

PATHOPHYSIOLOGICAL ASPECTS OF CYSTIC FIBROSIS AND MODERN TREATMENT

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Introduction: Cystic fibrosis is a genetic disorder caused by a mutation in the CFTR gene, which regulates the chloride transport through the epithelial cells.

Materials and Methods: The aim of this study is to present the cause of cystic fibrosis and its therapy.

Results: CFTR is a cAMP-activated ATP-gated ion channel, the most common mutation in its gene is the deletion of phenylalanine in position 508 (del508f). Cystic fibrosis is followed by abnormalities in the gastrointestinal, respiratory, endocrine and reproductive systems. The main problem is the thick mucus, low in NaCl concentration, determined by CFTR. The treatment involves an intake of antibiotics, mucus-modifying drugs, pancreatic enzymes, and many more. However, this affects only the symptoms not the cause. Hence, medications such as ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor are being implemented. Their usage is known as CFTR Modulator Therapy. Ivacaftor binds to the defective protein at the cell surface and increases its chance to be open, boosting the chloride flow. Lumacaftor/ivacaftor is a combination therapy for the F508del mutation. Lumacaftor is a corrector, which serves as a chaperone and helps with the proper folding of CFTR, increasing its quantity in the membrane. However, with the use of lumacaftor alone, only about a third of the CFTR protein reaches the cell surface. Therefore, the combination treatment is more successfully applied, reducing the hospitalization rate by 34%. Tezacaftor/ivacaftor is another option for people with del508f mutation.

Conclusion: CFTR Modulator Therapy is a modern and effective way of treating the underlying cause of cystic fibrosis.

Keywords: cystic fibrosis, CFTR gene, del508f, ivacaftor, lumacaftor, tezacaftor

THE OTHER FACE OF WHITE POISON

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Introduction: It is known that the expression “white poison” has to do with sugar and flour, but in this paper we present the other face of white poison - sodium chloride, commonly known as cooking salt. The excessive use of sodium chloride disturbs the normal function of the sodium-potassium pump. As a result, severe pathophysiological conditions may occur, such as hypernatraemia.

Aim: The aim of this study is to present the effect of excessive use of salt.

Results: The sodium-potassium pump is a universal biological structure located on the surface of the cell membrane. Its main function is to carry sodium and potassium ions in the cell. For example, hypernatraemia, which is a medical condition associated with high blood sodium levels. The increase in extracellular sodium causes the intracellular fluid to shift out of the cells into the extracellular spaces, which results in cellular dehydration. Common causes of hypernatraemia include: inadequate water intake, excessive fluid loss, diarrhoea and excessive steroid use. The treatment consists in restoring fluid balance. The patient should be treated with liquids free of salt - either orally or via intravenous infusions. The important thing is to reduce sodium levels gradually, as their rapid reduction may lead to serum osmolality in the brain.

Conclusion: It is important for every healthy organism to take a moderate amount of Na⁺ through food. In the case of pathological disorders of quantity, adequate methods of treatment should be undertaken, reducing the intake of salt.

Keywords: *sodium-potassium pump, sodium chloride, salt, hypernatraemia*

INFLUENCE OF BETA BLOCKERS ON REDUCING THE QT INTERVAL IN PATIENTS WITH LONG QT SYNDROME

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Introduction: The long QT syndrome (LQTS) is a channelopathy characterized by a prolongation of the QT interval of the cardiac cycle. This condition can be present at birth or it can be developed later in life after taking certain medications such as H-1-blockers, antiarrhythmic drugs, etc. Symptoms of LQTS include various types of heart arrhythmias, syncope and sudden cardiac death.

Results: The most common treatment of LQTS is through the use of beta blockers. They are a group of medications that are often used to normalize irregular heart rhythms. Some of the beta blockers include propranolol, pronethalol, atenolol, etc. They are competitive antagonists that block β -adrenergic receptors. The β_1 receptors are located mainly in the heart and are the ones that need to be targeted by beta blockers in patients with LQTS. Beta blockers demonstrate a differential effect on the QT interval in people with different heart rates. Research shows that beta blockers increase the QT and QTc intervals when the patient's heart rate is slower (< 90 bpm) but with the increase of the heart rate (> 100 bpm) the use of beta blockers is associated with a reduction in the QT and QTc intervals.

Conclusion: Beta blockers are currently the most effective treatment for LQTS but their effect is heart-rate-dependent. In the future, with better knowledge of the genetic causes of LQTS, more precise treatments will hopefully become available.

Keywords: LQTS, channelopathy, antiarrhythmic drugs, beta blockers

PHARMACOLOGICAL PROPERTIES AND PHYTOCHEMISTRY OF *BACOPA MONNIERI* – AN OVERVIEW

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Introduction: *Bacopa monnieri* (BM) (Brahmi, Water Hyssop) (Plantaginaceae) is a widespread perennial creeping plant that inhabits swampy places and wet climate territories. The plant contains many different bioactive substances – triterpenoid saponins (bacoside A and B), sterols, alkaloids, and others.

Materials and Methods: Scientific data on *Bacopa monnieri*'s bioactive components and their potential pharmacological effects were collected from various sources – ResearchGate, PubMed, ScienceDirect, etc.

Results: *Bacopa* is known for its nootropic effect, due to improving serotonergic transmission, resp. increasing acetylcholine levels in hippocampus. According to some researches the plant has a positive effect in epilepsy, improves blood supply to the brain and decreases neuronal inflammation. BM exhibits a neuronal protective effect due to its antioxidant properties. There is proof of its antidepressant and anxiolytic properties in experimental animals. The observed analgesic effects seem to be mediated through a combination of opioidergic, serotonergic and adrenergic mechanisms. *Bacopa* is a stress-answer modulator – it reduces HSP70 expression, the levels of which are high during stress. It protects the mucosa of the gastrointestinal tract in cases of pharmacogenic and *H. pylori*-induced ulcers. BM also affects men's fertility and increases serum T4 levels. The plant inhibits P-glycoprotein and some CYP450 isoenzymes functions, responsible for the metabolism of most of the xenobiotics in the human organism.

Conclusion: Our research summarizes that *Bacopa monnieri* has many positive effects on different conditions such as cognitive disorders, epilepsy, anxiety, nociceptive pain, hypothyroidism, etc., combined with the possibility of interaction with other exogenous substances as various medicines.

Keywords: *Bacopa monnieri*, pharmacology, phytochemistry, cognition, pain, epilepsy

BIOPHARMACEUTICAL AND MARKETING EVALUATION OF DIOSMIN- AND HESPERIDIN-CONTAINING PRODUCTS ON THE BULGARIAN MARKET

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Introduction: This study presents an independent evaluation of the market status, quality and biopharmaceutical characteristics of diosmin- and hesperidin-containing oral tablet-products (DHCPs) on the Bulgarian market.

Materials and Methods: Seven products, among which medicines (used as a reference) and food supplements, with sustainable or growing market were selected for the survey: Detrale^x 500 mg, Phlebo^{dia} 600 mg, Dioket 600 mg, Novarix 650 mg, Asketon 500 mg, Venocode and Dih max 1000 mg. Sales analysis for 2016, 2017 and 2018 (year-to-date) was done with the kind support of Iqvia TM. All products were subjected to European Pharmacopoeia (EP) tests for tablet quality - disintegration, friability, resistance to crushing, uniformity of mass and uniformity of dosage units. Next, the biopharmaceutical profile regarding tablet drug release and dissolution potency was investigated on EP Apparatus 2 (Paddle method).

Results: Although all products were found to almost fully fulfill the EP criteria, extremely unsatisfying drug release was established in all tested media (pH 1.5, pH 4.5, and pH 7.2), reaching no more than 1.5% of the labeled content after 24 h for the best performing products – Novarix and Venocode.

Conclusion: The observed results were not surprising considering diosmin and hesperidin's water insolubility and respective low bioavailability. However, it would be reasonable to approach these two bioflavonoids (diosmin and hesperidin) technologically in the preformulation stage in order to improve their solubility and thus, their therapeutical potency.

Keywords: *diosmin, hesperidin, biopharmaceutical evaluation, marketing, food supplements*

MARINE-DERIVED ANTICANCER DRUGS

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Introduction: Cancer is one of the most insidious and deadly diseases of our time. According to the American Cancer Society, it was defined as “a group of diseases characterized by the uncontrolled growth and spread of abnormal cells”. In the last few decades, there has been an increasing interest towards marine invertebrates and their natural biologically active compounds in search of new and non-toxic medicines. The researchers are looking for substances with a broad spectrum of anticancer effects, including induction of cellular apoptosis, inhibition of cancer cell growth, migration, invasion, formation of metastases, and angiogenesis.

Aim: The aim of the abstract is to review the information about the alternative anticancer agents from marine invertebrates - sponges, tunicates, etc.

Materials and Methods: The information was acquired through scientific papers, which presented analytical data and clinical trials of cancer therapy.

Results: There is a large number of approved drugs for treatment of cancer and there are many undergoing clinical trials or in preclinical stages. The main focus is on the synthetic nucleoside cytarabine, derived from its analogues spongothymidine and spongouridine, which were extracted from the sponge *Tectytethya crypta*. Another approved agent is the alkaloid trabectedin, isolated from the tunicate *Ecteinascidia turbinata*. Amongst those undergoing clinical trials is plitidepsin, a cyclic depsipeptide from the tunicate *Aplidium albicans*, which exhibits potential anticancer activities against a variety of human cell lines – breast, melanoma, and lung cancer.

Conclusion: Many of the tested compounds show high activity against human cancers. Therefore, the relatively new scientific field - marine drugs, is extremely fast developing.

Keywords: *marine invertebrates, cancer inhibition, clinical trials*

BROWN MACROALGAE – FOOD OR MEDICINE

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Introduction: In modern days, the attention towards macroalgae has risen dramatically due to its numerous applications - in medicine, pharmacy, and the food industry. Macroalgae are thallus organisms with complex classification – based on their habitat, they can be classified as freshwater or marine, based on their colour - green, red, and brown seaweeds. Due to their wide spread in the global network of seas and oceans, brown algae are the subject of numerous researches on their pharmaceutical and medicinal potential.

Aim: The aim of this abstract is to collect and review the information and provide the reader with knowledge about the chemical composition of biologically active substances in brown algae and their positive effects on human health.

Materials and Methods: The focus of this research is brown algae (class *Phaeophyceae*) and more specifically - genus *Sargassum* from the order *Fucales* and *Kelps*. The information was obtained from various scientific articles presenting information on biologically active component content and their physiological activity and therapeutic potential.

Results: *Kelp* and *Sargassum* are extremely rich in biologically active substances such as vitamins, minerals, carotenoids, iodine compounds, sulfated polysaccharides, polyphenols, sterols, and alginates, which possess anti-inflammatory, analgesic, antibacterial, antiviral, anticancerogenic properties, etc. The medical significance is related to the treatment and prevention of diseases of the thyroid gland, gastrointestinal tract, cardiovascular system, and urinary system.

Conclusion: The numerous studies have shown the positive effect of *Sargassum* and *Kelp* on human health, which demonstrates the need to raise public awareness of the benefits of brown seaweed.

Keywords: *macroalgae, brown seaweed, therapeutic potential, medical application*

RESUSCITATION OF PATIENTS WITH INTRAVENOUS LIPID EMULSIONS

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Introduction: Intravenous lipid emulsions (LEs) are designed to satisfy the need for essential fatty acids in parenteral nutrition patients. Over the past 15 years, a new effect has been identified, namely to capture lipophilic drugs and extract them from target organs such as heart and brain, thereby reducing their toxicity. Initially used in cardiovascular collapse as a complication of local anesthesia, they are now successfully used in other lipophilic drug intoxications.

Aim: The aim of this article is to conduct an investigation on the cardioprotective effect of LEs as an innovative method for the treatment of acute exogenous intoxications with lipophilic drugs.

Materials and Methods: Various reports of successful resuscitation of patients, poisoned with lipophilic drugs such as local anesthetics, cardiovascular medications, and antidepressants treated with LEs have been studied.

Results: For the first time, LE was administered for the resuscitation of a girl after receiving an overdose of antidepressants and suffering a subsequent total cardiovascular collapse. After seventy minutes of unsuccessful resuscitation, 20% of LE was administered. Within a minute, vital signs were restored. Weinberg reported a case of resuscitation of haloperidol-induced cardiac arrest. The patient has an extended QT interval and ventricular tachycardia. Following the application of LE, the sinus rhythm was restored. Tebbutt proves that LE doubles LD50 and weakens the bradycardia, caused by overdose of verapamil in rats.

Conclusion: Our analysis confirms the cardioprotective effect of LEs in the treatment of lipophilic drug intoxications. Their positive inotropic effect reduces bradycardia and hypotension, and improves hemodynamics.

Keywords: *lipid emulsions, parenteral nutrition, acute intoxications, lipophilic drugs*

CONTEMPORARY TREATMENT OF GLOMERULONEPHRITIS - METHODS AND RESULTS

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Introduction: Glomerulonephritis is an inflammatory disease, which affects the glomeruli - a basic functional unit of the kidney tissue. They carry out the cleansing function in the body and are essential in the maintenance of acid and electrolyte equilibrium. This paper describes the applied methods during treatment in two real-life cases.

Materials and Methods: For this examination, we have analyzed recent scientific publications and two real-life clinical cases of patients diagnosed with glomerulonephritis through kidney biopsy puncture. The first patient, aged 54, displayed typical symptoms: edemas, dyspnea, dysuria, diabetes mellitus, and the following blood indicators: creatinine – 580 $\mu\text{mol/L}$, urea – 35 $\mu\text{mol/L}$, blood protein – 52 g/L, albumin – 28 g/L. Given his condition, emergency hemodialysis was applied, as well as further diuretic treatment. The second patient, aged 48, exhibited similar physiological symptoms and the following blood indicators: creatinine – 180 $\mu\text{mol/L}$, urea – 15 $\mu\text{mol/L}$, blood protein – 48 g/L, albumin – 23 g/L, cholesterol - 8.7 $\mu\text{mol/L}$. After consultation with specialist cardiologist and nephrologist, he was assigned a similar diuretic treatment to reduce the edemas.

Results: In both cases the adjunctive diuretic treatments seemed to improve the patients' symptoms but showed limited results. Therefore, treatment with anticancer medication was applied. After administration of cyclophosphamide, their state rapidly improved. However, anticancer drug intake should be carefully monitored as it may cause further damage if not regulated.

Conclusion: Given the kidneys' important role, a better understanding of glomerulonephritis' pathogenesis is essential for developing more effective treatments. Contemporary studies show promising results but also certain drawbacks and unclearness. That is why glomerulonephritis remains a relevant subject of present-day research.

Keywords: *glomerulonephritis, diuretics, treatment*

GOOD DISTRIBUTION PRACTICE FOR MEDICINAL PRODUCTS: REGULATORY INSPECTION FINDINGS IN 2017

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Introduction: Today's distribution network for medicines is increasingly complex and demanding. The wholesalers are obliged to preserve the quality of the distributed medicines unchanged throughout the whole legal supply chain. Bulgarian Drug Agency (BDA) carries out inspections to check if they comply with the good distribution practice (GDP). Any departure from GDP compliance could risk the quality of the medicines and potentially their effectiveness and safety. The current study analyzes the regulatory inspection findings in wholesalers in Bulgaria in 2017.

Materials and Methods: The inspections were performed according to the GDP. The inspection methods used were interviews, review of documentation, and conduction of site visits. All reports were reviewed for the scope of the inspection, classification of findings, the content of findings, and the conclusion.

Results: In total, 48 GDP inspections were performed in 2017. Half of the inspections were performed in relation with issuing an authorization for wholesale of medicines, the remaining half were related to changes in already granted authorizations.

During the inspections, 17 non-conformities (NCs) have been documented. The NCs were identified in 3 wholesalers and 6 deficiencies were classified as major. No critical deficiencies were found. Recommendations were given to 5 companies.

Conclusion: During the regulatory inspections of pharmaceutical distributors in 2017, non-conformities to the requirements of GDP were found in 6.25% of the inspected companies. No critical NCs were identified and only 6 NCs were classified as major, which demonstrated a high level of compliance of distribution sites in Bulgaria with the requirements of GDP.

Keywords: *good distribution practice (GDP), medicinal products, non-conformities, supply chain, compliance, Bulgarian Drug Agency*

PATIENT'S ATTITUDE TO SELF-MEDICATION AND IMPACT OF THE PHARMACIST ON SELECTION OF OTC PRODUCTS

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Introduction: Self-medication with over-the-counter (OTC) products is a common practice among patients seeking rapid and effective response when some kind of symptoms occur. Free access and a variety of OTC information predispose them to the progressive increase in their use, which often hides a risk to the health of the patient.

Aim: The aim of the study is to analyze the rationality of OTC use and the influence of pharmacists on the choice of self-medication.

Materials and Methods: An anonymous survey was conducted between March and April, 2018 in pharmacies on the territory of the city of Shumen, which were randomly selected. A total of 114 OTC users were questioned when buying their drugs from pharmacies.

Results: Patients are interested in the active ingredient when buying medicines. However, irrational combinations are commonly seen. Pharmacists at the pharmacy should pay attention to people with lower education, 50 to 60-year-old male patients, who do not pay enough attention to the package leaflet, which is a risk of improper OTC use. Pharmacists enjoy the patient's trust and have a leading role in choosing OTC products.

Conclusion: Users of OTC products are interested in the content of medicines and related information, which determines their choice. The pharmacist enjoys the patient's trust when medicating with OTC products and the effective communication between him and the patient is the basis for the rational use of OTC products and the avoidance of drug-related problems.

Keywords: OTC, use, self-medication, pharmacists

CARDIOGENIC SHOCK - THE LETHAL RELATIVE OF THE HEART ATTACK

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Introduction: The most common cause of cardiogenic shock is a damage to the heart muscle from a severe heart attack. The damage prevents the heart's main pumping chamber - the left ventricle, from performing its main function. As a result of the heart failure, its pump function is impaired. Thus, blood pressure drops and organs may begin to fail.

Aim: The aim of the study is to explore the relation between heart attack and cardiogenic shock and the cardiogenic shock mortality.

Results: Cardiogenic shock is a clinical syndrome of poor tissue perfusion for more than 30 minutes, caused by severe hypotension. The main pathogenic mechanism is damaged pump function of the left chamber, which leads to poor cardiac output and inadequate blood circulation. Patients with acute myocardial infarction (AMI) presenting with clinical signs of heart failure are at increased risk of subsequent development of cardiogenic shock and death. Cardiogenic shock occurs in the range from 5 to 15% of AMI patients. In patients with AMI complicated by cardiogenic shock, early mechanical revascularization reduced 6- and 12-month mortality compared to initial medical stabilization, followed by late or no revascularization. According to a study, at 60 days, almost 34% of shock patients were rehospitalized or had died, compared to about 25% of non-shock patients. At 1 year, however, the difference was not as great.

Conclusion: Despite advances in treatment mainly by early revascularization with subsequent mortality reduction, cardiogenic shock remains the leading cause of death in AMI with mortality rates still approaching 40–50%.

Keywords: *cardiogenic shock, heart attack, heart failure, mortality*

COMPARATIVE ANALYSIS OF JUICES FROM WILD FOREST FRUITS BY MEANS OF APPLIED PHOTONICS

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Introduction: Fruit juices contain a large amount of vitamins and minerals and are often recommended by nutritionists and medics because of their healing effects. The extracts from wild berries have a positive effect on nephrolithiasis, pyelitis, cystitis, rheumatism of joints, and gout.

Aim: The aim of the present study is to compare the physicochemical properties of wild berry juices (raspberry (*Rubus Idaeus*), cornus (*Cornus Mas*) and lingonberry (*Vaccinium Vitis-Idaea*)) in order to detect correlations between chemical parameters and optical characteristics determined by means of applied photonics.

Materials and Methods: The content of anthocyanins, phenolic components and color characteristics were determined spectrophotometrically. A fiber optic spectrometer (Brolight) was used to measure the fluorescence spectra, and the antioxidant activity is determined by FRAP assay.

Results: The total phenolic content is highest for juice from cornus, while the juice from raspberry has the biggest content of anthocyanins. The antioxidant activity determined by the FRAP method is the highest for the juice from cornus and the lowest for raspberry juice.: The fluorescence intensities for juices with inulin or lactulose were determined by the methods of applied photonics. The peaks for $\lambda_{ex}=295$ nm are connected with anthocyanins, pigments and tannins, and for $\lambda_{ex}=265$ nm - with phenolic acids.

Conclusion: Applied photonics is a new method for quality determination of the biologically active substances in juices from wild forest fruits.

Keywords: *applied photonics, antioxidant activity, wild forest fruits*

RETINOIDS – STRUCTURE – ACTIVITY RELATIONSHIPS AND PROTEIN BINDING ABILITY BY SCHIFF BASE FORMATION

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Introduction: Bexarotene is an antineoplastic agent clinically used to treat cutaneous T-cell lymphoma and investigated for the possibility of curing other different forms of cancer. Chemically it refers to a group of compounds called retinoids, they are natural and synthetic derivatives of vitamin A (retinol). The possibility of retinoid therapy with representatives of first-generation retinoids is limited by their sensitivity to isomerization of the double bond and the possibility of oxidation by cytochrome P450 enzymes, which affects their activity and selectivity.

Aim: The aim of the present study was to present the change of effects as a result of structural variation and discuss the possibility of retinoids to bind to proteins and DNA.

Materials and Methods

This study contains summarized information about the structure and effects of retinoids from literature sources in international journals and data received from software application - OECD (Q) SAR Application Toolbox.

Results: The change in the structure of natural retinoids to be overcome results in the synthesis of a second generation retinoid in which the trimethylcyclohexenyl compound is replaced by a functionalized benzene ring and third-generation retinoids by polyaromatic systems. These changes allow their wider use and determine their increasing use in the treatment of many diseases.

Conclusion: More and more structurally diverse analogs of these natural compounds have emerged, making retinoid chemistry difficult to summarize. The reasons for this are many aspects that are poorly understood regarding the mechanism of action of retinoids and the unremitting search for structural change opportunities that lead to the synthesis of more selective compounds with less side effects.

Keywords: *new generation of retinoids, structural variation, protein binding*

RETINOIDS – BIOLOGICAL ACTIVITY, CANCER TREATMENT AND PREVENTION

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Introduction: Retinoids, vitamin A derivatives, are natural or synthetic molecules with pleiotropic effects, which regulate cell differentiation, proliferation, and apoptosis. Retinoids indicate a wide range of properties and are widely used. Their effect on cancer prevention and treatment has received a lot of attention. Currently, retinoids are systemically used for acute promyelocytic leukemia, psoriasis and related disorders, as well as other disorders of keratinization, for seborrhea, severe acne, rosacea and acneiform dermatoses. Systemic retinoids are also used for chemoprevention of epithelial skin cancer and cutaneous T-cell lymphoma.

Aim: The aim of this study is to summarize and present information about the biological activity of retinoids and their use in the treatment of certain oncological and neurodegenerative diseases as well as the possibility of use them for chemoprevention.

Materials and Methods: This study contains summarized information about the effects and uses of retinoids from literature sources in international journals and data received from PubMed.

Results: The results show that a growing number of retinoids are used in the treatment of oncological diseases, both as monotherapy and in combination with already established therapeutic regimens. Since retinoids can activate multiple nuclear receptor-mediated pathways, they show a wide spectrum of functions and many effects. Therefore, they are used in different aspects of medicine.

Conclusion: Almost every major retinoid is currently in clinical trials by itself or in combination with interferons and estrogen antagonists to treat or prevent the progression of breast cancer, which clearly outlines the growing interest in the broad possibilities of using this group of medications.

Keywords: *retinoids, oncology, cancer treatment*

THE TLC METHOD FOR QUALITY DETERMINATION OF METRONIDAZOLE DRUG FORMS

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Introduction: Thin-layer chromatography or TLC is a quick, inexpensive microscale technique that can be used to determine the number of components in a mixture, verify a substance's identity, monitor the progress of a reaction, determine appropriate conditions for column chromatography, and analyze the fractions obtained from column chromatography.

Aim: The aim of this article is to develop a new sensitive, accurate, rapid and reproducible TLC method to determine metronidazole drug forms.

Materials and Methods: A rapid and reproducible TLC determination of metronidazole drug forms is described. The method consists of extracting the drug into methylene chloride and spotting the extract on a thin layer of silica gel 60 with fluorescent indicator UV254. The sample and standard were separated on silica gel plates with acetic acid-ammonia-acetone-methylene chloride-hexane (1.3:1.1:2:3:1) as mobile phase.

Results: The sample and standard were not colored. They were visualized with a UV lamp. The spots were observed at the same level on the TLC plate. In terms of qualitative results, TLC can also provide a chromatographic measurement known as an R_f value. The R_f value is the "retardation factor" or the "ratio-to-front" value expressed as a decimal fraction.

Conclusion: This TLC method is enabling, simple, accurate, and precise for determination of metronidazole drug forms.

Keywords: *TLC, metronidazole, intravenous infusion, tablets, methylene chloride, silica gel*

THEORETICAL FOUNDATIONS OF THERAPEUTIC DRUG MONITORING

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Introduction: The scientific basis of therapeutic drug monitoring (TDM) was provided by the American pharmacologist E. K. Marshal in the 1940s. Today, TDM has already become a routine practice in many clinical laboratories as a major instrument of personalized medicine. It is defined as: “The usage of drug (and/or its metabolites) monitoring in body fluids in order to manage the therapeutic process.”

Aim: The aim of the present study was to make an exhaustive literature review of TDM.

Materials and Methods

Literature data was accessed through ScienceDirect, Google Scholar, PubMed, and the World Health Organization’s database.

Results: The drug dosage is typically based on the patient’s body weight and a subsequent adjustment depending on the clinical response. For a small group of medicines the pharmacokinetic and pharmacodynamic relationships cannot be predicted in accordance with the administered dose. The therapy management of this type of medicines is a challenge, which makes them an object of TDM. Drugs that are usually monitored are some cardioactive drugs, immunosuppressants, antiasthmatic drugs, antidepressants, antiretroviral drugs, antineoplastic drugs, and antibiotics with a narrow therapeutic index.

Conclusion: Taking into account the specificities of each patient is leading to therapy optimization. Furthermore, with the development of analytical instruments, the options for therapy individualization are yet to come.

Keywords: *therapeutic drug monitoring (TDM), personalized medicine, patient, treatment individualization*

THERAPEUTIC DRUG MONITORING IN THE FIELD OF ONCOLOGY

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Introduction: Therapeutic drug monitoring (TDM) is the clinical practice of measuring drug concentration in body fluids, thereby optimizing individual dosage regimens. Recently, TDM has become increasingly applicable in the field of oncology.

Aim: The aim of the present study was to make an exhaustive literature review of TDM in the field of oncology.

Materials and Methods: Literature data was accessed through ScienceDirect, Google Scholar and PubMed.

Results: Cytotoxic drugs meet many of the criteria for conducting TDM. The main reason for this is the wide pharmacokinetic variability and the functional differences in cancer diseases. It is important to note that the administration of maximum tolerated dose (MTD) of antineoplastics does not always correlate to the optimal one. In some cases, the treatment is subtherapeutic and the patient could receive a greater dose without any toxic events. This circumstance is due to the fact that the MTD value is determined in a small number of clinical trials. The measurement of plasma concentrations of antineoplastic drugs could be useful for the optimization of current or subsequent treatment cycle. It is also important for the observation of the patient's compliance. Therefore, TDM provides an improvement in the efficacy of therapy. In oncology practice, methotrexate, 5-fluorouracil, and busulfan are mainly monitored. There are some cases in which paclitaxel, docetaxel, etoposide or irinotecan have also been investigated.

Conclusion: Therapeutic drug monitoring is not a routine clinical practice in oncology. The reason is that there still is insufficient data available for randomized clinical trials, which include comparison of standard treatment and TDM-based therapy. That is why the categorical implementation of TDM in antineoplastic therapy is a subject of future work.

Keywords: *therapeutic drug monitoring (TDM), maximum tolerated dose (MTD), oncology, methotrexate, 5-fluorouracil*

PROBIOTICS AND PSYCHIATRIC DISORDERS: PLUS ULTRA

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Introduction: In the contemporary global society, where people are subjected to daily stress, ubiquitous antibiotic application, unhealthy diet and numerous harmful environmental factors, the balance of the gastrointestinal flora is disturbed constantly. Metagenomic approaches can help understand how the complex intestinal microbial ecosystem participates in the control of the development and function of the brain. This may be of significance in regard to the future work on therapeutic agents, such as probiotics, prebiotics and nutritional approaches in psychiatric disorders. The disorders related to microbiotic dysbiosis in humans are autism, anxiety, and depression.

Aim: The aim is to study the potential therapeutic approaches focused on microbiotic dysbiosis in psychiatric patients.

Materials and Methods: For the purpose of the paper two electronic databases (PubMed and ScienceDirect) were researched. The terms that were used for this search were as follows: “probiotics”, “psychiatric disorders”, “microbiota”.

Results: The study on the role of the human intestinal microbiota and its management with probiotics during the genesis and/or management of psychiatric disorders is at its initial stage, but it represents one of the most promising current fields of research in the sphere of psychiatry.

While an increase in the distribution of psychiatric disorders worldwide is predicted, the percentage of patients cured with the help of classic psychiatric therapy remains unsatisfactory. Psychotropic drug resistance may be a result of clinical, pharmacological, pharmacokinetic and pharmacodynamic factors.

Conclusion: Despite the proven health benefits, a probiotic, per se, is not capable of preventing or treating the vast array of human diseases. However, the thread of our knowledge must continue to disentangle.

Keywords: *probiotics, psychiatric disorders, microbiota*

CLINICAL APPLICATION OF INTRAVENOUS LIPID EMULSIONS IN INTOXICATION WITH XENOBIOTICS

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Introduction: Intravenous lipid emulsions (ILEs) have long been used clinically in parenteral nutrition as a source of essential fatty acids and as an energy source. Today, ILEs are an established therapy for systemic toxicity caused by topical anesthetics. The number of cases described in the literature of successful use of lipid emulsions against lipophilic xenobiotics intoxications is also increasing.

The predominant theory of mechanisms of action is the so-called “lipid sink phenomenon,” according to which the rapid application of the lipid emulsion creates a lipid phase in the bloodstream that extracts lipophilic xenobiotics from tissues. Alternative theories are related with the ILE capacity to improve cellular metabolism.

Aim: Summary analysis of the literary data on the administration of ILEs in clinical case reports and animal studies with successful resuscitation following acute intoxications were described. Potential benefits of ILEs for survival in cases of acute xenobiotics intoxications were demonstrated.

Materials and Methods

Systematic review of reports and studies presenting successful resuscitation of humans and experimental animals after administration of ILEs in xenobiotics poisoning was conducted.

Results: The clinical efficacy of ILEs has been established in many reports and studies in the treatment of acute intoxications with various lipophilic xenobiotics such as: local anesthetics, beta blockers, calcium channel blockers, antipsychotics, synthetic cannabinoids, herbicides, and insecticides. Lipid emulsions are administered when cardiac arrest is refractory to conventional therapy.

Conclusion: Advances in research provide information on the needs of lipid emulsions in acute xenobiotic intoxications. Based on the many studies, it can be concluded that ILE has a future in the treatment of acute intoxications in addition to standard therapy.

Keywords: acute intoxications, lipid emulsions, xenobiotics

PHARMACEUTICAL USE AND THE ROLE OF THE PHARMACIST IN THE THERAPY OF PATIENTS WITH DECREASED EYESIGHT

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Introduction: Unhealthy modern lifestyle and an aging population have led to an increase in the number of people with total or partial blindness. Recent studies show that over 80% of all vision impairments can be prevented or cured.

Aim: The study aims to examine the main difficulties faced by patients with impaired vision when using drugs and the factors that affect their treatment.

Materials and Methods: A direct anonymous survey was conducted among people with visual impairments in the city of Varna with the help of a direct anonymous questionnaire on paper. The survey included 65 respondents, nearly 68% of respondents suffered from complete blindness. An SPSS analysis was performed to investigate the factors.

Results: The analysis revealed that the difficulties are mainly related to access to the necessary drug information as well as insufficiently understandable explanations by the pharmacist. Factors that impede drug use are the age ($p = 0.018$), the level of education ($p = 0.037$), and the degree of damage ($p = 0.000$). The level of understanding of the information given in the pharmacy is a statistically significant factor ($p = 0.000$) that determines the correct use of drugs.

Conclusion: It is necessary to apply special pharmaceutical care, which is related to the specific needs of blind people to improve drug therapy and optimize the outcome of treatment.

Keywords: *blind people, difficulty, drug use, pharmacists*

DRUG USE AND ADHERENCE TO THE PRESCRIBED THERAPY IN PATIENTS WITH ASTHMA

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Introduction: The main goal of modern asthma treatment is to achieve and maintain disease control. In order to achieve the desired therapeutic outcome, active co-operation and patient compliance are required. Unsatisfactory control can be due to mistakes in administration and inhalation of the medication, misunderstanding of the goals of the treatment, leading to poor adherence.

Aim: The aim of the study is to analyze the degree of adherence of patients with asthma and the factors that affect them.

Materials and Methods: A survey was carried out on the territory of the city of Vratsa in the period March – July, 2018. A total of 49 patients were surveyed. They were clients of several pharmacies located in different parts of the city, as well as hospitalized patients in a specialized hospital for active treatment of pneumophysiatriac diseases - Vratsa. An adapted questionnaire was used, containing a tool for assessing the degree of adherence to therapy - the Morisky-Green test.

Results: The average level of adherence to the treatment of asthmatic patients was reported. It has been found that the unsatisfactory compliance of asthmatic patients is due to insufficient understanding of the treatment goals, fear of adverse drug reaction (ADR) and previous drug side effects, difficulties in the inhalation technique, complicated treatment regimen, and tendency to stop taking the medicine on their own or a change in dosage.

Conclusion: As the most accessible medical professionals, pharmacists should regularly monitor the compliances and explain to the patient the importance of their own role in the treatment and self-control of the disease, to state the importance of the mechanism of action of prescription drugs and the need to strictly adhere to the prescribed treatment to achieve optimal therapeutic result.

Keywords: *asthma, adherence, asthma medications*

OPTIMIZED SCHEME OF CHARACTERIZATION OF NANOSTRUCTURED LIPID CARRIERS

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Introduction: Nanostructured lipid carriers (NLCs) have been presented as the next generation lipid nanocarriers aimed to overcome the limitations of solid lipid nanoparticles (SLNs) related to limited drug loading, leakage, and drug expulsion during storage. The strict characterization of NLCs as drug delivery systems (DDS) is a huge challenge due to their complexity and gives guarantees for the quality of the product.

Aim: This study aims to provide optimized scheme of the process of complex characterization of NLC to produce an effective and safe colloidal DDS.

Materials and Methods

The investigation was done, based on original publications for NLC development and characterization over the past ten years.

Results: Several characterization steps have been considered as vital in developing new NLCs – microstructure characterization; in-vitro release study; stability testing; sterilization; and toxicity assessment. The microstructure characterization of NLC is in terms of average size and particle size distribution; surface morphology, functionalization, and zeta potential; structure, depending on the degree of crystallinity, lipid modification, drug incorporation and loading capacity; and co-existence of other nanostructures. Weak points in the characterization process that require special attention are investigations of the co-existence of additional colloidal structures and thorough exploration of the drug distribution into the lipid matrix using modern tools.

Conclusion: In order to produce effective and safe colloidal DDS, complex characterization of NLC, focused on the cited above weak points, is mandatory. The simultaneous application of reliable, highly sensitive analytical methods that can provide reproducible results ensures the quality of NLCs and enables their widespread use in pharmaceutical production.

Keywords: nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), drug delivery systems (DDS), analytical methods, colloidal structures, characterization process

RHODIOLA ROSEA – PERSPECTIVE IN THE THERAPY OF HUNTINGTON'S DISEASE

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Introduction: Golden root (*Rhodiola rosea* L.) well known as Bulgarian ginseng is one of the most interesting species in natural pharmacy. It grows on higher parts of Rila, Pirin and Stara Planina. It is entered in the Red Book of Republic of Bulgaria. *Rhodiola rosea* L. has proven its benefits in when used for treatment of a wide spectrum of disorders like stress, fatigue, depression and cognitive deficiency. It also has an effect on inducing autophagy in bladder cancer cell lines. This property of the golden root provides a basis for a research conducted by scientists at the University of California in 2018. It studied the ability of golden root to influence the symptoms of Huntington's disease. This is a rare, inherited, genetic disease, which leads to uncoordinated, jerky body movements, cognitive decline, and mental problems. It is caused by a mutation of Huntington's gene, which is responsible for the production of the same-named protein.

Materials and Methods: Several full-text publications were briefly analyzed. Literature was accessed through ScienceDirect and Google Scholar.

Results: The conducted research shows that golden root, through autophagy induction, improves lifespan, locomotion, and neurodegeneration in a *Drosophila melanogaster* Model of Huntington's disease.

Conclusion: Positive results promise to be a good reason for future research of *Rhodiola rosea* L. as a new potential natural therapy for attenuation of symptoms of Huntington's disease

Keywords: *Rhodiola rosea* L., Huntington's disease, *Drosophilla melanogaster*, autophagy

STUDY OF THE PROFESSIONAL BURNOUT SYNDROME IN PHARMACISTS

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Introduction: Burnout syndrome is widely seen in modern society and it is considered a 21st century disease. Its level is highest in medical professions. Pharmacists are part of the high-risk group. Up to now, there have been no studies in Bulgaria on burnout syndrome among pharmacists.

Aim: The study aims to analyze the prevalence of burnout syndrome and the related factors in people from different spheres of the pharmaceutical sector.

Materials and Methods: A direct anonymous survey was conducted in Varna in the period March – June, 2018 with the help of an adapted tool - Maslach Burnout Inventory, which explores the professional burnout on three scales: emotional exhaustion, depersonalization and professional achievements. A total of 142 people were surveyed - pharmacists working in public service pharmacies, hospital pharmacies, pharmaceutical companies, and higher education institutions.

Results: The most vulnerable to the development of a burnout syndrome are those in the 30 to 40-year-old group where the level of emotional exhaustion is highest, followed by depersonalization, and the level of perception of professional achievement is the lowest. The most vulnerable are men and people with work experience of 5-10 years.

The highest level of professional burnout is in pharmacies serving the population, and the lowest - in hospital pharmacies. For pharmacists working in pharmaceutical companies or those in the teaching sphere, emotional exhaustion is very high, but job satisfaction is high and provides a balance.

Conclusion: The work of pharmacists is directly related to patient care, which can cause exhaustion, lack of motivation, and problems in the performance of duties and the realization of quality pharmaceutical care.

Keywords: *burnout syndrome, spread, pharmacists*

MICROSCOPIC EVALUATION OF THE EFFECT OF GALLIC ACID IN A MODEL OF TRINITROBENZENESULFONIC ACID- INDUCED COLITIS IN RATS

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Introduction: Trinitrobenzenesulfonic acid (TNBS)-induced experimental colitis in animals is a commonly used model to investigate the pathogenesis of inflammatory bowel disease (IBD). Gallic acid (GA) is a naturally occurring phenolic acid possessing promising antioxidant and anti-inflammatory properties.

Aim: Using criteria for microscopic evaluation of colonic damage, the present study investigated the effects of GA in a TNBS-induced rat colitis model.

Materials and Methods: Male Wistar rats (250-350 g) were divided into 5 experimental groups, each consisting of 12 rats: Control, TNBS, TNBS+GA20, TNBS+GA40, and TNBS+GA80. For induction of colitis, TNBS was applied in the colon. The oral treatment of the animals began 24 hours after the induction of colitis and lasted for 8 days. Groups TNBS+GA20, TNBS+GA40, and TNBS+GA80 were treated with GA at doses of 20 mg/kg, 40 mg/kg and 80 mg/kg, respectively. On the 10th experimental day, the animals were sacrificed and colon samples were fixed in formalin. The severity of colitis was microscopically evaluated and scored with numbers from 0 to 3 regarding epithelium injury and inflammatory cell infiltration, respectively.

Results: The score of epithelium injury was the highest in the TNBS group. In all TNBS+GA groups, an improvement of the epithelium injury score was observed. Regarding the inflammatory cell infiltration, again the highest score was observed in the TNBS group. The lowest score was found in the TNBS+GA40 and TNBS+GA80 groups.

Conclusion: GA caused a tendency to decrease TNBS-induced damage in the experimental model of colitis probably due to its antioxidant and anti-inflammatory properties.

Keywords: *TNBS, colitis, gallic acid, rats*

APPLICATION OF RP-HPLC METHODS FOR STABILITY EVALUATION OF XANTHINE DERIVATIVES – A REVIEW

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Introduction: Xanthine derivatives are an important class of heterocyclic compounds, included in the structure of a number of natural products, as well as a variety of pharmaceutical substances.

An important characteristic of pharmaceutical formulations is their stability in various media. Thus, the development and application of suitable fast and contemporary methods for their evaluation is of utmost importance.

Results and Discussion: Various methods have been reported for determination of caffeine, theobromine, theophylline and its derivatives in different matrices such as food, drinks, and pharmaceutical products. The most widely used analytical techniques are mainly chromatography, such as high-performance liquid chromatography (HPLC) with spectrophotometric and amperometric detection; ionic chromatography and capillary electrophoresis, and gas chromatography coupled with mass spectrometry prior to solid-phase extraction (SPE) are also used.

Conclusion: Reversed phase HPLC (RP-HPLC) on the other hand is considered to be of greatest interest for us due to its simplicity, good separation quality, and specificity of the obtained results. Thus, it was of interest to summarize and evaluate the published in the literature developed and validated RP-HPLC methods for determination of the stability of xanthine derivatives.

Keywords: *RP-HPLC, stability, xanthine derivatives*

IN VITRO ACTIVITY OF 5-ETHYL-5 METHYL-4-BROMO-2-N-BUTYLAMIDO-2,5DIHYDRO-1,2-OXAPHOSPHOL-2-OXIDE (BR-OXPH-1) ON NON-CANCEROUS CELL CULTURES

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Introduction: Br-oxph-1 is a heterocycle compound containing phosphorus and oxygen in a stable 5-membered ring. Recent studies show its cytotoxic, genotoxic and apoptotic effects on human hepatoma cell line.

Aim: The goal of the study was to examine in vitro cytotoxic activity and the influence on cell antioxidant enzyme expression of Br-oxph-1 in non-cancerous cell cultures.

Materials and Methods: Murine preadipocytes and macrophage cells were cultured at standard conditions. Cells were treated with different concentrations of Br-oxph-1 in the culture medium. MTT test was used to assess the effect on cell viability. The levels of gene expression were determined by two-step quantitative Real Time PCR.

Results: Br-oxph-1 applied on murine preadipocytes at the lowest concentration stimulated cell viability. Inhibition of vitality was observed at a concentration of 0.25 mg/mL ($p < 0.001$). Upon increasing concentrations, the viability remained about 60%. Concentrations of up to 0.25 mg/mL stimulated macrophage vitality. At the next concentration, it dropped sharply to 25% and remained so to the maximum concentration. Expression of the Glutamate Cysteine Ligase gene in macrophages treated with selected concentrations showed that at a concentration of 0.25 mg/mL, the expression was increased seven times and significantly decreased at 0.5 mg/mL of Br-oxhp-1. The expression of glutathione peroxidase was also increased at 0.25 mg/mL of Br-oxhp-1.

Conclusion: In low concentrations Br-oxhp-1 stimulates cell proliferation and antioxidant enzyme expression and in higher concentrations, it has inhibitory activity on these processes. Further investigations are needed to obtain more data about possible therapeutic effects.

Keywords: *Br-oxph-1, effects, hepatoma cell line, murine preadipocytes, macrophage cells*

DEVELOPING AND VALIDATION OF A UPLC-UV-MS METHOD FOR QUANTITATIVE DETERMINATION OF FLAVONOIDS IN PLANT EXTRACTS

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Introduction: Flavonoids are a group of naturally occurring substances with a powerful antioxidant, anti-inflammatory and immune-modulatory activity. There is a growing need of a fast, sensitive and reliable method for their simultaneous identification and quantification in various natural sources.

Materials and Methods: A UPLC/UV/MS method for simultaneous determination of 7 flavonoids was developed and validated. The analysis was performed on UPLC Acquity H class, coupled with PDA and QDA detectors. The separation was carried out on Cortecs UPLC C18 column with gradient elution - mobile phase 0.2% HCOOH/methanol and 0.1% HCOOH/water, flow rate 0.3 mL/min.

Results: The method was selective for the determination of epicatechin, epigallocatechin gallate, rutin, resveratrol, myricetin, quercetin, and kaempferol. The calibration curves of the selected flavonoids were linear in the range 0.05 – 0.80 mg/L, 0.5 – 5 mg/L and 5 – 50 mg/L ($r^2 > 0.996$). The LODs and LOQs were determined - 0.05 mg/L and 0.1 mg/L, respectively. The accuracy was estimated to be between 1 and 13% for the lowest concentration of 0.05 mg/L; 0.2% - 6% for 0.4 mg/L, and 0.1-2% for 3.0 mg/L. A relatively higher relative error was found only for myricetin and kaempferol for 0.05 mg/L. No carry-over was observed. Matrix-matched calibration showed linearity for all of the flavonoids in the range 0.05 – 0.8 mg/L ($r^2 > 0.996$).

Conclusion: The proposed method was found to be linear, sensitive, precise, specific, accurate and robust. Therefore, it can be used for qualification and quantification of these flavonoids in plant extracts.

Keywords: *flavonoids, UPLC method, validation*

INFLUENCE OF PREBIOTICS AND GUT MICROBIOTA ON GLYCEMIC CONTROL IN DIABETES

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Introduction: Type I diabetes is influenced by non-genetic factors, such as optimal microbiome development during early life stages, which “programs” the immune system. The intake of oligosaccharides as prebiotics, acting on gut microbiota, can modulate the immune and inflammatory response.

Materials and Methods: References from different databases are used.

Results: The direct effect of oligosaccharides on pathogenic microorganism infections includes mimicry of receptors and influence on their virulence. The indirect effects involve the immune system as a result of stimulated growth of probiotic bacteria (*Bifidobacterium*, *Bacteroides*, etc.), as well as short-chain fatty acid production. The short-chain fatty acids bind with specific G protein-coupled receptors (GPCR41 and GPCR43), which play a significant role both in the functioning of the gut mucosa and the stimulation of the immune system. The gut microbiota - an important factor in the development of metabolic diseases in animals and humans, is under the double influence of the host genome and the nutrient medium. Intestinal microbes are key factors, included in the regulation of energy homeostasis, metabolic inflammation, lipid and glucose metabolism. Oligosaccharide prebiotics are relatively new, low-cost and low-risk functional supplements with great potential to influence favorably the glycemic control through glucagon-like peptide 1 secretion (GLP-1). Moreover, they reduce the intestinal permeability, thus preventing Gram-negative bacterial lipopolysaccharides (LPS) from entering systemic circulation, which would cause metabolic endotoxemia. LPS stimulate macrophageal overproduction of reactive oxygen species and proinflammatory cytokines (IL-6, TNF- α , MCP-1, etc.), which results in a low-grade chronic inflammation, weight gain and insulin resistance.

Conclusion: The metabolic function of gut microbiota could be important in the control of blood glucose. Therefore, its modulation aims at the study and application of probiotics and prebiotics.

Keywords: *diabetes, microbiota, microbioma, prebiotics, probiotics, oligosaccharide*

CHROMATOGRAPHIC AND SPECTROPHOTOMETRIC ANALYSES TO DETERMINE POSSIBLE PRESENCE OF UNDECLARED INGREDIENTS IN 108 FOOD SUPPLEMENTS

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Introduction: Food supplements have experienced increased popularity during the last years. Their global market values are expected to amount to 220.3 billion of US dollars by 2022 with an 8.8% increase in 2017 – 2022. Food supplements enjoy a liberal regulatory framework and lack of mandatory regulation, thus creating prerequisites for deteriorated product quality and adverse customer risk.

Aim: The current publication is an analysis of the most popular food supplements aiming to determine the possible presence of undeclared substances in their composition.

Materials and Methods: All tested food supplements (FS) were purchased randomly from the Internet, social networks, and drugstores. The analyses were performed jointly at the Bulgarian Drug Agency (BDA) and certified laboratories for testing FS and medicinal products. The tested FS samples were blind, pre-coded, sealed in individual sterile bags and submitted to the laboratory with a delivery-acceptance protocol.

The tests were made implementing HPLC and MS methods for determination of food supplement ingredients.

Results: The implemented analytical studies showed that 26% of the 108 tested FS contained undeclared pharmaceutical substances. Some supplements for weight loss contained *sibutramine* provoking dermal disorders and necrotic vasculitis (2 samples). *Sildenafil*, *tadalafil*, hazardous for consumers with cardiovascular disorders, were detected in supplements for erectile dysfunction (14 samples). The results from the chromatographic and spectrometric analyses for steroid content in 23 FS designed for athletes revealed that 12 samples contained steroid substances, banned by the World Anti-Doping Agency (WADA).

Conclusion: Our surveys and the large-scale use of FS lead to a high risk stemming from consumption of FS containing unregulated medicinal substances and steroids.

Keywords: *food supplements, undeclared ingredients in food supplements, WADA, sport and food supplements, weight loss and food supplements.*

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS: REGULATORY INSPECTION FINDINGS IN 2016

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Introduction: The contemporary manufacturing of medicines is one of the most complex and highly regulated activities of mankind. For many decades, the manufacturing of medicines was controlled by a regulatory framework that safeguarded the quality of the final product and performed testing of batch-based operations, raw material and end-product characteristics, as well as the manufacturing facilities and equipment. The Bulgarian Drug Agency (BDA) is exercising the regulatory control over the manufacturing sites located in Bulgaria and the EU (on request).

The current study analyzes the regulatory inspection findings of the pharmaceutical manufacturers inspected by the Agency in 2016.

Materials and Methods: The inspections were performed according to the GMP. The inspection methods used were interviews, review of documentation and conduction of site visits. All reports were reviewed for the scope of the inspection, classification of findings, the content of findings, and the conclusion.

Results: In total, 20 GMP inspections were performed in 2016 (19 sites). Five of the inspections were related to the authorization of medicinal products or change in the existing authorizations. Two inspections were performed abroad. During the inspections, non-conformities to GMP (NCs) were found on 16 sites. Out of the total number (n=137), 37 were classified as "major" and the rest – as "other".

Conclusion: During the regulatory inspections of pharmaceutical manufacturers in 2016, GMP non-conformities were found in 84.21% of the inspected companies. No critical NCs were identified. The most frequent were deficiencies related to the quality management system, personnel trainings, premises and equipment, etc., which corresponds to the findings from other regulators in EU.

Keywords: *good manufacturing practice (GMP), medicinal products, non-conformities, pharmaceutical manufacturing, compliance, Bulgarian Drug Agency.*

THE MEDICINE VERIFICATION SYSTEM – A STUDY ON PHARMACISTS’ OPINION ON INTRODUCING THE SYSTEM TO THE BULGARIAN MARKET

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Introduction: Worldwide there has been an increase in the number of counterfeit medicines. Due to the alarming growth trends, the European Union is taking measures to limit the entrance of falsified medicinal products to the market through legal channels for production and medicine supply. The measure, which will lead to the authentication of medicinal products, is the drug verification system.

Materials and Methods: A questionnaire was used to examine the opinion of pharmacists towards introducing verification of medicinal products in Bulgaria. The study included the society of pharmacists. It was conducted between March, 2018 and July, 2018. A total of 120 respondents were interviewed to explore the opinion of introducing a verification process in pharmacies, the impact of the innovation on their work, and the effectiveness of the method of excluding counterfeit medicines from the market.

Results and Conclusion: Bulgaria, as an EU Member State, follows the development trends of Europe. A drug verification system is a progressive step towards improving the level of health care and protecting community health. It aims to ensure that patients are supplied with authentic medicinal products by building, operating and maintaining an effective drug verification system in Bulgaria. The benefit of introducing a verification system covers all aspects of the supply chain - from the manufacturer to the final customer - the patient.

Keywords: *medicines, drug verification system, innovation, community health, pharmacist, opinion*

PHARMACISTS' ROLE IN PREVENTING DRUG INTERACTIONS DURING MEDICAL ABORTION

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Introduction: Medical abortion is safe and effective way for ending unwanted pregnancy. Many clinical studies prove that the combined use of mifepristone and misoprostol is an effective way to perform it. With the greater availability of these promising drugs, pharmacists who are the first-line healthcare providers have an increasingly important role to play in delivering accurate information about them and ensuring the increased access to such methods.

Materials and Methods: The study contains summarized information from available literature sources in national and international journals about the role of the pharmacist in advising patients on medical abortion drug intake.

Results: The visits included talking with pharmacists about evidence-based information and leaving them with written information, with the objective of improving the advice and information they offer to clients. Individualized outreach visits did affect provider behaviors, especially the prescribers. Training of pharmacists in using promotional materials, referral links, and educational courses is gaining success, but without strong evidence for longer-term impact.

Conclusion: Pharmacists' knowledge about medical abortion is limited. Many of them are willing to provide something to help a woman with an unwanted pregnancy but do not feel confident to recommend this way of ending unwanted pregnancy. Women rarely seek help and medicine information from pharmacists, but some of them are unable or unwilling to seek care from a trained clinical provider. There is an unmet need of approaches that successfully improve the pharmacists' ability and willingness to provide accurate information about medical abortion.

Keywords: *community pharmacy, pharmacist; abortion; medical abortion, women's health*

TREATMENT WITH BRACHYTHERAPY IN BULGARIA

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Introduction: Our research studied the development of brachytherapy in Bulgaria and the opportunities it provides for treatment of oncological diseases. Dating back to the middle of XX century, interstitial brachytherapy was used for the first time in the National Hospital for Oncology in Sofia. Recently, the application of brachytherapy has spread across the country, which led to the construction of a number of treatment centers in Sofia, Stara Zagora, Shumen, Burgas, Vratsa, Pazardzhik, Ruse, Haskovo, Varna, Pleven and Veliko Tarnovo.

Materials and Methods: The data was collected from the National Health Insurance Fund (NHIF) of Republic of Bulgaria in accordance with Access to Public Information Act with resolution RD-19-285/25.07.2018 and RD-19-376/25.09.2018 of the Secretary General of NHIF.

Results: In 2016, the total number of patients, treated with brachytherapy is 875, 594 of whom have been treated with brachytherapy, combined with chemotherapy and external beam radiation therapy (EBRT). In 2017, the total number of patients, treated with brachytherapy was 935, 524 of whom have been treated with brachytherapy, combined with chemotherapy and EBRT.

Conclusion: Brachytherapy is rarely used on its own. It is usually combined with chemotherapy and/or EBRT. Between 2016 and 2017, there has been a significant increase in the number of patients, treated only with brachytherapy in comparison to a slight decrease in the number of patients, treated with brachytherapy, combined with chemotherapy and EBRT. This is most likely due to the fact that the treatment is used in terminal cases, while standalone brachytherapy is generally used for treatment of less severe cases.

Keywords: *brachytherapy, treatment, oncological diseases, chemotherapy, external beam radiation therapy (EBRT)*

EFFECTS OF LONG-TERM TREATMENT OF YOUNG RATS WITH AZORUBINE

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Introduction: Dyes as excipients are widely used both in the pharmaceutical and in the food industry. Their use in pediatric drugs and in food supplements intended for children requires a more thorough examination of the risks of their chronic intake.

Aim: The aim of the present study is to investigate the behavioral and memory changes as well as their biochemical correlates after prolonged oral administration of azorubine (E122) to young sexually immature rats.

Materials and Methods: Male 21-day-old Wistar rats (60-80 g b.w.) were treated orally with azorubine (probe) at a dose of 2 mg/kg body weight for 90 days. The results were determined by evaluating the parameters on the first day before treatment, on the third day and 24 hours after the final application (91 days) using a Step-through test for memory and learning ability and a Rot-a-rod test for motor coordination. Catecholamine and acetylcholine levels in brain homogenates were compared to saline-treated controls.

Results: After a 90-day treatment, a significant decline of the cognitive parameters in the azorubine-treated animals compared to the control group was found. Motor coordination at the onset of dye intake was improved and at the end of the study period, it was decreased compared to control animals. In the azorubine-treated group, the levels of acetylcholine in the brain were reduced, as well as those of dopamine, adrenaline and noradrenaline. Only serotonin levels in the brain were increased in comparison to controls.

Conclusion: The aggravated cognitive and motor parameters of young rats after long-term azorubine intake were worsened and correlated with observed changes in the biochemical parameters of the brain. Our results confirmed the available data and gave a new aspect on the azorubine effect in young rats and its mechanism of action. Further study is required given the toxicological significance of the wide and chronic use of the dyes, especially in childhood.

Keywords: azorubine, E122, memory, neurotransmitters, rats

SOCIOMEDICAL ANALYSIS OF THE PROCEDURES AND REGULATIONS ON THE PROVISION OF MEDICAL ABORTION IN BULGARIA

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Introduction: Social medicine attempts to link together clinical medicine and preventive medicine in the hope of benefitting both. Social pharmacy is a discipline, which deals with the role of medicines from social, scientific and humanistic perspectives. Medical abortion is new and not a well-known alternative of surgical abortion.

Aim: The aim of this study is to analyze the sociomedical aspects of the procedure and regulations on the provision of medical abortion in Bulgaria.

Materials and Methods: We conducted a literature survey on the total number of abortions worldwide and the connection with medical abortion. We also conducted a research on the religious factor and the legislation of medical abortion. We made a mini survey among 3 Bulgarian women who have had a surgical abortion. Some sexual and reproductive healthcare services around the world were found during the survey.

Results: Abortion has been a controversial subject in many societies throughout history because of the moral, ethical, practical, and political power issues that surround it. Family planning as a human right challenges many social conventions. The International Planned Parenthood Federation (IPPF) and International Project Assistance Services (IPAS) are globally connected civil society movements. They work to ensure people are free to make choices about their sexuality and wellbeing.

Conclusion: Unsafe abortion contributes substantially to maternal mortality and morbidity worldwide. The stigma is a major contributor to the social, medical and legal marginalization of abortion. Medical abortion is a modern method of medically induced abortions. It is safe and effective when used in an appropriate way.

Keywords: *medical abortion, legislation, family planning*

CONTRIBUTION OF SULFUROUS MINERAL WATERS TO DIETARY SULFUR INTAKE AND METABOLISM

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Introduction: Sulfur is a non-metal macroelement with critical importance for the human body integrity and homeostasis. Sulfur-containing biomolecules have important functions in redox balance maintenance, enzyme functionality, DNA methylation and repair, modification of extracellular matrix components, detoxification of xenobiotics, etc.

Results: Many studies related to sulfur utilization and metabolism are focused on foods rich in organosulfates that are linked with healthy benefits. It is known that sulfur-containing mineral water also could have beneficial effects on the human health but this knowledge is currently based on empirical data.

Conclusion: It could be suggested that the intake of sulfurous mineral waters as a part of everyday diet will have a significant effect on the human metabolism.

Keywords: *sulfurous mineral water, health benefits, human metabolism*

THE ROLE OF THE PHARMACIST IN THE RECLASSIFICATION OF MEDICINAL PRODUCTS

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Introduction: Reclassification from prescription (Rx) to over-the-counter (OTC) can be considered a process that changes the regulatory status of a medicinal product, which has so far only been prescribed with a document, to a non-prescription regimen. This process essentially requires proving the safety and effectiveness of a given medicinal product for a specific indication.

Aim: The aim of the study is to analyze the role of a Master of Pharmacy professional in the reclassification process and his/her place in the self-medication stages of patients needing medicinal products that have been switched to OTC.

Materials and Methods: Analyzing data from a survey conducted by pharmacists on the reclassification process. This review contains summarized information from available literature sources in national and international journals about the role of the pharmacist in advising patients on the correct use of new OTC products obtained after the switching process.

Results: The results of the study show that pharmacists in Bulgaria are aware of the reclassification process of medicinal products and its role in patient self-treatment. Pharmacists define the reclassification process as an opportunity to improve their relationship with patients through consultation on their condition and the rational drug therapy.

Conclusions: Increasing the empowerment of patients in managing their own health and seeking broader and more convenient access to self-medication with non-prescription drugs based on in-depth knowledge of the condition of their illness are the main factors that have contributed to a steadily growing OTC business in the world.

Keywords: *reclassification, medicinal product, pharmacist, self-treatment, patients*

NIOSOMES: NON-IONIC SURFACTANT VESICULAR SYSTEMS FOR EFFECTIVE DRUG DELIVERY

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Introduction: Niosomes are vesicular systems, formed by self-association of non-ionic surfactants and cholesterol in an aqueous phase. Based on their amphiphilic nature, niosomes can be used as carriers of lipophilic or hydrophilic drugs. They have been applied to various routes of administration, such as intravenous, intramuscular, oral, ocular, subcutaneous, pulmonary, and transdermal. As an ocular drug delivery system, niosomes have been reported as possible approach to improve the low corneal penetration and bioavailability characteristics for many drugs, providing therapeutic effect in a controlled manner over a longer period of time.

Materials and Methods: The main structural components of niosomes are non-ionic surfactants (sorbitan fatty acid esters - Spans, polyoxyethylene fatty acid esters - Polysorbates) and cholesterol. Niosomes are prepared by different methods, such as thin-film hydration, reverse-phase evaporation, and multiple membrane extrusion.

Results: Characterization of niosomes is essential for their clinical applications. Therefore, parameters such as morphology, size, polydispersity index, zeta potential, entrapment efficiency, *in vitro* release and stability must be evaluated.

Conclusion: On the ground of proper physicochemical characteristics and being biodegradable, biocompatible and nonimmunogenic, it can be concluded that niosomes are a promising vehicle for effective ocular drug delivery.

Keywords: vesicular systems, niosomes, non-ionic surfactants, ocular drug delivery

CHANGES IN PRICE AND REIMBURSEMENT OF FIXED DOSE COMBINATION MEDICINES – ARBS AND ARBS + HYDROCHLOROTHIAZIDE EXAMPLE

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Introduction: The tendency in the development and manufacturing of medical products with a decreased rate of discovering new chemical formulae splits into two directions – personalized therapy and manufacturing of combined medical products, which contain active ingredients with well-established application. The combined medical products usually represent a fixed-dose combination of active substances that are used in therapeutic practice separately.

Aim: The aim of the present study is to conduct a pharmaco-economic analysis of the combined medical products (fixed-dose combinations) for the treatment of cardiovascular diseases and to study the influence of reference pricing and the level of their generic entry in Bulgaria.

Materials and Methods: The survey uses IMS Health statistical data, data from positive drug list (PDL) and data from the cash execution reports of the National Health Insurance Fund (NHIF), as well as data from NCPHP.

Results: The results of this study corroborate the conclusions of many other previous analyses, as well as the good practices of the EU countries, and evaluate the positive effects of conducting a progenitor drug policy within the angiotensin receptor blocker group (combined drugs). Over a six-year period, 2011–2017, there has been an increasing demand for generic medicines in this group, which would allow the achievement of lower costs on the basis of increasing consumption.

Conclusion: Over the years, there has been a natural demand for generic medicine products under the “no progenitor drug” policy conducted by national authorities. From this point of view, the state policy should work towards the rapid placement of generic medicines on the Bulgarian market, while avoiding the creation of additional obstacles, such as the extension of the original medicine’s patent.

Keywords: *fixed-dose combinations, changes in price, reimbursement, NHIF, DDD, ARBs*

CARDIOPROTECTIVE EFFECT OF LYCIUM BARBARUM-ISOLATED FRACTIONS IN DOXORUBICIN-INDUCED CARDIOTOXICITY

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Introduction: Cardiotoxicity is one of the most serious adverse effects of cancer treatment with antineoplastic anthracycline antibiotics. It can hinder the treatment and even lead to a fatal outcome.

Aim: The aim of the present study is to investigate whether *Lycium barbarum* (also known as goji berry)-isolated fractions could protect against doxorubicin-induced cardiotoxicity.

Materials and Methods: In this study, we have isolated and used two fractions of *Lycium barbarum* fruits – pectin-free (rich in polyphenols) and polysaccharide. Then, we investigated the cardioprotective effects of these two fractions in doxorubicin-induced cardiotoxicity model in rats. Biochemical assays and histopathology were used to evaluate changes in cardiac tissue.

Results: *Lycium barbarum*-isolated fractions have shown a significant decrease in the serum levels of creatinine kinase (CK) and lactate dehydrogenase (LDH), compared to the doxorubicin-induced cardiotoxicity group. The combination of the pectin-free and polysaccharide fraction showed the most significant decrease in these biomarkers. In addition, histological analysis showed significantly less damage in cardiac myofibrils in the group treated with that combination.

Conclusion: *Lycium barbarum*-isolated fractions have shown a promising cardioprotective effect in doxorubicin-induced cardiotoxicity in rats. The combination of the pectin-free with polysaccharide fraction contributes to its better pharmacological activity.

Keywords: *cardioprotective effect, Lycium barbarum, goji berry, doxorubicin*

STUDY OF THE DIFFERENCE IN PRICES OF DISCOUNTED OTC PRODUCTS OFFERED BY COMMUNITY PHARMACIES IN THE REGION OF VARNA

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Introduction: Pricing is one of the most important elements of the marketing mix. Many community pharmacies offer promotions and discounts in prices on a regular basis, thus dropping the price of certain over-the-counter (OTC) products for a limited period of time.

Aim: The aim of the study is to compare and analyze what are the price differences in randomly chosen community pharmacies in the region of Varna, which offer medicinal products without prescription, included in paper leaflets distributed among patients and consumers.

Materials and Methods: We have performed a review and comparison of the registered maximum price and the one offered by the wholesaler and the one by the retailer. Usually community pharmacies publish their discount offers either online or through printed materials. Comparison between the prices is made based on their online brochures for certain OTC products. Difference in the prices is shown in percentages and the final non-discounted price of the product is used as a base price.

Results: Results show the real discount offered by pharmacies and the potential impact in savings for the patients. We estimated the extent of the impact over the OTC retail prices of the overall promotion strategy of the community pharmacy.

Keywords: OTC, prices, promotion, leaflet

VANGUARD METHODS FOR PERSONAL ENHANCEMENT WITH CONTROLLED STRESS EFFORTS

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Introduction: The fast changing environment influences modern society in any aspect - economic, social and cognitive. The pace of that change is speeding up. Respectively, an adequate response is needed – a change on behalf of the individual, since s/he operates within this environment. The addition of new skills is needed for these new conditions. Hence, the response should be enhancement. Enhancement of the personal skills of the individual to overcome the shortage is related to including adapting mechanisms. Some skills are derived from our genes, but each skill can be improved. Improving one leads to potentially improving the rest. Part of the energy released for dealing with difficulties, which have been linked to the shortage of an already improved skill, is now released for other things. The flow is open for mastering new things.

Materials and Methods: Methods and tools shall be implemented with maximum efforts, in order for them to be continuous and strictly specific. For the adaptation, the level of high intensity stress shall be above the specialized. For improving specific skills, specific new tools shall be selected and implemented. New tools shall be used for peak efforts, and they shall be measurable and scalable. An important moment is the initial calibration of the efforts towards the individual, who should continue with a consequent and consistent increase of the efforts, staying in the high levels of stress.

Results and Conclusion: After the application of new tools amongst several groups, for a period of 12 months, an activation of adapting mechanisms and serious personal advancement has been observed.

Keywords: *advancement, personal development, public health, stress*

OPTICAL CHARACTERISTICS OF FRENCH WINES

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Introduction: Red wine is one of the most widely consumed alcoholic beverages in the world. Its composition is highly dependent on factors such as grape variety, soil type, climate conditions, and technology of production. For this reason, wine producers often compare properties of wine from a given country with the properties of wine from the same price class, and a wine variety from other country.

Aim: The aim of this investigation is to investigate the data on the physicochemical properties of Bulgarian and French wines from the same price class.

Materials and Methods: Near-infrared spectroscopy, acoustic and ultrasonic techniques are often used for these estimations but they are costly and difficult to be proved. Wine parameters such as color intensity, hue, chroma have been determined and correlated with their potential health beneficial antiradical effects. The fluorescence spectra for excitation wavelength 285 nm have been measured by a specially constructed scheme. Its advantage is that a small drop of 1-2 μ l allows measuring emission fluorescence without necessity of preparation of appropriate solution from the investigated samples.

Results: The antiradical activity against ABTS and DPPH using spectrophotometric methods was also measured. All the investigated samples demonstrated better scavenging properties in the ABTS model system compared to the DPPH one. All wines have one fluorescence peak at 411 nm, which is associated, according to the literature data, with flavonoid content. The wines from the Paris region have another peak at 290 nm, which is associated with epicatechin. There are the linear dependencies between the ratio I296/I285 and the antioxidant activity determined by the ABTS and DPPH methods.

Conclusion: The fluorescence spectroscopy can be used for evaluation of the quality of red wines from different countries.

Keywords: *fluorescence, red wine, antioxidant properties, scavenging properties*

NEW POTENTIAL TOXICANTS - “FAKE” MEDICINES

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Introduction: We live in a world where everything can be fake and cheap. This is also true for medicines. The words of Howard A. Zucker, MD Commissioner of Health: “People don’t die from carrying a fake handbag or wearing a fake t-shirt. They can die from taking a counterfeit medicine” are important. A report by the World Health Organization (WHO) shows that an estimated 1 in 10 medical products in low- and middle-income countries is substandard or falsified. “Fake” drugs = falsified medicines. Counterfeit medicines are products deliberately and fraudulently produced and/or mislabeled with respect to identity and/or source to make it appear to be a genuine product.

Materials and Methods: In our research the toxicants – fake medicines are categorized according to the following criteria: components of the counterfeit medicine and common types of medicines, which are being counterfeited most frequently.

Results: In our study we discuss the various harmful effects of the different types of new toxicants - the fake medicines. Based on the available literature, results on the frequency of appearance are provided. As counterfeit medicines are a global problem, we have compared results from various sources, such as the WHO and the Organisation for Economic Co-operation and Development (OECD). Cases of toxicity and other harmful effects reported by researchers for each of the categories in the research are also discussed.

Conclusion: The potential causes for the growing production of fake drugs should be discussed more and more, and the awareness of this problem should be raised.

Keywords: *fake drugs, counterfeit medication, WHO report, health risk*

CAN WE USE THE REGULATORY INDICATORS AND CRITERIA FOR EVALUATION OF PHARMACOVIGILANCE? THE OTHER VIEWPOINT!

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Introduction: The authors present a different perspective - Can we use the regulatory indicators and criteria for evaluation of pharmacovigilance?

Materials and Methods: We have analyzed retrospectively the work of the European Medicines Agency (EMA) related to the so-called centralized procedure for the period from its creation in 1995 to 2011. We used data from the EMA Annual Reports, the European Medicines Register maintained by the European Commission, European Public Assessment Reports on authorized medicines, and assessment history of medicinal products.

Results: For the analyzed period, 956 marketing authorization applications were submitted and 673 marketing authorizations (MAs) were approved. From the total number of submitted applications 165 were withdrawn and 46 rejected - 211 medicinal products did not reach the issuance of MA. In contrast to the 673 approved MA, 18 604 variations (type I and type II) were authorized, or 27.6 variations on average per medicinal product.

Conclusions: We have seen a tendency for a multiple increase in the number of variations to the MAs at every five years. On the 16th year of the establishment of EMA, an "epidemic" of variations to MAs was observed. Is the regulatory environment adequate? Are there safety data from which industry, regulators, doctors and patients have to draw conclusions? Are the conditions under which a medicinal product is authorized remain the same after its placing on the market? There are too many questions on which it is difficult to give a precise answer, and some of them are rhetorical in nature!

Keywords: *pharmacovigilance, marketing authorization, variations to marketing authorization, variations Type I, Type II, centralized procedure*

VACCINATION IN BULGARIA – ANALYSIS OF ITS DOCUMENTATION IN ELECTRONIC HEALTH RECORDS

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Introduction: Vaccination is a proven method of preventing infectious diseases. In Bulgaria, there is a special regulation for this medical activity, which defines age groups, schedules, specific vaccine characteristics, and requirements for usage. All vaccinations should be documented in specific immunization passport and the specific electronic health record of the patient at their general practitioner (GP).

Aim: The aim of the study is to analyze the role of a medical doctor and a Master of Pharmacy professional in the process of documenting vaccinations in electronic health records in Bulgaria.

Materials and Methods: We have analyzed the legal framework for vaccinations and developed a conceptual model for optimization of the documentation related to this activity. We put a special accent of the role of the Master of Pharmacy professional in the process as a consultant for adverse drug reactions and as an active participant in the public health promotion.

Results: Bulgaria has a well-developed immunization calendar, which divides the vaccines in three types: mandatory, recommended for people at risk and voluntary. The conceptual model, which we developed, shows that pharmacists in Bulgaria can play an active role in vaccine vigilance, also in pursuing the patients for immunizations and through analyzing electronic health records for preventing some drug interactions. Medical doctors are responsible for the procurement and administration of vaccines, and especially for the initial record of the immunization in the electronic dossier of the patient.

Conclusion: There is a great potential in using the community pharmacist as an active promoter of vaccines as medicinal products for prophylaxis. This will help increase the immunization coverage in marginalized and hard-to-reach groups.

After building the conceptual model for optimization of the documentation related to vaccinations, we have discovered that pharmacists are very important participants in the whole process and, for the moment, they are underestimated in the public health promotion.

Keywords: vaccination, Bulgaria, pharmacist, patients, electronic health records

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American Medical Association [Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: <http://www.ama-assn.org/ama/pub/category/1736.html>

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Zhang M, Holman CD, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *BMJ*. 2009 Jan 7;338:a2752. doi: 10.1136/bmj.a2752. PubMed PMID: 19129307; PubMed Central PMCID: PMC2615549

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Each figure should be accompanied by a title and an explanatory legend. The title should be part of the legend and not lettered onto the figure itself. Legends should be concise.

ABBREVIATIONS

Use abbreviations if a term appears three or more times. Spell out all abbreviations at first occurrence, and then introduce them by placing the abbreviation in parentheses. The metric system should be used for all volumes, lengths, weights, etc. Temperatures should be expressed in degrees Celsius (centigrade). Units should conform to the International System of Units (SI).

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