) inhibitors based on alkylammonium derivatives of 6-methyluracil of acyclic topology [7]. In the present study, taking acyclic derivatives of 6-methyluracil as a model AChE inhibitor, we attempted to develop AChE inhibitors that specifically bind to the PAS with weak binding to the active site of AChE. We attempted to increase the size of AChE ligands to restrict specific binding to the PAS of AChE. To this aim we synthesized pyrimidinophanes bearing two o-nitrobenzylethyldialkylammonium heads. Almost all of synthesized pyrimidinophanes inhibited AChE in the nanomolar range. Based on molecular docking simulations, it was suggested that compounds bind AChE to the active center as well as to the PAS or only to the PAS. Thus, we found that introduction of the spacer, flexible or rigid, between [5-(o-nitrobenzylethylammonium)pentyl] units at N atoms of the 6-methyluracil moiety allows tuning the binding of 6-methyluracil derivatives with AChE.

CONCLUSIONS: In conclusion, it can be stated that pyrimidinophanes are promising lead scaffold structures for further design of specific ligands for the PAS of AChE. Also AChE inhibitors with a

6-methyluracil moiety may be considered as potential drugs for the treatment of pathological muscle weakness syndromes.

Keywords: Pyrimidinophanes, beta-amyloid, peripheral anionic site, acetylcholinesterase

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References

[1] Brenner T1, Nizri E, Irony-Tur-Sinai M, Hamra-Amitay Y, Wirguin I. Acetylcholinesterase inhibitors and cholinergic modulation in Myasthenia Gravis and neuroinflammation. J Neuroimmunol. 2008 Sep 15;201-202:121-7. doi: 10.1016/j.jneuroim.2008.05.022. Epub 2008 Aug 5.
[2] Cummings JL. Alzheimer's disease. N Engl J Med. 2004;351:56-67. doi: 10.1056/NEJMra040223
[3] Dvir H, Silman I, Harel M, Rosenberry TL, Sussman JL.. Acetylcholinesterase: from 3D structure to function. Chem Biol Interact. 2010;187(1-3):10-22. doi: 10.1016/j.cbi.2010.01.042. Epub 2010 Feb 4.
[4] Singh M1, Kaur M, Kukreja H, Chugh R, Silakari O, Singh D. Acetylcholinesterase inhibitors as Alzheimer therapy: From nerve toxins to neuroprotection. Eur J Med Chem. 2013;70:165-88. doi: 10.1016/j.ejmech.2013.09.050. Epub 2013 Oct 6.
[5] Ellman GL, Courtney KD, Andres V Jr, Feather-stone RM. A new and rapid colometric determination of acetylcholinesterase activity. Biochem Pharmacol. 1961;7:88-95.
[6] Weiss ES. An abridged table of probits for use in the graphic solution of the dosage-effect curve. Am J Public Health Nations Health. 1948;38(1 Pt 1): 22-4.
[7] Anikienko KA, Bychikhin EA, Reznik VS, Akamsin D, Galyametdinova IV. Compounds with the dioxopyrimidine cycle inhibit cholinesterases from different groups of animals. Chem Biol Interact. 2008;175(1-3):286-92. doi: 10.1016/j.cbi.2008.05.037. Epub 2008 Jun 8.

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Molecular modeling of mechanism of action of anti-*myasthenia gravis* slow-binding inhibitor of acetylcholinesterase

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BACKGROUND: *Myasthenia gravis* (MG) is a chronic autoimmune neuromuscular disorder characterized by fluctuating weakness of voluntary skeletal muscles. The cause of autoimmune response is unknown and only symptomatic therapies for MG are currently available. Pharmacological correction of synaptic failure underlying MG, involves partial inhibition acetyl- and butyrylcholinesterase. Effectiveness of cholinesterase inhibitors in the symptomatic treatment of MG is based on their ability to potentiate the effects of acetylcholine by decreasing the rate of its enzymatic hydrolysis at neuromuscular junctions. Several new inhibitors of AChE were tested in animal model of MG and may be considered as valuable candidates for the treatment of pathological muscle weakness syndromes. In this study, we have investigated mechanisms of ChE inhibition by one of the most active 6-methyluracil derivatives (C547), as well as the possible benefits of using this compound for MG treatment compared to-traditionally used pyridostigmine bromide.

It was experimentally shown that C547 is a «pseudo-irreversible» slow-binding inhibitor of human AChE. Human BChE is reversibly inhibited by C547 with an affinity about 4 orders of magnitude lower than that of human AChE. Slow-binding inhibition of AChE leads to a lasting (over 24 hours) effect on the symptoms of muscle weakness in animal model of MG after a single administration of C547.

OBJECTIVE: The aim of the present molecular modeling study was to reveal mechanism of AChE inhibition by C547 and elucidate its apparent «pseudo-irreversibility».

METHODS: Two principle methods used in the present study were molecular docking and molecular dynamics (MD). Molecular docking was performed with Autodock 4.2.6 software, Lamarckian Genetic Algorithm to obtain structure of protein inhibitor complexes and Local Search for MD snapshots to compare relative binding affinity. For MD simulations NAMD 2.10 software with Charrm 36 force field was used, for the ligand C547 Charmm General Force Field was used, and missing parameters were obtained with quantum mechanical calculations. Unconstrained MD, steered MD (SMD) and free energy calculations with adaptive biasing force were performed.

RESULTS: During unconstrained MD, C547 very rapidly binded to the peripheral anionic site (PAS) of AChE. To pass the bottleneck, application of the external force was required (SMD). Both SMD

modelling and free energy calculation revealed that after crossing the AChE bottleneck, C547 falls into very favorable position. At the same time the rupture of interactions as well as overcoming the bottleneck gates in the course of pulling out procedure requires application of much higher force than during the pulling-in process. This difference between binding and dissociating processes explains apparent «pseudo-irreversibility» of the inhibitor.

CONCLUSIONS: These findings are in good agreement with kinetics study showing that C-547 is a slow-binding inhibitor of type B, i.e. after rapid initial binding of inhibitor, the enzyme-inhibitor complex undergoes an isomerization step. Position obtained by SMD is in good agreement with X-ray data obtained by F. Nachon, IBS, France.

Keywords: Molecular modeling, *myasthenia gravis,* slow-binding, inhibitor, acetylcholinesterase

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Rat paw oedema modeling and NSAIDs: Timing of effects

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BACKGROUND: Non-steroidal anti-inflammatory agents (NSAIDs), steroids and representatives of other pharmacological groups [1, 2] are widely used for pharmacological regulation of inflammation. However, their anti-inflammatory effects are accompanied by serious adverse reactions [3, 4]. There was a hope that newer NSAIDs, selective inhibitors of COX-2, would be safer, but their longer-term use appeared to cause an increased risk of heart attacks and stroke [5]. Carrageenan rat paw oedema model is traditionally used for search and development of new NSAIDs with assessment of effects after 3 to 5 hours after oedema induction [6, 7], neglecting longer-term effects [8].

OBJECTIVE: To compare effects of traditional NSAIDs (indomethacin, naproxen) on the development, duration and intensity of carrageenan rat paw oedema.

METHODS: Carrageenan paw oedema was induced in 18 rats by sub-plantar injection into the right hind paw of the animals of 0.1 ml of 1% aqueous gel of carrageenan-λ (22049 SIGMA λ-Carrageenan plant-mucopolysaccharide, Sigma-Aldrich). We assessed the intensity of the oedema development and its duration by measurements of rat paw volume using plethysmometer 37140 (UgoBasile, Italy). Measurements were made prior to induction of oedema (base-line volume) and at 1, 2, 3, 4, 5, 24, 48, 72, 96, 120, 144, 168 and 192 hours after sub-plantar carrageenan injection. Calculating the percentage of increase in paw volume assessed the intensity of the oedema. The base-line paw volume was taken for 100%.

Animals were divided into 3 groups of 6 rats each; group 1: control (solvent); group 2: naproxen 15 mg/kg and group 3: indomethacin 10 mg/kg. These doses are known as ED50 (effective doses 50) on carrageenan rat paw oedema with single-dose NSAIDs administration [9]. To get the most accurate estimate of the intensity of the simulated by carrageenan inflammatory response and the potential effects of some NSAIDs with their longer-term use we calculated areas under the curve «increase in paw volume – time» using standard method of numerical integration - trapezoidal method. Statistical analysis was performed using Microsoft Office Excel 2007 with the calculation of arithmetic means M, their standard deviations (δ) and standard errors (m). We applied Student's *t*-test and accepted as significant the differences with *P* values equal to or less than 0.05.

RESULTS: The inflammatory reaction induced by carrageenan, developed in a form of swelling/oedema with an increase in the rat paw volume up to 55% of the baseline volume. The maximum volume of oedema was observed in the control group at 3 h after the injection of carrageenan, which is in accordance with the literature data on the development of carrageenan paw edema in rats [10, 11]. Naproxen at a dose of 15 mg/kg showed anti-inflammatory activity at 1, 2, 3, 4 and 5 hours after

administration of carrageenan with suppression of oedema development by 59, 81, 73, 60 and 39% (p=0.03; 0.001; 0.001; 0.001 and 0.01), respectively. There was no oedema inhibition by naproxen at later time-points. Indomethacin at a dose of 10 mg/kg showed anti-inflammatory effect at 2, 3, 4, and 5 hours after carrageenan oedema induction with inhibition of oedema development by 54, 54, 54 and 33% (p = 0.01, 0.004, 0.001 and 0.01) respectively. Again there was no oedema inhibition by indomethacin at the later time-points.

When comparing the calculated areas under the curve «increase in paw volume – time» we found no differences between the values of control and study groups: naproxen (15 mg/kg) and indomethacin (10 mg/kg). We think that these values of areas under the curve «increase in paw volume – time» represent the total inflammatory reaction induced by carrageenan and need to be used for the assessment of future potential anti-inflammatory agents which should not only produce short-term symptomatic oedema suppression, but change the nature of the oedema response, potentially with alternative mechanisms of action. Our experimental findings are in accordance with the well-known lack of effects of NSAIDs on the outcomes of chronic inflammatory diseases [12]. This may be due to the fact that they suppress the development and symptoms of inflammation at the early stages, but the reaction to inflammatory stimuli develops fully over the longer period of time and takes its full course nonetheless. This proves that traditional modeling approaches to future potential anti-inflammatory agents development needs re-assessment.

CONCLUSIONS: Single-dose administration of naproxen (15 mg/kg) or indomethacin (10 mg/kg) exerts decrease in rat paw oedema volume at no later than 5 hours after oedema induction by carrageenan. Evaluating anti-inflammatory activity by the areas under the curve «increase in paw volume – time» proves that a single-dose NSAID's administration has no effect on the inflammatory response when evaluated not by single time-point index (at 3 or 5 hours), but by assessing the oedema development and duration over 192 hours (8 days).

Keywords: Rat paw oedema, NSAIDs, timing of effects, anti-inflammatory

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References

[1] Hardman JG, Limbird LE, Gilman AG, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill; 2001.
[2] Khaziakhmetova VN, Valeeva IH, Ziganshina LE. Anti-inflammatory effects of amitriptyline, diazepam and mebicar. Experimental and Clinical Pharmacology. 2011;12(74):19-22.
[3] Aronson JK. Meyler's side effects of analgesics and anti-inflammatory drugs. Amsterdam: Elsevier; 2009.
[4] Lanas A, Garcia-Tell G, Armada B, Oteo-Alvaro A. Prescription patterns and appropriateness of NSAID therapy according to gastrointestinal risk and cardiovascular history in patients with diagnoses of osteoarthritis. BMC Med. 2011;9:38.
[5] Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092-102.
[6] Haider S, Nazreen S, Alam MM, Gupta A, Hamid H, Alam MS. Anti-inflammatory and anti-nociceptive activities of ethanolic extract and its various fractions from Adiantum capillus veneris Linn. Journal of Ethnopharmacology. 2011;138:741-7.
[7] Shang X, Wang J, Li M, Miao X, Pan H, Yang Y, Wang Y. Antinociceptive and anti-inflammatory activities of Phlomis umbrosa Turcz extract. Fitoterapia. 2011;82(4):716-21.
[8] Cong HH, Khaziakhmetova VN, Ziganshina LE. Modeling inflammatory edema: Are the models interchangeable. Experimental and clinical pharmacology. 2015;78(7):24-31.
[9] Mironov AN. Guidelines for preclinical studies of drugs. Moscow: Grief and K; 2012.
[10] Chao M, Jang JM. Animal models of pain. Neuromethods. 2011;49:23-40.doi 10.1007 / 978-1-60761-880-5_2, © Springer Science + Business Media, LLC 2011.
[11] Lee OI, Crosby G. Halothane effect on formalin- induced paw edema and flinching in rat. J Korean Med Sci. 1999;14:34-8.
[12] Lanas A, Tornero J, Zamorano JL. Assessment of gastrointestinal and cardiovascular risk in patients with osteoarthritis who require NSAIDs: the LOGICA study. Ann Rheum Dis. 2010;69:1453-8.

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Pirimidine derivatives as hepatoprotective agents

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BACKGROUND: Research and development of effective hepatoprotective medicines is one of the priority areas of research in Russia. Literature data shows that active research and development of hepatoprotectors is carried out both in Russian and other countries [1–6]. Pirimidines are used as hepatoprotective medicines stimulating protein synthesis and reparation of hepatocytes in toxical and infectious liver disorders [7]. In our previous work ee have shown hepatoprotective properties of pyrimidine derivative, named Xymedon [8]. This research, funded by the Russian Science Foundation, is aimed at identifying the most effective hepatoprotectors among pirimidine derivatives.

OBJECTIVE: To test hepatoprotective properties of one of the new Xymedon (Xym) derivative - L-ascorbate 1-(2-hydroxyethyl)-4,6-dimethyl-1,2-dihydro-pirimidine-2-one (Asc-Xym) on the toxic liver damage model induce by carbon tetrachloride (CTC, CCl_4).

METHODS: The toxic liver damage in rats was modeled by subcutaneous injection of CTC (CCl_4) in vegetable oil (mixed at 1:1 ratio) at a dose of 2 ml per kg. The experiments were carried out under two schemes: 1) oral administration of Xym or Asc-Xym preparations by gavage at the doses of 10 and 20 mg/kg followed by subcutaneous injection of CTC 1 hour after pyrimidine oral administration and continued for 3-4 days; - this was the design of preventive pyrimidine use, 2) liver damage modeling by CTC subcutaneous injections for 3 days followed by oral administration of Xym, Asc-Xym or Thiotriazolin (Thi) preparations at the doses of 20 mg/kg for 5 days; - this was the design of therapeutic scheme. The rats of control groups were injected with CTC according to the same schemes, but did not get any preparations. We looked at some biochemical parameters of blood serum: alanine aminotransferase (AlAT), aspartate aminotransferase (AsAT), their ratio (de Rytis coefficient), and the total protein level as the markers of toxic liver damage. We performed statistical data analysis by rank nonparametric Mann-Whitney U-criterion for comparison of two independent groups. We evaluated pathomorphologic characteristics of liver damage on the histological slices colored with hematoxylin and eosin.

RESULTS: Carbon tetrachloride (CTC) caused profound changes in the studied biochemical parameters of rats' blood serum. The AlAT activity level in the serum of control animals in the preventive scheme was 116,23 (the median) with the lower quartile and the upper quartile of 76,96 and 211,71 U/l respectively; the AsAT level was 230,08/201,49-290,03 U/l; this was the increase in comparison with the reference values. De Rytis coefficient was 1,76 /1,47-2,67. This was the decrease in comparison with the reference values of intact group (36,37/28,18-43,3 U/l; 132,95 /118,24-164,00 U/l and 4,26/3,03-5,23 respectively). The differences were statistically significant at $P<0{,}001$. In the experimental groups the changes of the biochemical parameters with respect to the reference values were less marked than

in Control. The AlAT level was 89,86/87,06-165,15; 103,23/38,19-270,87 U/l; 80,28/6,12-141,82 and 100,33/62,24-144,64 U/l in the groups of rats treated with Xym at the doses of 10 and 20 mg/kg or Asc-Xym at the doses of 10 and 20 mg/kg respectively. Similarly, in the same groups the AsAT level was 211,19/170,20-250,16; 193,61 /181,57-274,69 U/l; 190,91 /65,21-198,65 and 173,25/135,50-210,70 U/l respectively. The differences of the AsAT level were statistically significant at $P<0,05$ in comparison with Control in the both groups treated with Asc-Xym.

Nnearly 2 times increase of the AlAT level (67,60/1,22-94,60 U/l) ($P=0,00002$) was shown in comparison with the reference values in the rats of Control group in the therapeutic scheme. However the AsAT level (163,80/130,1-178,8 U/l) was only slightly higher than reference values. De Rytis coefficient (2,07/1,78-3,48) was significantly lower than the reference values ($P=0,001$). The total protein level (59,36/55,17-60,10 g/l) was lower than the reference values (65,06/62,06-68,98 g/l) by 8,4%. The differences of biochemical parameters as compared with the reference values in rats of experimental groups treated with Xym, Thi and Asc-Xym at the doses 20 mg/kg were less than those in the Control groups. They were: AlAT 52,49/44,64-62,30 and 61,42/53,20-96,66 U/l, AsAT 105,00/94,7-142,3 and 235,35/111,7-335,6 U/l, de Rytis coefficient 2,09/1,87-2,28 and 3,24/1,86-4,53, total protein 63,10/62,46-64,27 and 62,46/58,70-64,43 g/l respectively in the groups treated with Xym and Thi. The values of the studied biochemical parameters AlAT (39,04/32,46-44,24 U/l), AsAT (111,9/105,27-155 U/l), de Rytis coefficient (2,87/2,72-3,30), total protein (62,89/61,46-68,14 g/l) of the rats, treated with Asc-Xym, were the most close to the reference values in comparison with other experimental groups.

The analysis of histological slices revealed large areas of steatosis and necrosis of hepatocytes in Control groups in both schemes. These were less pronounced in experimental groups than in Control groups and particularly in rats, treated with Asc-Xym.

CONCLUSIONS: Hepatoprtotective properties of the new compound L-ascorbate 1-(2-hydroxyethyl)-4,6-dimethyl-1,2-dihydropirimidine-2-one were established. The hepatoprotective efficacy of the compound is higher than that of Xymedon and Thiotriazolin.

Keywords: Rats, pyrimidine, liver damage, carbon tetrachloride, biochemical markers

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References

[1] Vengerovskii AI, Baturina NO, Chuchalin VS, Saratikov AS. Effect of polyphenol-containing hepatoprotectors on the experimental chronic hepatitis pattern. Pharmaceutical Chemistry Journal. 1996;30(2):69-71. doi: 10.1007/BF02218867

[2] Kabankin AS, Gabrielyan LI. Relationship between structure and hepatoprotector activity of adamantine derivatives. Pharmaceutical Chemistry Journal. 2005; 39(3):135-9. doi: 10.1007/s11094-005-0102-3

[3] Shilova IV, Zhavoronok TV, Souslov NI, Novozheeva TP, Mustafin RN, Losseva AM. Hepatoprotective properties of fractions from meadowsweet extract during experimental toxic hepatitis. Bulletin of Experimental Biology and Medicine. 2008;146(7):54-7. doi: 10.1007/s10517-008-0226-z

[4] Kushnerova NF, Sprygin VG, Rachmanin YuA. [Influence of complex plant polyphenol preparation Eklikit on process of liver functions recovery after alcohol intoxication]. Biomedical Chemistry. 2004;50(6):605-11. Russian

[5] Demirdag K, Bahcecioglu IH, Ozercan IH, Ozden M, Yilmaz S, Kalkan A. Role of L-carnitine in the prevention of acute liver damage induced by carbon tetrachloride in rats. Journal of Gastroenterology and Hepatology. 2004;19:333-8. doi: 10.1111/j.1440-1746.2003.03291.x

[6] Saratikov AS, Chuchalin VS, Ratkin AV, Ratkin EV, Fedoreev SA, Bulgakov VP. [Hepatoprotective properties of polyphenolic complexes from wood and cell culture Maak Amur]. Experimental and clinical pharmacology. 2005; 68(2):51-4. Russian

[7] Zobov VV, Nazarov NG, Vyshtakalyuk AB, Galyametdinova IV, Semenov VE, Reznik VS. Efficiency of new pirimidine derivatives influence on physical working capacity of rats in the test “swimming to failure”. Human ecology. 2015;1:28-35. Russian

[8] Vyshtakaliuk AB, Nazarov NG, Porfiriev AG, Zueva IV, Minnechanova OA, Mayatina OV, Reznik VS, Zobov VV, and Nicolskyi EE. The Influence of the Xymedon Preparation (Hydroxyethyldimethyldihydropyrimidine) on the Rat Liver Recovery under Toxic Damage Induced by Carbon Tetrachloride. Doklady Biochemistry and Biophysics. 2015;462(1):143-6. doi: 10.1134/S1607672915030011

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Human butyrylcholinesterase polymorphism: Molecular modeling

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BACKGROUND: Prolonged apnoea following injection of ester-containing myoralaxants was first described in 1953. Because a large part of administered succinylcholine is shortly hydrolyzed by plasma butyrylcholinesterase (BChE) under normal conditions, prolonged apnoea was attributed to deficiency in BChE. It was found that BChE deficiency was due to genetic variations. Human BChE gene shows a large polyallelism. About 75 natural mutations of the *BCHE* gene have been documented so far [1]. Most of them cause alteration in BChE activity through point mutation effect on catalytic activity. Frame shifts and stop codons may also affect expression, or cause truncations in the sequence.

OBJECTIVE: Recently, two novel BChE "silent" variants, Val204Asp [2] and Ala34Val [3], causing prolonged neuromuscular block after administration of mivacurium, were discovered. Mutations were genetically and kinetically characterized. The aim of the current study was to understand how these mutations determine "silent" phenotype.

METHODS: Molecular dynamics studies were carried out with NAMD 2.9 software at the Lomonosov supercomputer. Charmm 36 force field was used, periodical boundary conditions, 1 atm pressure, 298 K. 100 ns molecular dynamics runs were performed for the wild-type BChE and its mutants Val204Asp and Ala34Val.

RESULTS: Unlike wild-type BChE, which retained its operative catalytic triad through the whole MD simulation, the catalytic triad of mutants was disrupted, making chemical step impossible. Val204Asp mutation leads to reorganization of hydrogen bonding network around the catalytic triad, which in turn increases the distance between catalytic residue main chains. Mutation Ala34Val, located on the protein surface, leads to increased fluctuations in the Ω-loop and subsequent disruption of the gorge structure, including disruption of the catalytic triad and formation of new hydrogen bonds involving catalytic center residues.

CONCLUSIONS: Comparative study of the "silent" Ala328Asp mutant and the catalytically active mutant Ala328Cys shows that MD approach can discriminate between the differential effects of point mutations at a same position.

Keywords: Genetic, polymorphism, butyrylcholinesterase, molecular modeling, allelozymes

Conflict of interest statement: None.

References

[1] Lockridge, O. Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses. Pharmacol Ther. 2015;148:34-46. doi: 10.1016/j.pharmthera.2014.11.011. Epub 2014 Nov 20.

[2] Delacour, H., Lushchekina, S. et al. Characterization of a Novel BCHE "Silent" Allele: Point Mutation (p.Val204Asp) Causes Loss of Activity and Prolonged Apnea with Suxamethonium. PLoS One. 2014; 9(7): Published online 2014 Jul 23. doi: 10.1371/journal.pone.0101552

[3] Delacour, H., Lushchekina, S. et al. Characterization of a novel butyrylcholinesterase point mutation (p.Ala34Val), "silent" with mivacurium. Biochem Pharmacol. 2014;92(3):476-83. doi: 10.1016/j.bcp.2014.09.014. Epub 2014 Sep 28.

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ATP-induced changes in rat skeletal muscle contractility

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BACKGROUND: Extracellular purine compounds, adenosine triphosphate (ATP) and adenosine, are involved in regulation of many cell functions, engaging in rapid and long-term cellular processes. The nucleotides, including ATP, exert their extracellular effects by influencing membrane P2 receptors. ATP outside of the cell rapidly is metabolized by the ecto-enzyme system to produce adenosine, which acts on separate adenosine (P1) receptors. Since adenosine and ATP often are functional antagonists, ATP degradation not only limits its effect, but also brings new ligand with different, often opposing, properties. Great variety and widespread of P2 and adenosine receptors in the body emphasize the important physiological and pathophysiological significance of these receptors, and make them very attractive as targets for potential drug action.

The existence of several subtypes of P2 and adenosine receptors has been shown in the skeletal muscles. ATP as a co-transmitter is densely packed together with classical neurotransmitters in the presynaptic vesicles of vertebral motor units but until recently ATP was refused to have its own functional role there and was recognized only as a source of adenosine. However, on the eve of the third millennium there appeared data that ATP, released from the nerve ending and acting on presynaptic P2 receptors, suppresses subsequent quantum release of acetylcholine. The final product of its degradation, adenosine, performs a similar inhibitory effect acting on presynaptic adenosine receptors.

Despite the fact that the mechanisms of presynaptic inhibitory action of ATP and other purines were studied earlier, the object of those studies was usually neuromuscular synapse of cold-blooded animals. The few studies, in which experiments were carried out on preparations of warm-blooded animals, described the basic effects of purines. These often were guided by the convenience of preparation of the synapses of the diaphragm. We think that those results cannot be considered as typical effects of ATP and other purines on skeletal muscles and could not be extrapolated to all warm-blooded animals. Furthermore the role of ATP and its derivatives in the accumulation of vertebrate muscular effort has not been investigated.

It is known that in physiological conditions vertebrates may mobilize only up to a third of the maximum muscle force. Why the two-thirds of muscular strength are not used normally but may be used at stress, remains unknown.

It is known that the body's adaptive response to stress is a change in the activity of the endocrine system. The leading role in this is given to catechol amines and glucocorticoids, mobilized in significant quantities in blood under stress.

We have found previously that incubation of frog sartorius muscle with hydrocortisone resulted in a decrease of contraction amplitude. However, when hydrocortisone was used in combination with ATP, its inhibitory effect on contractile responses disappeared. It is interesting that hydrocortisone had

no effect on the inhibitory effect of adenosine. In the following experiments, assessing the effect of hydrocortisone on rat soleus muscle, it was established that hydrocortisone and purines had similar inhibitory effect. When ATP and hydrocortisone were given together the same oppression occurred.

OBJECTIVE: To study the effects of ATP and adenosine on contraction parameters of rat skeletal muscle and assess the impact of the catechol amines on these processes.

METHODS: Contractions of rat soleus muscles were recorded isometrically by mechanical sensor Linton FSG-01 (UK) according to standard procedures. The average of muscle parameters received within 30 seconds (30 responses) was treated as one result. Amplitude and time characteristics of the curve reductions were estimated. During all experiments standard Krebs solution flowed through the bath continuously to which agents were added at necessary concentrations. All experimental animals were maintained and prepared for dissection under the European Convention for the Protection of Vertebrate Animals used in scientific experiments. All agents used in the study were supplied by Sigma Chemical Company Ltd. (UK), Tocris Cookson and Research Biochemicals International (USA).

RESULTS: The concentration of 100 μM for adenosine is close to saturation [1], and for its predecessor ATP this concentration is created after the passage of a pulse through the synapse [2]. We used this concentration of purines to study the mechanism of action of adenosine and ATP on neuromuscular synapse.

The effect of adenosine was partially inhibited in the presence of 100 μM 8-SPT, an antagonist of adenosine receptors. The contraction force of "fast" and "slow" rat skeletal muscles was raised by half in the presence of norepinephrine. In the presence of norepinephrine adenosine exerted its effect fully, but ATP by half reduced its depressor effect on the contraction force of both muscles.

CONCLUSIONS:

1. Norepinephrine increases half times of the reduction of «fast» and «slow» skeletal muscle.
2. In the presence of norepinephrine, inhibitory effect of adenosine on contraction force is maintained.
3. Inhibitory effect of ATP on contraction force of studied skeletal muscles becomes twice less pronounced in the presence of norepinephrine.

We think that reduction of ATP depressive effect on the skeletal muscle by norepinephrine may be an adaptive response to acute stress.

Keywords: Norepinephrine, effect of ATP, rat, skeletal muscle, neuromuscular synapse

References

[1] Ribeiro JA, Walker J. The effects of adenosine triphosphate and adenosine diphosphate on transmission at the rat and frog neuromuscular junctions. Br J Pharmacol. 1975;54(2):213-8. doi:10.1111/j.1476-5381.1975.tb06931.x

[2] Hume RI, Honig MG. Excitatory action of ATP on embryonic chick muscle. J Neurosci. 1986;6(3):681-90. Available from: http://www.jneurosci.org/content/6/3/681.full.pdf

Approaching Evidence-Based Medicine

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Pharmaceutical counseling: Between evidence-based medicine and profits

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BACKGROUND: The number of pharmacies, which produce drug formulations locally, has recently considerably reduced in Russia. Pharmacies mainly operate as retailers of industrially manufactured drugs.

Pharmaceutical consultation of customers at pharmacies aimed at responsible self-medication is the most popular and accessible feature of pharmaceutical care. In Russia there is a significant list of medicines approved for sale in pharmacies on a non-prescription basis that is specified in the product label. In this regard, the role of pharmacists in public health in Russia increases. Pharmacist, working directly with population, is an important figure for the rational use of medicines. This type of work requires high level of professional training and appropriate ethics.

OBJECTIVES: To explore the current status of pharmaceutical counseling in Russia.

METHODS: Situation analysis, surveys of pharmacists.

RESULTS: Our experience in the system of postgraduate professional education, the results of the survey of pharmacists, and the long-term dialogue with pharmacists allowed us to identify several unresolved issues in the work of a pharmacist selling non-prescription drugs.

Lack of differentiation in the functions of a pharmacist with a higher education and pharmaceutical technologist: In production/industrial pharmacy technicians are engaged in manufacturing of pharmaceutical formulations. However, due to the loss of production functions technologists had to move away from production laboratories of apothecaries to the sales area. Currently, the apothecary's assignment to receive prescriptions and dispense medications can be fulfilled by either a pharmacist or a pharmaceutical technician. It significantly discerns the pharmacy from the medical organization with clearly delineated functions of doctors and nurses. Russian regulations should consider the level of education required for high-quality pharmaceutical counseling.

Contradiction between the pharmacist's special functions and trade procedure with the lack of pharmaceutical counseling standards: Article 1.1 "Code of Ethics of the pharmaceutical worker of Russia" states: *"The main task of the professional activity of the pharmaceutical worker - protection of human health",* Article 1.3 states that a pharmaceutical worker must take professional decisions solely in the interests of a patient [1]. However, the pharmacy is a trade organization, thus as a retailer the pharmacy is directly interested in making profits and increasing sales of pharmaceutical products, including non-prescription medicines. Moreover, while the clinical medicine is monitored for unjustified prescribing and measures are being taken to prevent polypharmacy, for a pharmacist the growing sales of over-the-counter drugs, active promotion of dietary supplements, homeopathic medicines, medical devices, and, consequently, an increase of financial indicators (particularly "average purchase size") – all are characteristics of success [2].

Rational use of over-the-counter medicines requires introduction of pharmaceutical counseling standards (pharmaceutical care) according to symptoms - major reasons to visit a pharmacy as part of responsible self-medication (cold, sore throat, headache, diarrhea, etc.). Standards of pharmaceutical counseling should be objective, reliable and up-to-date and contain recommendations for the rational use of over-the-counter drugs as well as indications requiring treatment to the doctor. Standardization of pharmaceutical counseling in terms of Evidence-based Pharmacy would enhance the efficiency, safety and cost-effectiveness of over-the-counter medicines.

Currently, the lack of clinical component in the higher pharmaceutical education and the lack of approved standards of pharmaceutical counseling lead to the introduction of cross-selling technologies (which are broadly applied in other areas of trade, for example, the offer of a boot-polish during the sale of shoes) to the pharmaceutical practice [2, 3]. However, drugs belong to a special group of products, proper selection of which requires special education, and the consumer is not always able to evaluate the quality of the recommendations. Marketing cross-selling recommendations are aimed at promotion of the over-the-counter medicines for customers buying prescription drugs. For example, business coaches recommend the pharmacists to make additional offers: with the purchase of physician-prescribed antibiotics – offer of vitamins, with prescribed nonsteroidal anti-inflammatory drugs - commercially available ointment with non-steroidal topical formulation ("to enhance the effect") and others. These recommendations do not agree with evidence-based medicine and lead to inefficient use of over-the-counter drugs and unjustified financial expenses.

CONCLUSIONS: Thus, to ensure the rational use of medicines permitted for free (non-prescription) dispensing at the pharmacies, pharmaceutical information needs standardization on the basis of evidence-based medicine as well as standardization of the pharmaceutical counseling service. The development of practical recommendations on the rational use of over-the counter medicines by doctors and pharmacists with further adoption at the state level, the recommendation of most secure, efficient and cost-effective over-the-counter medications during pharmaceutical counseling in pharmacies will contribute to the restoration and preservation of public health.

Keywords: Pharmaceutical counseling, evidence-based medicine, profits, pharmacy, pharmacist

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References

[1] Ethical code of pharmaceutical worker in Russia (pharmacists and druggists). Novaya Apteka. Apteka i rynok. 1999;8: p. 17-21. Russian

[2] Tchertkov J. "Pyramid of apothecary's sales" – proven tool to increase average purchase size. [Internet]. 2012 Feb 13 [cited 2012 Feb 13]; Available from: http://www.apteka.ua/article/124706 . Russian

[3] Lisovsky P. Sales management in the apothecary of high-profit goods. [Internet]. 2012 May 15 [cited 2012 May 15]; Available from: http://www.pharmvestnik.ru/publs/lenta/obzory/organizatsija-prodazhi-v-apteke-vysokopribyljnyx-tovarov.html#.UClW3qBadiA. Russian

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Meta-analysis: Problems with Russian Publications

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BACKGROUND: Meta-analysis is a powerful tool to identify Evidence Based medical technologies (interventions) for use in every day practice. Meta-analysis uses statistical approaches to combine results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree. Meta-analysis is a quantitative, formal study design used to systematically assess previous research studies to derive conclusions from this research. Meta-analysis may provide more precise estimate of the effect of treatment or risk factor for a disease, or other outcomes, than any individual study contributing to the pooled analysis.

We have quite a substantial number of Russian medical publications, but not so many Meta-Analyses published in Russian. Russian publications are cited in English language papers not so often. A total of 90% of clinical studies included in published Meta-Analyses incorporate only English language papers. International studies or papers with Russian co-authors are published in English language.

OBJECTIVES: The main question is: what is the problem with inclusion of Russian medical publications in Meta-Analysis?

RESULTS: The main reasons for this are the following:

1) **It is difficult to find Russian papers, difficult to work with them and to work with Russian journals:**
    a. There are single Russian Biomedical Journals, which are translated into English and are included in databases (PubMed, Scopus and other), despite the fact that all of them have English language abstracts.
    b. The majority the meta-analyses authors use in their work different citation management software such as the Mendeley, Reference Manager, ProCite, EndNote, and others. These citation management systems allow scientists to organize their own literature databases with internet searches and have adds-on for the Office programs what makes process of literature citation very convenient. The Internet sites of the majority of International Journals have built-in tools for saving citations to reference manager software. The majority of articles in Russian journals cannot be captured by citation management systems: they do not have special coding of articles descriptors.
    c. Some journals still have PDF files of the whole journal issue without dividing it into articles and do not provide any descriptors, making manual time-consuming input of information the only possibility. Moreover the context search of the article content is unavailable for search engines.
2) **The quality of research.** This problem has been discussed for more than twenty years already. Still we have too many publications of poor quality of study design and statistical analysis. With

the exception of pharmacological clinical tails, designed and supervised by international Pharma industry, many interventional studies, conducted in Russia, have methodological flaws inferring a high risk of bias:

a. Absence of adequate control,
b. No standard endpoints, duration of therapy and follow up,
c. Absence of randomization and blinding,
d. Low power of studies: sample sizes are calculated (if calculated at all) in such a way, that the main goal is to have as small sample size as possible. Very often statisticians have to solve the problem how to substantiate a small number of subjects, that sponsor could afford, instead of calculating the needed sample size to reach enough power.
e. No standards of statistical analysis.
f. Russian journals do not have standards for description and presentation of study results, in particular, results of statistical analysis (a reader even cannot see what is presented: standard deviation (SD) or standard error of the mean (SEM).

We have a long standing experience in analysis of methodological and statistical quality of Russian biomedical publications and have found up to 80% publications with statistical and methodological errors and high risk of bias.

In our practice, we had tried to perform two Meta-analyses for two local pharmaceutical products for prevention of stroke recurrence. For the first product, we did not found even two single Russian language studies suitable for the analysis (incomparable populations, different designs, endpoints, doses etc.). For the second product, only four studies had comparable populations and standard internationally approved scales for effectiveness analysis. However, the combinations of scales, the length of treatment and follow up differed widely, so that we could combine the results of only 2 or 3 studies for each end point.

CONCLUSIONS: Russian researchers have to follow internationally recognised standards in study design, selection of endpoint, timelines and therapy regimens, data analysis and presentation of results. Russian journals need to develop consolidate rules for authors of clinical trials and epidemiological research of result reporting close to international standards. In this case the international Network EQUATOR (Enhancing the QUAlity and Transparency Of health Research http://www.equator-network.org/) is one to be taken into account. In addition, Russian Journals have to improve their online information for better interaction with search engines and citation managers.

Keywords: Meta-analysis, evidence-based medicine, Russian publications, epidemiological research, clinical trials

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Clinical conferences for physicians: Who sets the agenda?

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BACKGROUND: Clinical conferences are generally defined as scheduled events at which practicing physicians themselves present to their colleagues interesting clinical cases, share their new experiences and learn about the latest achievements of medical science and practice. The value of a clinical conference is thought to be in direct communication between physicians, in analysis of topical issues in a given specialty with the aim to improve the quality of care. Speakers based on their own observations and studies reveal the most urgent problems, analyze results and offer potential decisions to their colleagues interested in the same questions. The event format may be different: workshops, highly specialized sections, round tables and seminars with participation of the leading specialists in a given field. These conferences are generally organised by the Ministries and Departments of Health, by leading research and/or educational institutions in the field, by recognised medical centres and other institutions. Recently pharmaceutical companies got actively involved in medical events, acting as sponsors of various scientific conferences and congresses, however threatening the mission of these events [1]. This brings up some uneasy questions: who are the medical conferences for? Who is in charge of setting the conference agenda? Do they contribute to evidence-based medicine; do they contribute to better health? Unfortunately, there is a trend to duplication or multiplication of conferences: various agencies and departments deliver the same conferences, presentations at which are often pre-arranged by pharmaceutical companies and do not have clear scientific novelty, while the conferences themselves have largely transformed into advertising of new pharmaceuticals or new technologies [2]. Pharmaceutical corporations sponsor invited speakers paying for their trips and paying honoraria, organising cocktail parties as part of medical activities. With the help of leading experts with impressive titles serving as speakers at the conferences, pharmaceutical companies are trying to be as close as possible to routine practice of prescribing of certain drugs, manipulating evidence, controlling scientific societies as well as the process of clinical guideline development and publication of research results [3]. The degree of expert involvement depends on their level of influence [4].

OBJECTIVE: We aimed to study how often regular medical practitioners attend these conferences; to analyse who were keynote speakers and where they were coming from; to identify which organizations were responsible for organisation of these conferences and for sending out invitations to these conferences and for disseminating information about them.

METHODS: We summarized all the invitations (printed on paper) received by one regular medical practitioner employed with the outpatient clinical of the city of Kazan for the period of two years (2012-2013).

RESULTS: During the study period (2012-2013), a regular medical practitioner received 47 printed paper invitations to scientific conferences: 22 in 2012 and 25 in 2013. The conferences were not distributed evenly over the months of the years. November appeared to be the month with the highest density/ number of medical conferences: 7 conferences in 2012 and 10 in 2013. If the distribution was even, then we could calculate the number per month dividing the number per year by 9 active months (excluding July, August and September). This resulted in 2.4 and 2.8 conferences per month. Among these studied conferences 4 were organized by public health agencies: invitation tickets were accompanied by the corresponding official order to organise a conference, issued by the Health Department. Noteworthy, that 2 of these conferences were held in conference rooms of the largest hotels of the city. Forty-one out of 47 medical conferences were sponsored by big pharma: either jointly with the major medical higher educational institutions of the city or plainly by pharmaceutical companies. Seventeen conferences were held during official working hours, in the first half of the day. Not only the logo of the pharmaceutical companies was printed on invitation tickets, but there was also an advert of the promoted pharmaceutical brand.

Nine conference invitations contained invitation to dinner. In one of the invitations to a conference on neuroscience it was written: "dinner under the unforgettable music". Two conference invitations contained invitation to a lunch. Programs of 20 conferences (which were included) listed guest lecturers, coming from the leading medical universities in Moscow and St. Petersburg. Opinion leaders' involvement: some of the leading experts acted as speakers from 4 to 7 conferences a month in this sample conference invitations package of a regular polyclinic physician.

CONCLUSIONS: In 2012-2013 health practitioners were invited to attend medical conferences regularly, at least 2 times a month, with November being the busiest month. The keynote speakers were the opinion leaders from the local medical educational institutions and visitors from Moscow and St. Petersburg; their involvement with the conferences was repetitive. Governmental institutions jointly with big pharma were responsible for organisation of these conferences and attracting audience.

Limitations of these observations: Unfortunately, the information on printed-paper conference invitations was not complete because not all tickets have survived. From the interview with the physician we know that in addition to these printed on paper invitations there were many invitations and alerts sent out by e-mail, SMS messages and personal phone calls, making the regularity of these conferences much higher. The physician, who kindly provided this information to us, asked not to be named or thanked in any public presentation of the results of these analyses.

Keywords: Conferences, opinion leaders, health practitioners, physicians, pharmaceutical companies

Conflict of interest statement: We declare that we have no conflict of interest.

References

[1] Shaderkin VA. Conference of doctors in life. [Internet] 2012 [cited 2012 Dec 14]. Available from: http://uroweb.ru/db/article/konferentsii-v-zhizni-vrachei
[2] Giovanni A Fava. Should the drug industry work with key opinion leade rs? BMJ. 2008;336(7658): 1404-5. doi: 10.1136/bmj.39541.702870.59
[3] Soans A. KOL Relationship Management in Pharma Device- Workshop Highlights MedicineMan [Internet]. 2010 Aug 23 [cited 2010 Aug 23]; Available from: http://medicinman.net/download/MedicinMan_August_2014.pdf
[4] Arzhanov NA. Pharmacy and medicine: The two sides of the same coin. pharmacist. -2007 Dec; 12-s; 15-17.

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Quality of postgraduate medical education

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BACKGROUND: In recent years, huge efforts to improve quality control process and efficiency of healthcare were put in advancing health systems in Russia. There are measurable and noteworthy achievements, there are unresolved issues.

It's impossible to manage the process of improving the quality and efficiency of care without high-quality training of respective troops. However, in the last decade a phrase about the poor quality of postgraduate medical education has been heard periodically in the speeches of the leaders at various levels. The source is unknown, but this information continues to be spread by word of mouth as a regular component of speeches about health issues. Considering that the "poor quality" of postgraduate education has not been substantiated by solid evidence, this informational spam, of course, needs to be overcome. It is not only harmful to health system overall, it is harmful in particular for the process of formation of personnel reserve, but it also discredits the whole system of postgraduate education and a titanic work of thousands of teachers, who work as enthusiasts, most of them performing valuable research, teaching and organizational work.

OBJECTIVE: To provide situation analysis in the field of postgraduate medical education.

RESULTS: First of all, it begs the question – how and who measures the quality of education. What indicators in the evaluation process are key? As a rule, when assessing quality in any field, preference is given to the opinion of the consumer.

Our direct customers are the heads of health organs and institutions who regularly undergo advanced training in the specialty "Public Health and Health Care" at sub-faculty. After the completion of each cycle of training and exams, each participant fills out a questionnaire, which points out the level of quality of pedagogical activity of the sub-faculty. The analysis of these questionnaires shows that the students generally give high assessment of the quality of pedagogical process. The health authorities of subjects of Russia that send the heads of their subordinate medical organizations to study public health and healthcare are satisfied with the work of sub-faculty, professorial teaching staff, they send thank-you letters to the educational organization.

In this regard, natural questions related to the overall methodology for the assessment of the quality of education in the system of postgraduate training of doctors arise, which today is still very insufficiently developed.

The quality of education in the system of continuous medical education of physicians can be assessed in the following levels with the help of quality indicators, which have to be developed appropriately for each particular level. In our opinion, the following levels should be included:

1) The level of the sub-faculty
2) The level of the faculty

3) The level of the medical organization
4) The level of the territorial health authority
5) The level of the subject of the federation.

CONCLUSIONS: Multidimensional assessment of the results of evaluation in the mentioned levels will allow providing an integrated assessment system of quality of continuous medical education in the country.

Keywords: Continuous medical education, quality control, assessments

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Evidence-based medicine Training: Kazakhstan experience

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BACKGROUND: Understanding principles of evidence-based medicine is of vital importance for improving quality of care, promoting public health and health system development. Understanding principles of evidence-based medicine allows using the most powerful information source, which have ever existed in medicine.

OBJECTIVE: To evaluate the effectiveness of teaching Evidence-Based Medicine, including long-term outcomes of training.

METHODS: The study was conducted at the Medical University of Astana, where the Scientific and Educational Center of Evidence-Based Medicine was established in 2010 with the help of the corresponding project of the World Bank. The participants of the study were the faculty trained in Evidence-Based Medicine at the workshop "Introduction to Evidence-Based Medicine" for the period of 2010–2015 years. There were a total of 16 workshops during the period, and 323 employees were trained. All participants were asked to complete our questionnaire two times: before the training - pre-training (to determine the initial level of a listener) and after the training – post-training (to determine the acquired level and get the feedback). Questionnaires were prepared in such a way, that the majority of questions before and after training were identical. Thus, it provided a clear picture of the effectiveness of training. Questions in the survey were open-ended so that the respondents had the opportunity to freely and fully express their views. The main part of the questionnaires included the following questions: "Do you understand what evidence-based medicine is", "how do you understand what the study design means", "what is randomization", "how research is classified", "do you know the steps of decision-making according to Evidence-Based Medicine, list them", "what literature do you prefer to use when searching for information (print, electronic, etc.)", "what resources on the Internet do you prefer to use".

RESULTS: Only 30–35% of respondents gave correct answers to the questions on understanding EBM, understanding study designs, randomization. There were no correct or complete answers to the question on study classification. Again, 35% of respondents provided correct answer to the question about the stages of decision-making process from the perspective of EBM, 65% - provided no answer. One fourth (25%) of the respondents preferred using printed literature. Only very few respondents indicated Cochrane Library, Medline (PubMed), Tripdatabasa as preferred Internet sources of information, with 40% indicating Google and 60% - other sources.

The results of post-training survey showed that nearly 90% of the respondents gave correct answers to all the questions.

With the aim to identify knowledge survival (the long-term training outcomes) we conducted the third survey in May 2014 in previously trained people at the seminar "Introduction to Evidence-Based Medicine". The respondents were asked to answer 4 questions, and to assess previously obtained information on the basics of Evidence-Based Medicine on a 10-point scale.

We found that 100% of the respondents answered «Yes» to the question: «Have you changed your behavior after the seminar?» To the question: «Have you encountered difficulties in implementing the principles of evidence-based medicine in the educational process?» 56% of the respondents answered that they had not encountered any difficulties. The other 44% faced the difficulties associated with implementation of Evidence-Based Medicine: lack of understanding by students, low knowledge survival rate among students, too many questions from the students, difficult disputes and discussions.

To the question: «Have you encountered difficulties in implementing the principles of Evidence-Based Medicine in practical health-care?» only 37.5% of the respondents answered that they had not encountered difficulties. But the remaining 62.5% of the respondents faced the problems and difficulties in implementing the principles of evidence-based medicine in their practice. These were: failure in implementing, lack of understanding on the part of colleagues, commitment to traditional obsolete methods of treatment, discrepancy between some of the existing standards of diagnosis and treatment and principles of evidence-based medicine.

To the question: «Are there any end products after listening to the seminar?» 67% of the respondents answered in affirmative. The end products were mainly marked by the publication of articles and abstracts, including international publications, and participation in the working group on the revision and development of clinical protocols.

CONCLUSIONS: Barriers to implementation of Evidence-Based Medicine in education and practice are lack of funding to provide access to reliable sources of information, websites; outdated research methodology skills in medical education, lack of skills in critical evaluation of medical information; tradition of authoritarian relationships, use of past experience stencils; failure to comply with continuing education programs ("from training to professional development"). Knowledge of Evidence-Based Medicine, skills to perform searches for scientific data, to evaluate their validity and to transform scientific data into practical solutions are necessary for health workers in their daily activities. This culture needs to be rooted in modern medical education.

Keywords: Evidence-based medicine, training, education, practice, survey, questionnaire

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Evidence-based pharmacogenetics: Is it possible?

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BACKGROUND: For improving quality, safety and efficiency of care, health systems perform a paradigm change towards personalized medicine, also referred to as genomic medicine. It uses combined knowledge (genomics, transcriptomics, proteomics, metabolomics) about a person to predict disease susceptibility, disease prognosis or treatment response and thereby to improve the person's health. The last decade has witnessed a steady embrace of personalized medicine by senior government officials, industry leadership and health care providers [1]. On the 12th December of 2013 Russian President Vladimir Putin in his annual address to the Federal Assembly said: "The Ministry of Health and the Russian Academy of Sciences must give priority to fundamental and applied research in medicine, including genomic studies" [2]. A year earlier, in 2012 the Ministry of Health of the Russian Federation, headed by Veronika Skvortsova established the strategy of personalized medicine development in Russia [3]. But still a lot of work is focused on using clinical research findings to aid the delivery of optimum clinical care to patients. Pharmacogenetic testing (using genetic information to guide drug therapy) is an actively developing field of personalized medicine and its current state indicates that it can be usefully introduced into clinical practice in the nearest future. In Russia pharmacogenetic testing is already used for personalizing prescription of certain drugs [4].

OBJECTIVE: To assess the extent of genetic testing use for improving use of medicines.

METHODS: PubMed and E-Library searches for the period of 2004–2015.

RESULTS: The number of publications retrieved in PubMed search for the term "pharmacogenetics" for 2004 year was 538 and was more than 15500 publications for 2015. 800 Russian-language publications in total were retrieved using a domestic scientific database E-Library search for the term "pharmacogenetics" for 2015 year. The sharp rise in the number of publications (including Russia) reflects growing interest not only among scientists, but also among practitioners. However evidence that is actually available on some key topics may not be of sufficiently high quality to support confident conclusions. As a rule, retrospective cohort studies, also known as historical cohort studies, are carried out. The number of randomized, prospective studies is not large, though in recent years, there has been an increase in their number. However, surrogate outcomes are commonly used in the mentioned studies as trial end points. The main reason for this is the lack of sponsorship. Quite often studies are not interesting for pharmaceutical companies and are carried out within the confines of the small grants. Nevertheless, systematic reviews and meta-analyses of some pharmacogenetic tests provide the high

level of evidence (pharmacogenetic testing for clopidogrel, abacavir and antineoplastic drugs) so they appear even in clinical guidelines with the evidence level IIb. It is important to mention that for certain drugs FDA has already approved pharmacogenetic testing [5].

CONCLUSIONS: Evidence is often inconsistent. This leads to the fact that clinical use of pharmacogenetic testing seems to be most appropriate for the management of patients with high risk of adverse drug reactions.

Keywords: Pharmacogenetics, evidence, personalized medicine

Conflict of interest statement: None.

References

[1] Blobel B. Translational medicine meets new technologies for enabling personalized care. stud Health Technol Inform. 2013;189:8-23 doi: 10.3233/978-1-61499-268-4-8
[2] V.V. Putin, the annual address to the Federal Assembly [Internet] 2013 Dec 12 [cited 2013 Dec 12]. Available from: http://www.kremlin.ru/news/19825
[3] Strategy of personalized medicine development in Russia [Internet] 2012 Dec 10 [cited 2012 Dec 10]. Available from: http://medportal.ru/mednovosti/news/2012/12/10/personal
[4] Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease–implications for personalized medicine. Pharmacol Rev. 2013 May 17;65(3):987-1009. doi: 10.1124/pr.112.007252
[5] Table of Pharmacogenomic Biomarkers in Drug Labeling. [Internet] 2015 May 20 [last updated 2015 May 20]. Available from: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

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Effects of balance training on post-sprained ankle joint instability

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BACKGROUND: Ankle sprain is a medical condition when ankle ligaments are totally or partially torn. The primary cause of ankle sprain is sharp movements like turning or rolling the foot [1]. The ankle sprain needs to be treated right after the trauma, because if not treated it could lead to decreased stability of the ankle joint and lead to chronic ankle instability, which is characterized by increased risk of the ankle sprain [2] . We suppose that rehabilitation after the ankle sprain could significantly increase the performance of sportsmen.

OBJECTIVE: To investigate effects of balance exercise training on instable ankle due to the previous ankle sprain injury. In addition, the secondary aim of this systematic review was to find the effectiveness of different balance training exercises on instable ankle in order to find better opportunities for rehabilitation of sportsmen.

METHODS: The studies were selected from PubMed and Scopus using the library of the Friedrich-Alexander University of Erlangen-Nuremberg (further- UB FAU), we used full texts, and only texts in English were included in this review. The literature search was conducted at the end of December 2014. Texts included randomised controlled trials, which were published in the last 5 years (2009–2014). The literature was included in this review only if it was published in English and if the randomised controlled trial was conducted in the study and if the full text was available from UB FAU. The articles, which were found only in PubMed search, were excluded during Scopus search.

PubMed search. First MeSH term was "Balance training for the ankle sprain" and 44 articles were found in PubMed. Then 29 articles were filtered by title and excluded from the study. Remaining 15 articles were assessed reading their abstracts, 6 of them were excluded and only 4 articles were left. The second MeSH term was "Balance training for ankle injury". Four additional articles were found by initial search. Two of them were filtered by the title and 2 were excluded at the stage of reading abstracts. The third MeSH term was "Balance exercises for instable ankle". One additional article was found by initial search and was excluded after reading the abstract.

Scopus search. The same MeSH terms were used as in PubMed search. With the first MeSH term one article was found and filtered by the title. With the second MeSH term no results were found in the initial search and with the third term 2 articles were picked up by the initial search. One of these articles was filtered by the title. The other one was filtered after reading the abstract. Overall 8 articles were taken into consideration for conducting a systematic review. Nevertheless, three of them could not be

downloaded for free even using UB FAU up to the 28th of December, 2014. Thus, five articles were taken for the systematic review. After reading all 5 articles, one article by Maraike Alice Wortmann and Carrie L. Docherty was excluded from the study because it was a systematic review per se and at the same time it was not mentioned neither in the article title, nor in the abstract that the current study was a systematic review [3]. Also the article by Borreani et al. 2014 [4] was excluded after reading the paragraph "Methods" as this was not an RCT but a descriptive study. Therefore, 3 articles were taken for conducting a systematic review.

RESULTS: The first article by Janssen et al. 2011 [5] was a 3-way randomised controlled trial with 1 year follow-up. Participants aged from 12 to 70 years used this intervention. People with active participation in sports with a lateral ankle sprain during the last 2 months were eligible for inclusion in the study. Participants were divided into 3 groups. Group 1 undertook an 8 week neuromuscular training programme. Group 2 wore sports brace during their sport activities for the duration of 1 year, and group 3 was a control group and used the combination of neuromuscular training program and wore sports brace for 8 weeks. There were 122 participants in the neuromuscular training group, 126 in the brace group and 136 in combined group. The drawback of this intervention was that there was no control over the care provid.

In the second study by Ben Moussa Zouita, A et al. 2013 [6] the objective was to investigate how the proprioceptive exercises effect the postural balance and isokinetic strength in athletes with ankle sprain. 16 participants were recruited in the study and divided into two groups. The experimental group consisted of 8 participants with unilateral ankle sprain symptoms. The control group included another 8 participants with bilateral non-injured ankles. The training programme included 24 sessions during 8 weeks, every session lasted between 20 and 30 minutes. Four prescribed exercises were used during the intervention: one exercise without any material, one exercise with a ball only, one exercise with a balance board only and one exercise with a ball and a balance board. As a result, after 8 weeks of proprioceptive rehabilitation a significant improvement in extensor and flexor strength of ankle at a speed of 60-deg/sec was registered.

The third study by Emery, Meeuwisse 2010 [7] was aimed to examine the effectiveness of the neuromuscular prevention strategy in youth soccer players. The inclusion criteria were adolescents between 13 and 18 years of age. The exclusion criteria were injury within 6 weeks and the history of systemic disease in anamnesis (i.e. cerebral palsy, head injury). 82 soccer teams were invited to take part in the intervention. 12 trainers declined the invitation, other 10 teams declined participation. Overall 60 teams took part in the intervention programme. The teams were randomised by a club. 32 training group teams ($n=380$ players) and 28 control group players ($n=364$ players) took part in the intervention. The training programme included dynamic stretching exercises, agility, jumping and balance and eccentric strength. The control programme was a standardized warm-up including static, dynamic and aerobic components and home-based stretching programme using 16-inch diameter wobble board used for 15 minutes during exercises. The injury rate in the training group was 2.08 injuries/1000 player-hours, and in the control group 3.35 injuries/1000 player-hours. The neuromuscular training programme was protective in injuries of youth soccer players.

CONCLUSIONS: Balance training is an effective training method for rehabilitation of instable ankle. Different approaches to balance training provide in general similar improvement for sprained ankle.

Implications for future studies: More RCTs on chronic ankle instability are needed with large sample size and use of different intensities of exercises. It would be better for the UB FAU to provide access to articles so that students and researches could download articles for free from different electronic sources.

Keywords*:* Ankle sprain, balance training, ankle injury, instable ankle

Conflicts of interest statement: The authors declare that there are no conflicts of interest.

References

[1] American Academy of Orthopaedic Surgeons (2014): Sprained Ankle. Your connection to expert orthopaedic information. Available from: http://orthoinfo.aaos.org/topic.cfm?topic=A00150

[2] Coughlin, Michael J.; Saltzman, Charles L.; Anderson, Robert B.; Mann, Roger A. (op. 2014): Mann's surgery of the foot and ankle. 9th ed. Philadelphia: Saunders/Elsevier.

[3] Wortmann, Maraike Alice; Docherty, Carrie L. (2013): Effect of balance training on postural stability in subjects with chronic ankle instability. In *J Sport Rehabil* 22 (2), pp. 143-149

[4] Borreani, Sebastien; Calatayud, Joaquin; Martin, Julio; Colado, Juan Carlos; Tella, Victor; Behm, David (2014): Exercise intensity progression for exercises performed on unstable and stable platforms based on ankle muscle activation. In *Gait & posture* 39 (1), pp. 404–409. DOI: 10.1016/j.gaitpost.2013.08.006

[5] Janssen, Kasper W.; van Mechelen, Willem; Verhagen, Evert Alm (2011): Ankles back in randomized controlled trial (ABrCt): braces versus neuromuscular exercises for the secondary prevention of ankle sprains. Design of a randomised controlled trial. In *BMC musculoskeletal disorders* 12, p. 210. DOI: 10.1186/1471-2474-12-210

[6] Ben Moussa Zouita, A; Majdoub, O.; Ferchichi, H.; Grandy, K.; Dziri, C.; Ben Salah, F Z (2013): The effect of 8-weeks proprioceptive exercise program in postural sway and isokinetic strength of ankle sprains of Tunisian athletes. In *Annals of Physical and Rehabilitation Medicine* 56 (9-10), pp. 634–643. DOI: 10.1016/j.rehab.2013.08.003

[7] Emery, C.A.; Meeuwisse, W.H. (2010): The effectiveness of a neuromuscular prevention strategy to reduce injuries in youth soccer: A cluster-randomised controlled trial. In British journal of sports medicine 44 (8), pp. 555-562. DOI: 10.1136/bjsm.2010.074377

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Paradoxes of evidence in Russian addiction medicine

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BACKGROUND: For many years, clinical protocols for treatment of drug abuse patients and treatment standards in Russian Federation were not grounded on the principles of evidence-based medicine [1]. Recommendations for use of certain drugs were not accompanied by any indication of the level of credibility of the evidence supporting it. The appearance in 2014 of such indications in clinical recommendations can be considered a significant step forward for the science of addiction medicine [2].

OBJECTIVES: To compare Russian evidence and practice in addiction medicines with international standards.

METHODS: Situation and literature analysis.

RESULTS: The analysis shows that in the wording of recommendations on the use of medicines, some were subject of serious methodological errors. For some drugs globally there is high quality evidence supporting effects of certain drugs globally, but this is not recognized in Russia. As a result, Russian standards of clinical care for the treatment of dependency syndrome are radically different to the standards of therapy, presented in the WHO recommendations. This is due both to the disregard of the meta-analyses presented in the Cochrane reviews and also to the specific bioethical preferences in drug treatment in Russia.

According to the Cochrane review, drugs with proven efficacy are antagonists and agonists of opioid receptors (for opioid dependence) and antagonists of opioid receptors (for alcohol dependence). In Russian clinical protocols treatment of dependence syndrome with drug of proven efficacy include antipsychotics, antidepressants and anticonvulsants (the level of credibility of evidence A and B according to Russian scientists).

It is known that there is no convincing data on the effectiveness and safety of antipsychotics in the treatment of alcohol dependence syndrome [3]. 13 randomized trials with a double blind placebo-controlled design involving 1593 patients assessing effects of amisulpride, aripiprazole, flupentixolum dekonoat, olanzapine, quetiapine, tiapride showed that antipsychotics do not result in abstinence, do not reduce abuse and do not stop craving in alcoholic patients: *"Antipsychotics should not be used in patients with a primary diagnosis of dependence. Appointment of antipsychotics for the treatment of substance abuse disorders are contraindicated, since not only does it not improve the condition of patients, but it can even worsen the course of the disease, leading to a reduction in the duration and quality of the remission, and is fraught with serious side effects that threaten the health of patients."*

SSRI antidepressants indirectly improve the results of treatment of comorbid alcoholism in depressed patients, without affecting alcohol dependence *per se*. Also, there is currently no convincing evidence of the efficacy of anticonvulsants in the treatment of dependence syndrome, particularly alcohol.

Despite the fact that traditional psychotherapeutic interventions remain widespread in practice, and treatment of alcohol dependence syndrome showed high efficiency, there is no convincing evidence for long-term benefits as opposed to short-term benefits.

The Cochrane Review with data based on 146 scientific studies involving 21,404 patients confirmed the effectiveness of opioid receptor agonists in treatment of opioid dependence. This therapy showed a statistically significant reduction in the use of illegal drugs, HIV transmission and risky sexual behavior, and was significantly more effective compared to the conventional maintenance therapy with opioid receptor antagonists. In countries, where law prohibits prescribing and use of opioid agonists for opioid dependence treatment, the drugs of choice are antagonists.

A meta-analysis of thirteen randomized placebo-controlled trials of oral form of naltrexone (1158 subjects), did not show any advantages of this type of treatment both for management and prevention of relapse compared with placebo [4]. Special studies also showed no inclination to reduce the use of opiates in patients receiving naltrexone [5]. However, studies carried out in Russia, showed the best results for daily intake of naltrexone after detoxification, which increased the duration of remission [6]. It was noted that the effect is associated with higher levels of adherence and family support in the examined population.

An overview based on controlled clinical studies on the use of antipsychotic drugs (neuroleptics) in patients dependent on opioids revealed no evidence of effectiveness of this approach. It was concluded that the use of antipsychotics is justified only in the presence of co-morbid psychiatric problems in patients [7]. In a recent meta-analytic review on the use of atypical antipsychotics for off-label indications (off-label), there was a lack of data to support the effectiveness of their use in substance abuse [8, 9]. The effectiveness of anticonvulsants in the treatment of opioid dependence syndrome has not been proven.

In connection with the above puzzling fact, for Russian standards of treatment (clinical guidelines) the level of credibility of the effectiveness of antipsychotics and antidepressants in treatment of substance abuse is assessed as A or B. This paradox raises the question of the methodology for determining the level of credibility of evidence. It should be noted that Russian recommendations for inclusion of certain drugs and therapies are based on sufficient consensus of experts rather than on the results of meta-analyses [2].

CONCLUSIONS: This fact casts doubt on credibility and validity of scientific recommendations. Thus, one may say that Russian addiction medicine is not based on evidence, which is, in our view, erroneous and may impair the quality of care.

Keywords: Paradoxes, evidence-based medicine, addiction medicine

Conflict of interest statement: None.

References

[1] Mendelevich V.D. Sovremennaya rossiiskaya narkologiya: Paradoksal'nost' printsipov i nebezuprechnost' protsedur [Modern Russian Narcology: Paradoxical Principles and Faulty Procedures]. Narcologia 2005,1:56-64. (in Russ.)
[2] Federal'nye klinicheskie rekomendatsii po diagnostike i lecheniyu sindroma zavisimosti [Federal Guidelines for the Diagnosis and Treatment of Dependence Syndrome]. Available from: http://www.nncn.ru/2_595.html (in Russ.)
[3] Kishi T., Sevy S., Chekuri R. et al. Antipsychotics for Primary Alcohol Dependence: A Systematic Review and Meta-Analysis of Placebo-Controlled Trials. J Clin Psychiatry 2013;74(7): 642-54. doi: 10.4088/JCP.12r08178
[4] Minozzi S., Amato L., Vecchi S. et al. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews 2011, 4. Art. No.: CD001333. doi: 10.1002/14651858.CD001333.pub4
[5] Dijkstra B.A., De Jong C.A., Bluschke S.M. et al. Does naltrexone affect craving in abstinent opioid-dependent patients? Addict Biol. 2007;12:176-82. doi: 10.1111/j.1369-1600.2007.00067.x
[6] Zvartau E., Woody G., Krupitsky E. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. Current Psychiatry Reports 2010;5:448-53. doi: 10.1007/s11920-010-0135-5
[7] Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. CNS Drugs 2004,18(8): 485-504. doi: 10.2165/00023210-200418080-00002
[8] Maglione M., Maher A.R., Hu J. et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. Rockville, MD: Agency for Healthcare Research and Quality 2011.
[9] Maher A.R., Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. J Manag Care Pharm 2012, 18 (5 Suppl B): S1-20.

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Decision support systems in clinical practice: The case of venous thromboembolism prevention

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BACKGROUND: Today medicine is facing a ''knowledge crisis'' in that explosively expanding medical knowledge encounters limited abilities to disseminate new practices [1]. Clinical practice guidelines (CPGs) are intended to promote high standards of care in specific areas of medicine by summarizing best clinical practice based on careful reviews of current research. However, doctors are often short of time to study these documents and check their updates, have little motivation for strict adherence to them. A systematic review of 11 studies reporting on 29 recommendations has found that median adherence to all recommendations was 34%, suggesting that potential benefits for patients from health research may be lost [2].

Clinical decision support systems (CDSS) can serve as a knowledge translation tool, mediator between clinical guidelines and physicians by providing the right information to the right person at the right time.

OBJECTIVE: To evaluate the effectiveness of implementation of international and national CPGs for venous thromboembolism (VTE) prevention with the help of CDSS in a general hospital.

METHODS: A multifunctional CDSS based on national and international guidelines on the VTE prevention was developed and implemented in the Medical Center of the Bank of Russia (MC). The system has the following functionalities: 1) it supports the decision on the VTE prevention based on individual risk assessment of thrombosis (scales of Caprini, Rogers and Khorana, Padua Prediction Score, additional risk factors) and bleeding (IMPROVE scale for non-surgical patients, major bleeding scale for surgical patients and major orthopedic surgeries, hemorrhagic complications risk in cancer patients); 2) generates the summary containing the grade of recommendations and the level of evidence, personalized recommendations on regimen and duration of preventive antithrombotic therapy, dose correction according to creatinine clearance; 3) provides an audit form for and statistical analysis of VTE cases; 3) automatically generates a quality register for VTE prevention.

CDSS was implemented in June 2014. We analyzed VTE cases identified by triggers (deep vein thrombosis diagnosed by Doppler ultrasound and pulmonary embolism at the chest CT) that occurred in 2014 before and after CDSS implementation, as well as in the first half of 2015. Patients with VTE diagnosed during the first 48 hours of hospitalization or receiving anticoagulants in therapeutic doses were excluded from the analysis. Chi-square test for linear trend and non-parametric methods of descriptive statistics were used for data analysis.

RESULTS: CDSS utilization was regulated by a special hospital-wide policy; lectures were organized to educate doctors how to use the system. Although international recommendations require VTE risk assessment for all hospitalized patients (except those receiving anticoagulant in therapeutic doses), the doctors filled forms for only 306 patients during the first 6 months of CDSS functioning (14.1% of discharges with length of stay >48 hours during this period). In the first half of 2015 the coverage of VTE risk assessment with CDSS was 19% ($n=506$). Correctness of filling out the forms was 78.4%, in the rest of cases doctors made mistakes in choosing patient's profile or when filling in risk scales.

Doctors adhere to given recommendations in 85.4% of cases. Most often (47.5%) pharmacotherapy with low molecular weight heparin (LMWH), preventive doses, was recommended by the system, and in this category the adherence to recommended practice was the lowest (74.6%). Among patients who underwent pharmacoprophylaxis, in 21.1% cases the use of anticoagulants was inconsistent with clinical guidelines or drug package insert (typically inappropriate choice of LMWH prophylactic doses, delaying or reducing the duration of prophylaxis).

The rate of hospital-acquired VTE significantly decreased after CDSS implementation and was 11.71, 8.28 and 4.84 per 1,000 hospitalizations in the first and second half of 2014 and in the first half of 2015, respectively ($\chi^2=7.325$, df=1, $p = 0.0068$). The rate of postoperative VTE for the same period amounted to 8.76, 3.39 and 4.17 per 1,000 operations, respectively ($\chi^2=7.266$, df=1, $p=0.007$), reaching a level of the correspondent AHRQ safety indicator (4.99 per 1,000 operations) [3]. Deviations from clinical guidelines or anticoagulant package inserts were revealed in 74% of VTE cases; and more than 1/3 of deviations affected treatment outcomes.

CONCLUSIONS: Coverage of hospitalized patients with documented VTE risk assessment gradually increased after the CDSS implementation, but remained at a low level (19% of eligible patients). Partly it may be attributed to the lack of CDSS integration in electronic health record or computerized physician order entry systems that would facilitate routine documentation of VTE and bleeding risks. However, the introduction of CDSS has allowed reducing significantly the rate of hospital-acquired VTE. This can be explained by drawing doctor's attention to the VTE problem and by training effect of CDSS. After receiving appropriate recommendations doctors adhere to them, on average, in 85.4% of cases, although for LMWH pharmacoprophylaxis this level was lower (74.6%). Development of hospital-acquired VTE in most cases (74%) was accompanied by non-compliance with CPGs recommendations, emphasizing the importance of additional measures for better adherence to evidence-based clinical practices.

Keywords: Decision support system, clinical practice guidelines, hospital-acquired, venous thromboembolism, prevention

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References

[1] Fox J, Gutenstein M, Khan O, South M, Thomson R. OpenClinical.net: A platform for creating and sharing knowledge and promoting best practice in healthcare. Computers in Industry. 2015; 66: 63-72. doi:10.1016/j.compind.2014.10.001

[2] Mickan S, Burls A, Glasziou P. Patterns of 'leakage' in the utilisation of clinical guidelines: A systematic review. Postgrad Med J. 2011; 87: 670-9. doi: 10.1136/pgmj

[3] Agency for Healthcare Research and Quality. Patient safety indicators™ V5.0 benchmark data tables. Truven Health Analytics, 2015. 12 p. Available from: http://www.qualityindicators.ahrq.gov/Downloads/Modules/PSI/V50/Version_50_Benchmark_Tables_PSI.pdf

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Improving data retrieval quality: Evidence based medicine perspective

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BACKGROUND: The actively developing approach in modern medicine is the approach focused on principles of evidence-based medicine. The assessment of quality and reliability of studies is needed. However, in some cases studies corresponding to the first level of evidence may contain errors in randomized control trials (RCTs). Solution of the problem is the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Studies both in the fields of medicine and information retrieval are conducted for developing search engines for the MEDLINE database [1]; combined techniques for summarization and information retrieval targeted to solving problems of finding the best medication based on the levels of evidence are being developed [2].

OBJECTIVE: Based on the relevance and demand for studies both in the field of medicine and information retrieval, it was decided to start the development of a search engine for the MEDLINE database search on the basis of the Saint-Petersburg State University with the support of Pavlov First Saint-Petersburg State Medical University and Tashkent Institute of Postgraduate Medical Education. Novelty and value of the proposed system are characterized by the use of ranking method of relevant abstracts. It is suggested that the system will be able to perform ranking based on studies level of evidence and to apply GRADE criteria for system evaluation.

METHODS: The assigned task falls within the domain of information retrieval and machine learning. Based on the results of implementation from previous work [3], in which the main goal was to cluster abstracts from MEDLINE database by subtypes of medical interventions, a set of algorithms for clustering in this study was selected: K-means, K-means ++, EM from the sklearn (http://scikit-learn.org**)** and WEKA (http://www.cs.waikato.ac.nz/~ml/weka/) libraries, together with the methods of Latent Semantic Analysis (LSA) [4] choosing the first 210 facts and the model "bag of words" [5] to represent clustered documents. During the process of abstracts classification, few algorithms were tested including: Complement Naive Bayes [6], Sequential Minimal Optimization (SMO) [7] and non linear SVM from the WEKA library.

RESULTS: The first step of this study was to markup abstracts of articles from the MEDLINE by containing and not containing a medical intervention. For this purpose, based on our previous work [8] a web-crawler was modified to perform the necessary markuping. The next step was to evaluate the clustering algorithms at the markup abstracts. As a result of clustering abstracts by two groups, when applying the LSA and choosing first 210 facts, the following results were obtained:

1) K-means: Purity = 0,5598, Normalized Entropy = 0.5994;
2) K-means ++: Purity = 0,6743, Normalized Entropy = 0.4996;
3) EM: Purity = 0,5443, Normalized Entropy = 0.6344.

When applying the model "bag of words":

1) K-means: Purity = 0,5134, Normalized Entropy = 0.6254;
2) K-means ++: Purity = 0,5645, Normalized Entropy = 0.5299;
3) EM: Purity = 0,5247, Normalized Entropy = 0.6345.

Then, studies which contain medical intervention have been considered and classified by the subtypes of medical interventions. At the process of classification abstracts by subtypes of medical interventions, abstracts were presented as a "bag of words" model with the removal of stop words. The results:

1) Complement Naive Bayes: macro F-measure = 0.6934, micro F-measure = 0.7234;
2) Sequantial Minimal Optimization: macro F-measure = 0.6543, micro F-measure = 0.7042;
3) Non linear SVM: macro F-measure = 0.6835, micro F-measure = 0.7642.

CONCLUSIONS: Based on the results of computational experiments, the best results of abstract clustering by containing and not containing medical intervention were obtained using the K-Means ++ algorithm together with LSA, choosing the first 210 facts. The quality of classification abstracts by subtypes of medical interventions value for existing ones [8] has been improved using non linear SVM algorithm, with "bag of words" model and the removal of stop words. The results of clustering obtained in this study will help in grouping abstracts by levels of evidence, using the classification by subtypes of medical interventions and it will be possible to extract information from the abstracts on specific types of interventions.

Keywords: Data retrieval, computational experiments

References

[1] T. Ohta, Y. Tsuruoka, J. Takeuchi, J. Kim, Y. Miyao, A. Yakushiji, K. Yoshida, Y. Tateisi, T. Ninomiya, K. Masuda, T. Hara, J. Tsujii, "An intelligent search engine and GUI-based efficient MEDLINE search tool based on deep syntactic parsing," *Proceedings of the COLING/ACL on Interactive presentation sessions*, Stroudsburg, PA, USA, 2006, vol. 4, pp. 17-20, doi: 10.3115/1225403.1225408

[2] D. Demner-Fushman, J. Lin, "Answer extraction, semantic clustering, and extractive summarization for clinical question answering," *Proceedings of the 21st International Conference on Computational Linguistics and the 44th annual meeting of the Association for Computational Linguistics*, Stroudsburg, USA, 2006, pp. 841-848, doi: 10.3115/1220175.1220281

[3] V. Dobrynin, J. Balykina, M. Kamalov, "**Analysis of standard clustering algorithms for grouping MEDLINE abstracts into evidence-based medicine intervention categories**," (**Editorial**) *Proceedings of the III International Conference in memory of V.I.Zubov Stability and Control Processes*, Saint-Petersburg, Russia, 2015.

[4] T. Kolda, D. O'Leary, "A semidiscrete matrix decomposition for latent semantic indexing information retrieval," *Journal of ACM Transactions on Information Systems*, New York, USA, 1998, vol. 16, pp. 322-346, doi: 10.1145/291128.291131

[5] Ch. D. Manning, P. Raghavan, H. Schutze, "Introduction to Information Retrieval," *Cambridge University Press*, Cambridge, England, 2008, pp. 482, isbn: 9780521865715

[6] J. D. M. Rennie , L. Shih , J. Teevan , D. R. Karger, "Tackling the Poor Assumptions of Naive Bayes Text Classifiers," *Proceedings of the Twentieth International Conference on Machine Learning,* 2003, pp. 616-623

[7] S. S. Keerthi, S.K. Shevade, C. Bhattacharyya, K.R.K. Murthy, "Improvements to Platt's SMO Algorithm for SVM Classifier Design," *Journal Neural Computation,* USA, 2001, vol. 13, pp. 637–649, doi: 10.1162/089976601300014493

[8] V. Dobrynin, J. Balykina, M. Kamalov, A. Kolbin, E. Verbitskaya, M. Kasimova "The data retrieval optimization from the perspective of evidence-based medicine," (**Editorial**) *Proceedings of the Federated Conference on Computer Science and Information Systems 2015*, Lodz, Poland, 2015.

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Cognitive IT-systems for big data analysis in medicine

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BACKGROUND: Rapid development of medicine requires regular update of clinical data evidence. This task accomplishment requires participation of numerous specialists in evidence-based medicine, who are proficient in various statistical methods and can work with big data analysis tools in biomedical sciences. This, in turn, requires significant time and other resources. Today, at the peak of IT development, cognitive systems in the field of medicine with special technologies of data collection and analysis, is the start of a new trend.

OBJECTIVE: The development of cognitive IT system for drug prescription with the potential to analyze automatically the information about drugs effectiveness and safety on the basis of clinical practice experience and scientific data according to evidence levels and patients' personal characteristics.

METHODS: The cognitive system was developed with the use of United Medical Knowledge Base (UMKB). UMKB is a semantic network of medical knowledge, which is structured according to the medical ontologies and the theory of fuzzy logic. UMKB is being filled simultaneously in all the areas of medicine. From one side it is filled by means of the linguistic module analyzing medical texts, from the second side - by academic institutions, from the third side – by the cognitive IT systems with the data from electronic health records (EHRs). Native language of UMKB is Russian. It is designed primarily for use in the Russian clinical practice. However the platform for filling knowledge is multilingual and supports any other languages. This means that the practice of world schools may also be integrated and used in UMKB. The peculiarity lies in the fact that UMKB is presented as a semantic network where biomedical knowledge are structured according to certain medical ontologies (special rules of information storage that "carries" data: phenomena, processes, simple and complex concepts in medicine, - in the form of interrelated objects). The keystone underlying UMKB is the model of medical knowledge representation, which is able to describe any area of medicine. With the help of this model one can accurately simulate risk factors, etiology, and pathogenesis of a disease (probability, time of development and the sequence of pathological signs at each stage of a disease). While describing pathological and compensatory mechanisms the database provides an opportunity to clarify a lot of conditions that affect this mechanism. It is also simple to simulate structural and functional features of the concept and its relationships (for example, compensatory mechanisms, reflexes, complex anatomical structures, all the features of variant anatomy and other characteristics), which form reactivity and resistance of the organism. All this is very important for cognitive IT systems concerning personalized and evidence-based medicine. When describing medical knowledge there are often situations of uncertainty, lack of sufficiently complete and accurate data on the subject area, poorly understood phenomena, conflicting

theories or imprecise concepts. Semantic network of UMKB presents complex relationships among medical concepts characterized by the following features: type and direction of relationship, its weight and value, accuracy and personalization of the weight or value of relationship, date of actualization. Multifactorial influence on the weight or value of relationship, a lot of elementary and intermediate traits that influence weight, the moment of actualization are supported to formalize. United Medical Knowledge Base is a large-scale project, its main goal is to increase the quality and duration of life through personalized care based on evidence that can only be achieved by combining medical big data from various fields of biomedical sciences.

RESULTS: On the basis of UMKB a prototype of the cognitive IT system PharmExpert with analytical potential was developed. PharmExpert is a clinical decision support system for drug prescribing, which is integrated into medical information system at health institutions and analyzes electronic health records (EHRs) in any format of the background mode, correcting drug therapy according to personal patient's profile and data about compatibility of the drugs. The system has a very important function – self-learning that will help it to absorb a huge mountain of medical data from routine clinical practice in the nearest future. Now it works on the basis of data from UMKB, handbooks in pharmacology, summaries of medical products characteristics (SmPCs), available reviews of scientific literature and clinical guidelines on drugs interactions and compatibility. In the short term, at the stage of clinical testing, PharmExpert memorizing all the cases of clinical experience and the reaction of the physicians (accepting or ignoring the recommendations of the system), will be able to realize self-learning function by rebuilding ties and remodeling knowledge of the semantic network according to clinical data and generating the best standards of drug therapy taking into account personal characteristics of the patient and levels of data evidence. Working in the background mode is one of the most important advantages of the system. The physician is not asked to enter any additional data beyond that the specialist enters into the EHR on an everyday basis. Now PharmExpert is installed in the medical information systems of the range of clinical centers in the Russian Federation.

CONCLUSION: We developed a prototype of cognitive IT system for drug prescription with the potential to analyze automatically the information about drugs effectiveness and safety on the basis of clinical practice experience and scientific data according to evidence levels and patients' personal characteristics. The system is based on the structured semantic network of medical knowledge from UMKB.

Keywords: Cognitive IT-systems, big data, medicine, medical knowledge, semantic, network

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Screening for colon cancer: A test for occult blood

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BACKGROUND: The relevance of the problem of colorectal cancer (CRC) is evident because of extremely high morbidity and mortality rates, associated with this disease. CRC is mostly diagnosed only at very advanced stages. The reduction of mortality can be achieved by the popularization of screening-methods for early identification of CRC and adenomatous polyps of the colon, which are proved to be precancerous condition. Fecal occult blood test is a well-known method of screening for CRC. The advantages of this method when compared, for example, with colonoscopy are its simplicity and cost-effectiveness.

Two techniques are usually used for detection of occult blood in the stool: Hemoccult (Guaiac) test and immunochemical test for hemoglobin. There is no consensus among researchers regarding the validity of these tests for the diagnosis of colorectal cancer. For example, J.S. Mandel (1996) notes 60% sensitivity of Guaiac-test for the detection of the early forms of colorectal cancer, while O.I. Kit (2014) suggets that it is not higher than 30%. There are also various opinions about specificity of these two tests.

OBJECTIVE: To review the literature on the validity of the fecal occult blood tests for the diagnosis of CRC.

METHODS: We looked for articles (electronic versions) available for free in the full-text versions, published from June 1, 1990 to December 31, 2014 in Russian or English. The following databases were used for search: E-LIBRARY; Cochrane; MEDLINE; EMBASE; Google search. Only original research papers were analyzed. Literature reviews or systematic reviews were not taken for analyses. Selection criteria: 1) use of Guaiac and/or immunochemical fecal occult blood test as screening-tests for the detection of colorectal cancer and/or colon polyps (1 cm or more in diameter) in people older than 45 years; 2) comparing of results with the results of colonoscopy (colonoscopy is counted by majority of the authors as a "gold standard" for the diagnosis of CRC and adenomatous polyps).

Articles were selected independently by five researchers. The final decision on the inclusion/exclusion was taken collegially by all five researchers. Extracting data (two-by-two-tables were used) and recalculation of original studies were performed independently by three experts and then rechecked by two other experts. The data were statistically processed using Excel 2010 and RevMan.

RESULTS: Initial keyword search returned 803 000 results, of which 449 sources were selected. After reading the abstracts, 29 articles that met inclusion criteria were kept. 10 other articles were excluded after that because they did not contain enough data for extraction or did not contain a control group. At the final step 19 articles were used for meta-analysis.

Forest plot and Rock curve, which were developed with inclusion of the data from all studies, showed heterogeneity of the data. Additional analyzes were performed in subgroups with different diagnoses and various tests.

The sensitivity of the Guaiac test for the diagnosis of colorectal cancer varied from 0.13 to 1.00, and specificity - from 0.69 to 0.99. The sensitivity of the immunochemical test for the diagnosis of CRC ranged from 0.42 to 0.94 with specificity ranging from 0.40 to 1.00.

The sensitivity of the Guaiac test for the diagnosis of the colon polyps was between 0.05 and 0.69, and its specificity - from 0.67 to 0.98. The sensitivity of the immunochemical test for the diagnosis of polyps was from 0.24 to 0.75, and its specificity - from 0.40 to 0.97.

Bivariate analysis of the validity of Guaiac test and immunochemical method for the diagnosis of colorectal cancer showed better results for the immunochemical test compared to Guaiac test. The tests showed very similar results when used for the diagnosis of polyposis. Bivariate analysis, comparing the validity of tests for the diagnosis of colorectal cancer versus polyposis demonstrated better results for CRC.

Multivariate analysis of the validity of the Guaiac and immunochemical tests for the diagnosis of colorectal cancer and polyps also showed better results for detection of colorectal cancer compared with the polyps for both tests. At the same time the highest validity for the diagnosis of CRC was demonstrated for immunochemical analysis.

CONCLUSIONS

1. The sensitivity of the Guaiac test for occult blood in stool is lower than its specificity.
2. Broad dispersion of the validity characteristics of the fecal occult blood tests was observed.
3. The validity of tests for occult blood was higher when they were used for detection of colorectal cancer than of colon polyposis.
4. The highest validity rate has been demonstrated for the immunochemical test when it was used for colon cancer screening.

Keywords: Screening, colon cancer, occult blood

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Russian translations for Cochrane

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BACKGROUND: Cochrane collaboration has made a huge contribution to the development of evidence-based medicine; Cochrane work is the international gold standard of independent, credible and reliable high-quality information in medicine. Over the past 20 years the Cochrane Collaboration helped transforming decision-making in health and reforming it significantly, saving lives and contributing to longevity [1]. Until recently, Cochrane evidence were available only in English, which represents a significant barrier to their wider use in non-English speaking countries. To provide access to evidence, obtained from Cochrane Reviews, for health professionals and general public (from non-English-speaking countries), bypassing language barriers, Cochrane collaboration in 2014 initiated an international project of translating Plain language summaries of Cochrane Reviews into other languages [2, 3]. Russian translations of Plain language summaries were started in May 2014 by the team from Kazan Federal University (Department of Basic and Clinical Pharmacology; 2014-2015 as an Affiliated Centre in Tatarstan of the Nordic Cochrane Centre, since August 2015 as Cochrane Russia, a Russian branch of Cochrane Nordic, Head – Liliya Eugenevna Ziganshina) on a voluntary basis.

OBJECTIVE: To assess the quality of Russian translations of Cochrane Plain Language Summaries (PLS) and their potential impact on the Russian speaking community through user feedback with the overarching aim of furthering the translations project.

METHODS: We conducted the continuous online survey via Google Docs. We invited respondents through the electronic Russian language discussion forum on Essential Medicines (E-lek), links to survey on the Russian Cochrane.org website, invitations to Cochrane contributors registered in Archie from potential Russian-speaking countries. We set up the survey in Russian and English. The respondents were asked to respond to the questionnaire regarding the relevance and potential impact of the Cochrane Russian translations project, topics of interest in the field of health and health care, the quality and clarity of translated content, the preferred style of presentation and suggestions to improve the quality of translations of Plain language summaries of Cochrane Reviews.

RESULTS: Currently the team of translators includes volunteers from the staff, Masters and PhD students of the Department of Basic and Clinical Pharmacology of the Kazan Federal University, and Kazan Medical University, our colleagues from Kazan and other cities of Russia, from the Republic of Armenia and the USA. By September 20th 2015, 446 Plain language summaries of Cochrane Reviews were translated into Russian and published on the web-site http://www.cochrane.org/ru/evidence. Our project "Russian translations for Cochrane" has already covered a wide range of health priority areas with translations of Plain language summaries and abstracts of the most topical and priority Cochrane reviews. During the period from 03.03.2015 to 20.09.2015 we received 113 answers from our respondents (103 answers in Russian and 10 answers in English). These were representatives of the medical and pharmaceutical professions (60%), representatives of non-medical professions (17%), students/graduate

students (16%), retirees (4%) and others categories of citizens among the respondents. Half of the respondents (50%) belonged to the age group of 36–60 years, followed by the group of 18–35 years (41%). According to the survey the vast majority of respondents consider that the Cochrane Russian translations project is needed for Russia and Russian speaking countries (94%; $n=106$), it is needed for their work, studies, and life in general (91%; $n=103$). Nobody answered "No" to the question: "Do you think that this project is needed for Russia and Russian-speaking countries?" Information from the Cochrane evidence can affect (change) individual practice and/or attitude to drugs or diagnostic procedures of 87% ($n=98$) of respondents. Only two people answered negatively to this question. However, only one third of respondents would like to become volunteer members of the translations project. The Russian texts of translations of Cochrane summaries and their main message were completely understandable or mostly clear to the vast majority of respondents (92%; $n=104$). Respondents, proficient in English ($n=61$), answered that the Russian-language translations fully complied (43%; $n=26$) or in general corresponded to (57%; $n=35$) the original English text. The majority of respondents (85%, $n=96$) rated the quality of the translated texts as excellent and good. "More than half of respondents (61%; $n=69$) would prefer the translations to be adapted to the usual style of presentation in Russian. The respondents agreed that mistakes, or typos or both very few. Our respondents provided valuable suggestions for further improvement of the Russian translations project. We would like to present here some of these: "More translations needed", "The ultimate goal… is to try to adapt the summaries to Russian language style as much as possible. This is a very challenging task, however and at present format the summaries are already great", "Go great as you do!" "Move forward and be efficient!" "Distribute information about the project through social networks and different means of social media", "Studying Cochrane Database should be included in the Russian medical school's curriculum at a much larger extent than it is included (if at all) now. It would be beneficial for high school students as well."

CONCLUSIONS: The survey provided positive feedback on the Russian translations project concerning the clarity and quality of Russian texts and overall satisfaction of the readers. It confirmed the importance and relevance of the Russian translations project for Russian speaking audience, representing various professions and age groups. The survey results with detailed feedback contribute to further improvement of the Russian translations project.

Limitations: Selective and subjective evaluation of translations by the respondents, difficulties with clear criteria for the objective evaluation. Further quality improvement of original PLS texts would contribute to higher translation quality.

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Keywords: Cochrane, russian translations, plain language summaries

Conflict of Interest Statement: We declare that we have no conflicts of interest.

References

[1] Cochrane. About us. (Cochrane Collaborations) [Internet]. 2015 [cited 2015 Ceptember 20]. Available from: http://www.cochrane.org/about-us

[2] von Elm E, Ravaud P, MacLehose H, Mbuagbaw L, Garner P, Ried J, et al. (2013) Translating Cochrane Reviews to Ensure that Healthcare Decision-Making is Informed by High-Quality Research Evidence. PLoS Med 10(9): e1001516. doi:10.1371/journal.pmed.1001516

[3] National Center for the Dissemination of Disability Research (2010). The Cochrane Collaboration: A valuable knowledge translation resource. FOCUS Technical Brief (29). Austin, TX: SEDL, Author.