

CFTR MODULATOR THERAPIES

Vanesa Slavcheva¹, Emilia Ilieva¹, Detelina Ilieva²

¹*Student, Faculty of Medicine, Medical University of Varna*

²*Department of Physics and Biophysics, Faculty of Pharmacy, Medical University of Varna*

Introduction: Cystic fibrosis is a hereditary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR is an ion channel responsible for Cl⁻ efflux through epithelial surfaces in the body. The primary symptom of cystic fibrosis is a build-up of thick mucus in the lungs and other organs, leading to frequent infections and other complications. Clinical trials indicate that mutation-specific approach appears to be most successful so far. Drugs targeting the defective protein (the CFTR modulators) are classified into three main groups: potentiators, correctors and amplifiers.

Materials and Methods: Ivacaftor (Kalydeco) and IVA combined with lumacaftor (Orkambi) have been approved for use in patients with CF. Lumacaftor/ivacaftor is a combination therapy that works in people with two copies of the F508del mutation. Lumacaftor is a modulator known as a corrector that helps the CFTR protein form the right shape. With lumacaftor only part of the CFTR protein reaches the cell surface resulting in decreased membrane transport of Cl⁻. When used in combination with a potentiator, such as ivacaftor, to hold the gate of the protein open, enough chloride can then flow to reduce the symptoms of CF. Tezacaftor/ivacaftor is another treatment option. Tezacaftor, another corrector, acts in the same way that lumacaftor does, but the tezacaftor/ivacaftor combination seems to cause less side effects than the lumacaftor/ivacaftor one. Furthermore, tezacaftor/ivacaftor is approved for people with a single copy in some specified mutations.

Conclusion: Modulating therapies have great impact on the life span of cystic fibrosis patients. Entirely new direction in the overall treatment of the disease includes stem cell therapy to repair the airway tissue.

Keywords: CFTR, mutation-specific approach, CFTR modulators, lumacaftor/ivacaftor, tezacaftor ivacaftor

PREDICTING BEXAROTENE MICROBIAL METABOLISM

Yana Koleva¹, Svetlana Georgieva²

¹*Department of Physical Chemistry and Organic Chemistry,
University 'Prof. Assen Zlatarov', Bulgaria*

²*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna, Bulgaria*

Introduction: Bexarotene is a synthetic retinoic acid agent with potential antineoplastic properties and selectively binds to and activates retinoid X receptors (RXRs), thereby inducing changes in gene expression. Humans are increasingly exposed to various xenobiotics (drugs/pharmaceuticals) and their metabolism, elimination and toxicity have become a major concern for researches working in areas of health sciences.

Aim: The aim of this work is to examine the possible microbial metabolic activity of third generation retinoid (bexarotene) and to predict the protein and DNA binding of its metabolites by OECD (Q)SAR Application Toolbox.

Materials and Methods: The compound, which was investigated, was retinoid bexarotene. The methods that have been applied are pledged in OECD (Q)SAR Application Toolbox.

Results and Conclusion: The data analysis of microbial metabolism prediction of bexarotene shows that it has metabolic activation (51 metabolites). They have DNA binding (aliphatic epoxides, aziridines and epoxyethers – 1 metabolite) and twelve of them have the ability to bind to proteins by Michael-type nucleophilic addition (2 metabolites), nucleophilic addition to ketones (4 metabolites), nucleophilic heterocycle ring opening (1 metabolite) and Schiff base formation (5 metabolites). Metabolites with electrophilic character may react with nucleophilic sites in DNA and proteins and show the possibility of potential adverse effects.

Keywords: *bexarotene, metabolism, microbial, predicting, OECD (Q)SAR Application Toolbox*

ESTIMATING MICROBIAL METABOLISM OF NEWLY SYNTHESIZED DERIVATIVES OF BEXAROTENE

Yana Koleva¹, Svetlana Georgieva²

¹*Department of Physical Chemistry and Organic Chemistry,
University 'Prof. Assen Zlatarov', Bulgaria*

²*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna, Bulgaria*

Introduction: Drug/pharmaceutical efficacy, modulation of pharmacological properties and their links to human physiology are important issues that need to be investigated prior to their administration.

Aim: The aim of this work is to examine the probable microbial metabolic activity of five newly synthesized derivatives of bexarotene and to predict the protein and DNA binding of their metabolites by OECD (Q)SAR Application Toolbox.

Materials and Methods: The compounds, which were investigated, were five bexarotene derivatives. The methods that have been applied are pledged in OECD (Q)SAR Application Toolbox.

Results and Conclusion: Microbial metabolic activation was not observed for the five newly synthesized bexarotene derivatives. In the microbial metabolism simulator, between sixty-four and sixty-nine metabolites were predicted for all derivatives. They had DNA binding (aliphatic epoxides, aziridines and epoxyethers – 1 metabolite and azo compounds – 2 metabolites) and some of metabolites of the five newly synthesized derivatives of bexarotene had the ability to bind to proteins by Michael-type nucleophilic addition, nucleophilic addition to ketones, nucleophilic heterocycle ring opening, nucleophilic cycloaddition to diketones and Schiff base formation. Therefore, some electrophilic metabolites show the possibility of potential adverse effects.

Keywords: bexarotene derivatives, metabolism, microbial, predicting, OECD (Q)SAR Application Toolbox

PARENTS' AWARENESS OF CHOOSING IMMUNOSTIMULATORY PRODUCTS FOR CHILDREN

Daniel Argilashki, Bozhidarka Hadzhieva, Anna Mihaylova, Nina Koleva

Medical College, Medical University of Plovdiv, Bulgaria

Introduction: To study the use of immunostimulants in children and the parents' awareness of their choice.

Materials and Methods: We used the following databases - Google Scholar, Pubmed, and official sites. The applied method was an instrumental one in the form of a survey. A statistical method was used for processing survey data.

Results: Immunity is the resistance of the body against the physical, chemical and biological pathogenetic factors of its environment. The immune system in children is less developed and this requires more frequent use of immunostimulating agents. A parental survey was conducted, which consisted of two modules - a passport and parents' awareness of immunostimulants in children. The study showed that more and more parents were trusting different methods to build their child's immune system - using stimulants, hardening, eating right, and more. The most preferred by parents immunostimulants were products containing vitamins, black elderberry and/or echinacea. Black elderberry contains a number of active substances, including anthocyanins (mainly cyanide 3-glucoside and cyanidin 3-sambubioside), which have been shown to increase immune function and exhibit antiviral effects. Echinacea exhibits an immunomodulatory effect by increasing phagocytosis, total monocytes, neutrophils and NK cells.

Conclusion: The use of traditional medicinal plants and herbs products provides great immunomodulation opportunities, and any therapy should be age-appropriate. Due to the increased demand from parents for various immunostimulants, we would recommend the organization of training modules and programs for parents to be better informed about immunostimulation.

Keywords: *immunity, parents' awareness, immunostimulants*

THERAPEUTIC EFFECTS OF *LACTOBACILLUS BULGARICUS*

Milena Viliyanova¹, Ersin Ismail¹, Silvia Gancheva²

¹Student, Faculty of Medicine, Medical University of Varna

²Department of Pharmacology and Clinical Pharmacology and Therapeutics,
Faculty of Medicine, Medical University of Varna

Introduction: *Lactobacillus bulgaricus* is the bacterium fermenting Bulgarian milk into yogurt. Nowadays it is classified as *Lactobacillus delbrueckii subspecies bulgaricus*. A subspecies strain is named *L. bulgaricus* GLB44 and is extracted from the Bulgarian snowdrop flower. These bacteria produce similar effects. They fulfill all criteria to be called probiotics - living microorganisms that provide health benefits when administered in appropriate amount to the organism.

Materials and Methods: Scientific articles concerning the beneficial effects of *L. bulgaricus* in clinical and experimental settings were collected using the PubMed database.

Results: A meta-analysis suggests that probiotics containing *L. bulgaricus* significantly reduce the risk of antibiotic-associated diarrhea, *C. difficile*-associated diarrhea and acute diarrhea of different origin. Many researches examine the effect of *L. bulgaricus* supplementation before and after conducting triple therapy for eradication of *H. pylori*. They demonstrate that probiotic administration improves the eradication rate. Another study shows that *L. bulgaricus*, added to pinaverium bromide therapy, significantly relieves abdominal pain in patients with irritable bowel syndrome (IBS). In addition, this probiotic possesses an important role as a modulator of the immune system. There is data that daily consumption of yogurt increases the level of IgA in the saliva of elderly people, thus reducing the risk of colds. An experiment using *in vivo* mouse model of intestinal inflammation and colon carcinogenesis reveals that *L. bulgaricus* is able to prevent them. The therapy of bacterial vaginosis is more efficient and the recovery rates are improved by daily intake of *L. bulgaricus*.

Conclusion: *L. bulgaricus* possesses a modulatory effect on the immune system. The administration of this probiotic improves the efficacy of therapy in many diseases, such as IBS, diarrhea, *H. pylori* eradication, and bacterial vaginosis.

Keywords: *Lactobacillus bulgaricus*, probiotics, immune system

INTRODUCTION TO EUROPEAN CODE AGAINST CANCER

Krassimira Zaykova¹, Assena Stoimenova²

¹*Faculty of Medicine, Medical University of Varna*

²*Faculty of Public Health, Medical University – Sofia*

Introduction: The European Code Against Cancer (ECAC) is an initiative of the European Commission, first launched in 1987. Since then the ECAC has undergone several editions, resulting in the current 4th edition, published in 2014. The Code aims to inform people about actions possible to take to reduce their risk of cancer.

Aim: The aim of this article is to introduce ECAC, promote the 12 recommendations and raise their visibility.

Materials and Methods: ECAC contains 12 evidence-based recommendations, which can be implemented in daily life and most people can follow without any specific skills. The Code was compiled by leading cancer scientists from across Europe, based on the latest scientific evidence on cancer prevention. In 2015 the Association of European Cancer Leagues (ECL) launched an initiative to draw on the enthusiasm of young health advocates to help disseminate ECAC. This initiative today brings together 66 highly motivated young people from 36 countries, who promote cancer prevention.

Results: It is estimated that almost 50% of all deaths due to cancer in Europe could be avoided if everyone followed the recommendations. The recommendations concern tobacco and second-hand smoke, healthy body weight, physical activity and diet, alcohol, sun/UV exposure, pollutants and radiation, breastfeeding, hormonal therapy, vaccination and screening.

Conclusion: There is a need of constant actions aiming at education on primary cancer prevention in Bulgaria. The long-term goal is to evaluate the impact of effective compliance with ECAC after dissemination of ECAC to the Bulgarian population.

Keywords: cancer, recommendations, European Code Against Cancer (ECAC), European Commission (EC), European Union (EU), Bulgaria

SYNTHESIS AND STRUCTURE CHARACTERIZATION OF NEW *iodo-FUNCTIONALIZED 5'-DEOXY-5'- FLUOROCYTIDINE ANALOGUES*

Nadya Hadzhieva, Stanila Stoeva, Iliyan Kolev

Faculty of Pharmacy, Medical University of Varna

Introduction: It is well-known that the introduction of a halogen atom into the organic backbone may influence the biological activity of many pharmaceutical compounds. In many examples, it has been demonstrated that drug analogs with improved therapeutic properties can be obtained by incorporating iodine substituents into their compositions.

Aim: The aim of this work is to develop a novel synthetic methodology which will allow us to synthesize new halogeno-substituted 5'-deoxy-5'-fluorocytidine derivatives – 5-fluorocytidine analogs with a potential anticancer activity.

Materials and Methods: The course of the reactions was monitored by TLC and HPLC analysis. The reaction products were analyzed by FTIR spectroscopy and HPLC.

Chromatography analysis was performed with a Thermo Scientific UltiMate 3000 Analytical LC System, equipped with a quaternary pump, an automatic injector, and a diode array detector. The FTIR spectra were recorded on a Bruker Tensor II FTIR spectrophotometer equipped with a MIRacle ATR-Attachment.

Results: The vibrational frequency assignments were performed by comparing the ATR-FTIR spectra of the so-obtained products with the spectrum of their precursor. The most noticeable changes in the registered spectra were successfully analyzed.

The applied pro- and de-protection synthetic steps were also studied in details. The scope of the coupling reaction with DCC reagent has been studied too.

Conclusion: The presented synthetic procedure is a convenient route to the direct synthesis of new 5'-deoxy-5'-fluorocytidine analogues. The products have been characterized by FTIR spectroscopy, and the progress of all reactions has been followed by LC techniques.

Keywords: *pharmaceutical synthesis, iodo-functionalized 5-DFCR analogues, FTIR analysis*

AEROSOL VACCINATION METHOD – APPLICATION AND THERAPEUTIC SIGNIFICANCE

Stanimira Zasheva¹, Presian Bonev¹, Viliana Gugleva², Velichka Andonova²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Pharmaceutical Technologies, Faculty of Pharmacy,
Medical University of Varna*

Introduction: Subcutaneous injection is the most common route of vaccination and despite the achieved effectiveness, its application, especially in developing countries, is facing some limitations – necessity of trained medical professionals, risk of reuse of disposable syringes and needles followed by potential transmission of bloodborne pathogens. Aerosol vaccination is an attractive alternative immunization approach. Since this application route closely resembles the natural entrance mechanism for many infections it can provide immunity at the portal of entry and enhanced defense. An aerosol vaccine can be applied via the nasal or respiratory route. The mucosal epithelium of the respiratory and gastrointestinal tracts, in addition, contributes towards the occurrence of a stronger immune response. The type of aerosol dosage forms, such as nasal sprays, nebulizers, metered-dose inhalers, and dry powder inhalers also influences the achieved therapeutic effect. The aerosol vaccination method could be successfully applied in case of diseases such as measles, influenza A and tuberculosis.

Materials and Methods: This study is based on our thorough research on various articles, preclinical, and clinical studies regarding the use of aerosol vaccination in comparison to the conventional subcutaneous route.

Results and Conclusion: Based on the obtained results from conducted preclinical and clinical studies, we can conclude that aerosol vaccination is a promising and practical approach that avoids associated with injection risks and can ensure control and potential eradication of life-threatening diseases in developing countries.

Keywords: *immunization, influenza, measles, nasal mucosa, respiratory tract, tuberculosis*

TOXIC AND MINERAL ELEMENTS IN SELECTED HERBS FROM VARNA REGION, BULGARIA

Angelika Georgieva, Stanislava K. Georgieva, Zlatina Peteva, Dilyana Dimova

Department of Chemistry, Faculty of Pharmacy, Medical University of Varna

Introduction: Medicinal plants contain important biologically active components, such as vitamins, minerals and phenolic compounds, and are used for therapeutic purposes as teas and nutritional supplements. Toxic elements in plants might originate from rainfall and atmospheric dust and subsequently could be absorbed through the leaves in herbs.

Aim: The aim of the study was to determine the concentrations of some elements (Cd, Pb, Cr, Fe, Zn, Mn, Cu, Al, and Ni) in medicinal plants: linden (*Tilia sp.*) and elder (*Sambucus nigra L.*).

Materials and Methods: The blossoms of the selected species were collected in the summer of 2018 from the natural environment in two different locations: Varna (urban) and the Fichoza (rural) region near Varna, Bulgaria. The concentrations of toxic and essential elements were determined by inductively coupled plasma optical emission spectrometer (ICP-OES).

Results: The results showed low concentrations of the toxic elements Cd, Pb in both studied medicinal plants. The values of Cd in elder were found to be from none detected (nd) to 0.01 mg/kg and Pb values were measured to be from 0.03 to 0.10 mg/kg. The concentrations of Cd in linden from the urban area (0.02 mg/kg) were measured higher than in that from the rural region (<LOQ). The same trends were established for Pb levels in linden (urban area – 0.15 mg/kg and 0.08 mg/kg - rural region). The determined values for the essential elements Zn and Cu in elder ranged from 1.91 to 7.92 mg/kg and from 1.87 to 5.93 mg/kg, respectively.

Conclusion: The levels of toxic elements Pb and Cd were found far below the permissible limit recommended by WHO for medicinal plants and do not pose any human health risk.

Keywords: *toxic elements, medicinal plants, ICP-OES*

DEVELOPMENT OF AN ANALYTICAL PROCEDURE FOR QUALITATIVE AND QUANTITATIVE DETERMINATION OF CAPECITABINE IN PLASMA

Stanila Stoeva¹, Iliyan Kolev², Ivan Iliev³, Petko Marinov¹

¹*Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy,
Medical University of Varna*

²*Department of Pharmaceutical chemistry, Faculty of Pharmacy,
Medical University of Varna*

³*Institute of Experimental Morphology and Anthropology with Museum,
Bulgarian Academy of Sciences*

Introduction: Capecitabine (CAP) is one of the latest fluoropyrimidine carbamate prodrug forms of 5-fluorouracil. Pharmacokinetic analyses in cancer patients show high interindividual variability in the exposure of both the drug and its metabolites. Thus, the focus of the present study is oriented to the development of an effective, simple, and ecofriendly procedure for sample preparation and subsequent HPLC-UV analysis of CAP in plasma.

Materials and Methods: In the chromatographic separation, Hypersil Gold aQ column was applied and gradient elution was conducted at a flow rate of 0.8 mL/min. A mobile phase consisting of water, methanol and 1% HCOOH was used.

Results: The proposed method was successfully utilized for the measurement of CAP in plasma. It meets the requirements of the *International Conference on Harmonisation Q2(R1) Validation of Analytical Procedures* guideline for precision, accuracy, and specificity. The average recovery for the analyte was $\geq 90\%$. The limit of quantitation of CAP in plasma was 0.1 $\mu\text{g/mL}$.

Conclusion: The presented procedure could be accepted as a convenient method for a qualitative and a quantitative analysis of CAP in plasma.

Keywords: HPLC, Capecitabine, plasma

MEDICINAL PLANTS USED AS A BEVERAGE COLORANT BY THE LOCAL POPULATION ALONG THE NORTHERN BLACK SEA COAST

Petya Boycheva, Jenny Cherneva, Dobri Ivanov

Department of Biology, Faculty of Pharmacy, Medical University of Varna

Introduction: Traditionally, Bulgarians use medicinal plants to color drinks. Most often colored homemade wines and spirits drinks.

Materials and Methods: The study was conducted using the face-to-face questionnaire method. Survey participants were randomly selected. They are of different age groups, ethnicity, gender, education and employment.

Results: A total of 709 locals from 32 settlements - 8 cities and 24 villages located along the North Black Sea coast participated in this study. Of the 709 people surveyed, 353 (49.78%) answered that they use medicinal plants to color drinks. From the study we found that the local population uses 35 species of medicinal plants belonging to 29 genera and 19 families to color drinks. This includes medicinal plants typical for the area, species from other floristic regions of Bulgaria, alien species and cultivated plants. The most commonly used staining plants are: *Morus sp.*, *Quercus sp.*, *Cotinus cogygria* Scop. Some more interesting and not traditional types of medicinal plants are also used, such as: *Mahonia aquifolium* (Pursh) Nutt., *Diospyros lotus* L., *Phytolacca americana* L.

Conclusion: The prevalent use of medicinal plants from the local flora confirms the fact that Northern Black Sea coast residents have retained the traditional knowledge of medicinal plant application. At the same time, the use of medicinal plants, alien to the Bulgarian flora, shows the impact of globalization and socio-cultural development, even with the use of herbal products today.

Keywords: *medicinal plants, coloring of beverages, Northern Black Sea coast*

REVIEW OF THE STRENGTHS OF NEW GENERIC MEDICINAL PRODUCT APPEARANCE AT THE MARKET

Jivko Kolev¹, Evgeni Grigorov², Galina Petrova², Todorka Kostadinova³

¹PhD Student, Faculty of Public Health, Medical University of Varna

²Department of Organization and Economics of Pharmacy Faculty of Pharmacy,
Medical University of Varna

³Faculty of Public Health, Medical University of Varna

Introduction: Over the last decade, the generic drug market in Europe has grown by 12-15% per year compared to 5-7% for the one of original medicines. Generic medicines have an important role to play in society as a whole, including not only patients, but also the health insurance system. They reduce costs and ensure rational sparing and use of drugs. This conclusion is based on savings made by the increased use of generic products and access to costly innovative medicines.

Aim: The aim of the study is to explore and analyze the benefits of market entry of generic medicinal products.

Materials and Methods: A retrospective analysis of 17 articles published in the period 2001-2016 was performed. All the selected research papers were related to the market penetration of generic medicines in different countries of the European Union. We searched the following databases: Google Scholar and PubMed for published articles on the topic, using combinations of the following keywords: „market entry“, „market penetration“, „generic medicinal products“, „generics“.

Results: Market shares of generic medicines in different EU countries are varied. The countries of Central and Eastern Europe have a tradition in local production of generic medicines. As a result, generic market shares have always been relatively high (> 50%). Economically developed countries in Western Europe have already recognized the need to take initiatives to promote the use of generic medicines.

Conclusion: On a European scale, generics make up 40% of all prescriptions and save over 35 billion euros each year. Generic drugs generate several major benefits for society: encouraging competition between generic and original drug manufacturers, lower prices (from 20 to 80%), opportunity for savings in the budget, and redirection of saved money to purchase expensive original medicines when needed.

Keywords: market entry, market penetration, generic medicinal products, generics, benefits

INNOVATIVE MEDICAL DEVICE CONCEPT AND DESIGN FOR IMPROVED PERCUTANEOUS PENETRATION OF MEDICINAL PRODUCTS

Oganes Vardanyan¹, Evgeni Grigorov²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Organization and economics of pharmacy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: With the creation and introduction of new technology, medicine and pharmacy have achieved significant progress in improving patients' lives. The development of ever more innovative, up-to-date and effective medical devices foreshadows an advance in maintenance, monitoring and treatment on the side of the patients themselves.

Aim: The primary aim of this paper is the creation of a design concept for an innovative medical device, which can help the percutaneous penetration of medicaments, as well as preparing a plan and marketing strategy for the product.

Materials and Methods: A documentary method - research of scientific literature and regulations on registration of medical devices, was used. The monitoring method was applied to the overall organization of the process of developing a concept for an innovative medical device. Analysis and synthesis methods were used to create a plan and marketing strategy for the developed product.

Results: The design of medical devices has a substantial importance to their safety and subsequently obtaining CE marking post-production. The created medical device allows for increased therapeutic effects of medication by providing better penetration and subsequent absorption of the medical substance.

Conclusions: Design has a large impact on the overall appearance and acceptance of the product by customers, and thus plays a major role in concept development. Good product placement and a thorough marketing strategy are vital to the project's realization upon completion. Another important aspect is also product merchandising.

Keywords: *design, medical device, innovation, penetration*

THE PATIENT INFORMATION LEAFLET AS PART OF THE RATIONAL USE OF DRUGS

Paola Petkova¹, Bogdan Kirilov², Evgeni Grigorov²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Organization and economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: Rational use of drugs is one of the major issues in the health system. It requires that patients receive medicines appropriate for their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. The patient information leaflet (PIL) is a major technical document included in every medicine package with the main purpose of informing patients about their medication regarding its administration, precautions and potential side effects.

Aim: The aim of this article is to analyze specific data presented in PIL of 5 main anatomical/pharmacological groups from 1st level of ATC classification and to determine which type of medical specialist is mentioned in it as a consultant responsible for the rational use of medicines or provider of advice and care if needed.

Materials and Methods: The study contains comparative analysis of extracted and summarized information from PIL of 1200 drugs from the ATC anatomical groups: A- Alimentary tract and metabolism, B- Blood and blood forming organs, C- Cardiovascular system, D- Dermatologicals, G- Genitourinary system and sex hormones, which are available on the Bulgarian market. The following criteria were included in our research - "consult if you need with...", dosage forms, duration of drug administration, pregnancy intake, influence on the ability to drive and use machines, reporting adverse reactions.

Results: In 15.9% of PILs there was no address or invocation for reporting adverse reactions. Almost 71.6% advised to consult with doctor or pharmacist for more information, 20.77 % to consult with a pharmacist and only 5.19% to consult with a doctor. A total of 78.15% of medicines had no restrictions on the duration of administration, and 58.80% of the drugs had multiple dosage variants.

Conclusion: All these results lead to the conclusion that pharmaceutical care is an integral part of rational drug use.

Keywords: *rational drug use, patient leaflet*

MODERN METHODS FOR THE IDENTIFICATION OF NARCOTIC SUBSTANCES WITH MEDICAL DEVICES

Ivan Uzunov¹, Valentina Belcheva², Evgeni Grigorov²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Organization and Economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: Narcotic substances as pharmacological substances act mainly on the central nervous system (CNS) and, when introduced into the body, cause sedation or euphoria. Drug testing can detect not only starting materials but also metabolites in the user. They can be identified in various biological fluids such as blood, urine, saliva, sweat and hair.

Aim: The purpose of the conducted research is to study the modern methods of identification of narcotic substances by means of medical devices, including to find out what tests the traffic police in Bulgaria use.

Materials and Methods: The research uses common scientific methods of observation, analysis and synthesis and expert evaluation. The monitoring method is used to determine the process of drug testing. Analysis and synthesis are applied to extract data and interpret information from study materials.

Results: The testing algorithm is determined by the testing authority and by the types of material. The Bulgarian police works with field tests for saliva DrugCheck 3000 and 5000, which can detect seven of the most commonly used types of drugs. The result is obtained within minutes with an accuracy of 99%.

Conclusion: The conducted research on the advancement of technology, as well as the lessons learned from the historical development of drug testing methods, shows that there will continue to be a large range of data and development bases in the field, which in turn will lead to more accurate and reliable results.

Keywords: *narcotic substances, types of testing, control bodies, medical devices*

STUDY OF THE STANDARD TERMS LIST USE AND ROLE IN EUROPEAN PHARMACOPEIA

Rostislav Atanasov¹, Tsvetelina Stefanova¹, Bogdan Kirilov², Evgeni Grigorov²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Organization and Economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: The list of Standard Terms is part of the European Pharmacopeia and is drawn up by the Standard Term Working Party, which is part of European Pharmacopeia Commission for use in marketing authorisation applications, labeling, and patient information leaflet and electronic communications. In Bulgaria the original list is translated for the needs of the Bulgarian Pharmacopeia by the Experts' Standard Terms Group.

Aim: The main purpose of our study is to conduct a detailed analysis of the standard terms that are approved for use in the Bulgarian Pharmacopeia and to find the most common routes and methods of administration of the different pharmaceutical dosage forms.

Materials and Methods: The study features critical analysis of the list of standard terms used in Bulgaria and Standard Term database provided by the European Directorate for the Quality of Medicines & Health-Care, which is available online and comparison between them is made. We also performed a comparative sorting of the standard terms in different categories by several criteria.

Results: The results of the study showed that in the original list of standard terms made by European Pharmacopeia Commission there are terms that are not yet translated into Bulgarian. Out of all 457 terms for pharmaceutical dosage form included in the Bulgarian list of standard terms 32 % or 92 of them are meant for oral use, 11% are related to application to the skin. Other methods of administration with significant percentage are ocular, nasal, rectal and vaginal use each with between 6% and 8%. Only 7% of all dosage forms have no applicable route of administration.

Conclusion: As a conclusion, we can say that the most common route of administration is oral, also the percentage of pharmaceutical dosage forms with no applicable route of administration is pretty low in comparison to the other dose forms.

Keywords: *standard terms, route of administration, European Pharmacopeia, Bulgarian Pharmacopeia*

PROSTATE CARCINOMA - NEW PHARMACOTHERAPY OPPORTUNITIES

Desislava Boyanova¹, Stamen Bankovsky², Evgeni Grigorov^{2,3}

¹Student, Faculty of Pharmacy, Medical University of Varna

²National Center for Public Health and Analysis, Sofia

³Department of Organization and Economics of Pharmacy, Faculty of Pharmacy, Medical University of Varna

Introduction: Prostate cancer is the most common solid tumor in men worldwide, affecting 1,112,000 people in 2012. Its incidence is rising due to an aging population and a higher frequency of screening for it. Castration-resistant prostate cancer (CRPC) is an advanced, incurable form of prostate cancer, not amenable to surgical or drug castration. The severity of the disease for the patient is exacerbated by the presence of bone metastases that occur in 80-90% of patients with CRPC. Bone metastases slowly alter their structure and are associated with an increased risk of symptomatic skeletal events (SSEs). The development of bone metastases and subsequent SSEs significantly reduce survival and quality of life.

Aim: The purpose of this study is to provide a documentary analysis of new pharmacotherapeutic options for the treatment of prostate cancer.

Materials and Methods: The research was done through a review of published research articles based on search for predefined keywords.

Results: The published data indicate that alpha-emitting drugs ("alpha pharmacists") have a potent targeted antitumor effect on bone metastases with the potential to provide both a survival benefit and a very well tolerated safety profile, including limiting the chronic radiation exposure of the patient. Radium-223 can be administered on an outpatient basis in less than 5 minutes, with minimal screening and restrictions on the patient's contact with others.

Conclusion: The data on the therapeutic efficacy of radium-223 included in the model were obtained from a clinical trial and a meta-analysis including clinical trials with alternatives. The cited clinical studies have broad internal and external validity, which allows their inclusion in the adaptation of the model to the local environment.

Keywords: prostate cancer, pharmacotherapy, radium-223

NONSPECIALISTS' METHODS OF CHOICE FOR AT-HOME PREPARATION OF SEMI-PREPARED MEDICINAL ORAL SUSPENSIONS AND SOLUTIONS

Dessislava Valcheva¹, Elen Aleksova¹, Viktor Tenev², Anton Valev¹, Barash Murad³

¹*Bulgarian Scientific Pharmaceutical Laboratory to Erudita Pharmacy of Pediatrics, Sofia*

²*Student, Faculty of Pharmacy, Medical University of Sofia*

³*Student, Faculty of Veterinary Medicine, Trakia University, Stara Zagora*

Introduction: The Semi-Prepared Medicinal Oral Suspensions and Solutions (SPMOSS) are medicinal forms of choice intended for the pediatric population, as the ready-prepared ones lack either expiry period or need to be kept refrigerated. SPMOSS consist of two components: (A) a powder mixture of API and excipients, and (B) water as a dispersion medium, which should be added just before use. There is no unified method for at-home preparation of SPMOSS, a fact that often causes burden to the caring parents.

Materials and Methods: Based on the availability of SPMOSS on the Bulgarian market, the most frequent methods of water measurement have been put as possible answers into a questionnaire. Subject to questioning were parents of patients of age between 3 months and 5 years. Our survey examined the parents' preferences for a water measuring method: a) with a measuring syringe; b) with a measuring cup; c) with a measuring mark on the bottle; d) only as information in the patient's leaflet, and d) other.

Results: The results of our survey showed that the respondents classified the measuring syringe as the best choice (most easy to work with, assume it to be the most hygienic and most accurate in measuring) and the measuring mark on the bottle was their second choice (the less frustrating method).

Conclusion: In conclusion, we advise that clearer, more available and unified methods for at-home preparation of SPMOSS should be developed in order to decrease the amount of measuring mistakes.

Keywords: *oral suspensions and solutions, water volume measuring, at-home drug preparation*

NEW SURVEILLANCES ON IVERMECTIN'S EFFICIENCY

Barash Murad¹, Debora Sabotinova², Kaloyan Mihalev², Presian Bonev²,
Anton Valev³

¹*Student, Faculty of Veterinary Medicine, Trakia University, Stara Zagora*

²*Student, Faculty of Pharmacy, Medical University of Varna*

³*Bulgarian Scientific Pharmaceutical Laboratory, Sofia*

Ivermectin is an antiparasitic drug, a derivate of avermectins, product of fermentation of an actinomycete, *Streptomyces avermitilis*. It acts as interrupting neurotransmission agent in invertebrates.

It exhibits unprecedented systemic anti-helminthic, anti-arachnidic and anti-insectic effects, but not against flatworms, protozoa, bacteria or fungi. It is labelled as the first endectocide. Ivermectin is effective at fairly low doses. It may be used orally, topically and parenterally and leads to no problems of cross-resistance with existing compounds.

Ivermectin is active against *Ascaris lumbricoides*, *Trichuris trichuria* and *Enterobius* spp. and *Strongyloides stercoralis*. The common treatment uses thiabendazole, which has undesired side effects, while ivermectin provides better and safer treatment in low doses. It has potent activity against cutaneous larva migrans, for which treatment is not available, and has the potential to become the drug of choice for ectoparasitic infestations (mites and lice) in humans. Scabies treatment is extremely difficult, but oral ivermectin is combating the condition, including severe *Sarcoptes scabiei* infestation that has no response to conventional treatment. Yet ivermectin is a drug that many people will never have heard of.

Drug combinations with ivermectin/albendazole are thoroughly effective and are now recommended for use in the GAELF programmes, which have a disease elimination target date of 2020.

Studies managed in children and infants have shown good tolerance of ivermectin. However, its use in infants who weigh less than 15 kg is a problem because of the absence of marketing authorization for this age group.

The aim of our research is to inform the Bulgarian audience about the advantages of ivermectin and its availability in the country since May 2019. The Bulgarian Scientific Pharmaceutical Laboratory has launched ivermectin as prescription-only magistral preparations for both oral and topical use in human and animal populations.

Keywords: ivermectin, drug, treatment, parasites, humans, children

ANTINOCICEPTIVE ACTIVITY OF *VANDA TESSELLATA* ROXB

Velislav Kotevski¹, Maria Kaykueva¹, Krassimira Zaykova², Djeni Cherneva³

¹Student, Faculty of Pharmacy, Medical University of Varna

²Student, Faculty of Medicine, Medical University of Varna

³Department of Biology, Faculty of Pharmacy, Medical University of Varna

Introduction: *Vanda tessellata* Roxb. (Orchidaceae) is an epiphytic orchid which is found in many parts of India, Sri Lanka and Burma. The leaf juice is used in the indigenous medicine for the treatment of certain inflammatory conditions. The roots are also used for treating rheumatism and neurotic conditions. The orchid is of interest to the scientists from the International Islamic University in Chitagong, who are motivated by the lack of modern pharmaceutical researches about the medicinal properties of *Vanda tessellata* Roxb. They started to test the biochemical properties and the antinociceptive activities on experimental animals.

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

Results: For the purposes of their study, the researchers tested in white mice using the acute oral toxicity test and the acetic acid-induced writhing test with aqueous and methanol extracts from *Vanda tessellata* Roxb. The achieved results showed that the aqueous and methanol leaves extracts from the orchid have significant and dose-dependent analgetic properties with low cytotoxicity.

Conclusion: The results are showing the need of more studies on *Vanda tessellata* Roxb. in order for it to be included in pharmaceutical products used as analgetics.

Keywords: *Vanda tessellata* Roxb., Orchidaceae, antinociceptive activity

THE DUALISM OF RADIOPHARMACEUTICALS IN THEIR REGULATORY FRAMEWORK IN BULGARIA

Tsvetelina Stefanova¹, Evgeni Grigorov^{2,3}

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Organization and economics of pharmacy, Faculty of Pharmacy,
Medical University of Varna*

³*National Center of Public Health and Analyses, Sofia*

Introduction: Radiopharmaceuticals (RPs) are part of a specific health technology that has an important role in the innovative therapeutic approach and imaging in recent years. They are a specific group of medicinal products that differ in many aspects from conventional medicines. The most significant difference between them and the rest is related to the properties of the radionuclide.

Aim: The aim of this study is to provide a documentary analysis of the regulatory framework for registration and applicable law in Bulgaria, which regulates the activities of radiopharmaceuticals.

Materials and Methods: The methods of analysis and synthesis have been applied for data extraction and interpretation of normative documents, regulating the manner, order and organization of work with radioactive sources and radiopharmaceuticals. The peer review method was used to summarize the key factors associated with the preparation of RPs as part of pharmaceutical work.

Results: RPs are a specific group of pharmaceuticals that are, in regulatory terms, regarded as medicinal products and as sources of ionizing radiation. They often require hospital preparation prior to administration to the patient. The production and use of RP is subject to regulation and licensing, both as a medicinal product and as a radioactive source.

Conclusion: Radiopharmaceutical medicinal products are specific medicines for therapy or diagnosis. The regulation regarding them in Bulgaria is very specific. This specificity stems from the dual nature of these medicines and places them under the regulatory scrutiny of different institutions - EMA and BDA on the one hand, IAEA and NRA - on the other hand.

Keywords: radiopharmaceuticals, regulation, drugs, sources of ionizing radiation

UNIVERSAL WINE MODELING USING APPLIED PHOTONICS METHODS

Stefka Minkova¹, Krastena Nikolova¹, Tinko Eftimov²

¹*Department of Physics and Biophysics, Faculty of Pharmacy, Medical University of Varna*

²*Université du Québec en Outaouais, Gatineau, Québec, Canada*

Introduction: Fluorescence spectroscopy is a powerful method for studying complex food systems to obtain models according to their chemical composition.

Aim: The aim of the study is to find correlation dependencies between optical parameters of Bulgarian wines, certain methods of applied photonics and parameters that determine the quality and composition of red wine. These links can serve to develop sensor systems for rapid analysis in wineries.

Materials and Methods: For obtaining the connections between the biochemical wine components and quality parameters for wine producers are UV and VIS spectroscopy, fluorescence spectroscopy and colorimetry.

Results: A quality relationship has been determined between fluorophores (such as flavanols, phenolic acids and anthocyanins) and the intensity of fluorescence peak. The excitation-emission matrixes can be used as a non-targeted approach to image interpretation. They are the base of interpretation of fluorescence spectra as fingerprints according to the region of production or the kind of grapes.

Conclusion: A wine is a complex biological system, which can be interpreted by applied photonics by using a photo album of an excitation-emission matrix for a given kind of grapes. Fluorophore contents show separation of wines of diverse origin or elaboration methods. Working progress will be towards making a universal wine model useful for the characterization of wines of any type.

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

Acknowledgements: *Special thanks for the financial support of the National Program “Young Scientists and Postdoctoral Fellows”*

INSTRUMENTAL METHODS FOR THE ANALYSIS OF THE HYDRAZONE DERIVATIVE OF BEXAROTENE

Boryana Mihaylova¹, Svetlana Georgieva², Nadya Agova², Alexander Zlatkov³

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna*

³*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University – Sofia*

Introduction: Bexarotene belongs to the group of retinoids. It is used as an antineoplastic drug in the fight against some cancers. In our study, we use the following instrumental methods of analysis: infrared spectroscopy (IR) and ¹H-NMR, to characterize the structural differences between the parent compound and a newly synthesized hydrazine derivative with potential biological activity. Infrared spectroscopy is a major pharmacopoeial method for the qualitative determination of compounds. Over time, it has established itself as a fast and reliable analytical method. This method covers the long-wavelength region of the spectrum. According to the infrared absorption spectra, the construction of a number of substances with relatively small molecules can be determined. With ¹H-NMR, resonant bands are observed, each corresponding to a specific proton absorption of the individual functional groups. The area under the signals is proportional to the number of protons that give the corresponding signal. It is automatically calculated mathematically by the software of the apparatus.

Aim: The aim of this article is to present a structural characterization of the compound obtained by us - bexarotene hydrazone.

Materials and Methods: In order to demonstrate the structure of the newly prepared compounds, a comparative ATR-FTIR analysis was performed in the range 4000-500 cm⁻¹. ¹H-NMR was applied as well as appropriate software to process the data obtained. Bexarotene and 3-chlorophenyl-methylidene-4 - [(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl) ethenyl] benzohydrazide were used as substances.

Results: As a result of the analyses, the structural similarity of the compounds, the result of their overall structural skeleton, and the structural differences that occurred upon introduction of the hydrazone component into the newly obtained compound were confirmed.

Conclusion: Bexarotene and newly synthesized bexarotene hydrazone were successfully analyzed and structurally characterized.

Keywords: bexarotene, analytical method, ¹H-NMR, infrared spectroscopy

ENTENAR PLUS: STEP-BY-STEP DEVELOPMENT OF A FOOD SUPPLEMENT FROM SCIENTIFIC LAB TO PATIENTS

Yoana Sotirova¹, Mirena Dobрева², Velichka Andonova², Stella Schekerdjiiska³,
Nikolay Georgiev³, Rahamin Schekerdjiski⁴

¹*Student, Faculty of Pharmacy Medical University of Varna,*

²*Department of Pharmaceutical Technologies, Faculty of Pharmacy,
Medical University of Varna*

³*Natstim LTD*

⁴*Faculty of Pharmacy, Medical University of Sofia*

Introduction: The aim of this study is to develop a science-based food supplement with original formulation to improve various symptoms of gastrointestinal disorders. A multidiscipline team of scientists and students took part in every step of the production and distribution of the final product across the local pharmacies.

Materials and Methods: Based on previous researches, establishing their beneficial effect on physiological function of gastrointestinal tract, four plant extracts were selected in optimal ratio and concentration: dry peel extract from pomegranate (*Punica granatum*), dry root extract from ginger (*Zingiber officinale*), dry fruit extract from coriander (*Coriandrum sativum*) and dry seed extract from fennel (*Foeniculum vulgare*). Oral tablets, containing the above plant extracts, have been prepared and dosed in appropriate manner as food supplement.

Results: In cooperation with Natstim LTD, an established pharmaceutical manufacturer, a food supplement, containing plant extracts, rich in various biologically active substances, was developed. Entenar Plus has positive influence on the gastrointestinal mucosa, decreasing the discomfort and reducing meteorism. It can be used to relieve symptoms of acute and chronic diarrhea. After successful registration of the product, the food supplement has been distributed in local pharmacies, including Medical University of Varna's pharmacies – Medunipharm.

Conclusion: Entenar Plus showed promising results and good patient tolerability. To estimate its effectiveness, a clinical research will be conducted in the Medical University of Varna's Clinic of Gastroenterology.

Keywords: *food supplement, formulation, gastro-intestinal disorder, plant extracts*

STRATEGIES FOR COPING WITH OCCUPATIONAL BURNOUT AMONG PHARMACISTS

Mariya Ivanova¹, Anna Todorova², Ivo Kumanov²

¹Pharmacy "MEDUNIPHARM" 2, Medical University of Varna

²Department of Organization and Economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna

Introduction: The term burnout was first seen in physical theory and practice in the 1980s. It describes severe emotional, psychological and physical exhaustion, directly connected to the professional sphere. That exhaustion is observed in healthy individuals, mostly professionals in the social care industry. It is established that everyday contact between pharmacists and clients leads to occupational burnout.

Aim: The aim of this research is to develop recommendations for coping with the burnout experienced by pharmacists.

Materials and Methods: A literary review has been done using different databases such as PubMed, Scopus, Medline, etc. and searching with previously set keywords: burnout, medical specialists, pharmacists, prevention.

Results and Conclusion: Recommendations have been developed for coping with the individual as well as the organizational burnout syndrome.

The method for prevention is individual. It involves switching between working and resting intervals, performing enjoyable activities outside of work and support from families and friends. Lack of organization in the work place, conflicts with colleagues and poor leadership skill of the leading team can also be causes of a burnout. The recruitment of the right people, needed for the specific volume of work and stimulating and motivating the team is also crucial for preventing the burnout syndrome.

Keywords: burnout, medical specialists, pharmacists, prevention

DETERMINATION OF METRONIDAZOLE IN TABLET DOSAGE FORMS

Viktoria Yankova¹, Sezgin Alkov¹, Sylvia Stamova², Svetlana Georgieva²,
Maya Georgieva³

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna*

³*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University –Sofia*

Introduction: Metronidazole is a broad spectrum antibiotic targeting Gram-positive, Gram-negative bacteria and anaerobic protozoa.

Aim: The aim of the present study is to introduce various analytical methods in regard to quality and quantity determination of metronidazole tablet dosage forms.

Materials and Methods: The methods that were used in these experiments were pharmacopean – quality reaction with Zn and hydrochloric acid, and nonpharmacopean experimentally proven methods. The latter consist of solutions with different concentrations of metronidazole tablets that were prepared and qualitatively and quantitatively determined by various methods. The experiments included thin-layer chromatography with the following mobile phase: toluen: chloroform: methanol (2:7:0,6); UV-VIS spectrophotometric determination; titrimetric estimation by perchloric acid with indicator crystal violet for determination of metronidazole.

Results: The pharmacopean quality reaction was proven positive for primary aromatic amines.

The samples from the thin-layer chromatography were observed under a UV lamp and it was determined that both samples and standard have the same R_f value (R_f=0.23)

The UV-Vis spectrophotometric analysis was conducted with 340 nm wavelength and the concentrations for both samples were calculated as follows – sample 1 – 64.68 mg and sample 2 – 63.12 mg.

The results from the titrimetric experiment were as follows – sample 1 – 6.5 mL (1 mL HClO₄ equals 17.2 mg C₆H₉N₃O₃)=111.28 mg metronidazole. Sample 2 – 7.1 mL (1 mL HClO₄ equals to 17.2 mg C₆H₉N₃O₃)=121.55 mg metronidazole.

Conclusion: The presented analytical methods are suitable for quality and quantity determination of metronidazole tablet dosage forms and will be relevantly used for analysis of novel synthesized nitroimidazole derivatives.

Keywords: *quality, quantity, determination, metronidazole*

THE CHALLENGE IN COUNSELING PATIENTS WITH OSTEOARTHRITIS

Antonia Andonova¹, Ivo Kumanov², Iskra Mircheva³

¹Student, Faculty of Pharmacy, Medical University of Plovdiv

*²Department of Organization and Economic of Pharmacy, Faculty of Pharmacy,
Medical University of Varna*

*³Department of Social Medicine and Health Care Organization, Faculty of Public Health,
Medical University of Varna*

Introduction: Pharmaceutical care is the process by which the pharmacist collaborates with the patient and other healthcare professionals during the design, implementation, and monitoring of the therapeutic plan, which should lead to specific therapeutic outcomes for the particular patient. They can be used when it comes to patients with osteoarthritis. This is the most common form of arthrosis that occurs due to the natural aging of the body and wear of the joints. The clinically expressed disease is a definitive picture, secondary to the effects of numerous predisposing factors, but mainly to age, joint injury, impaired biomechanics and obesity.

Aim: The purpose of this study is to investigate the role of the Master of Pharmacy in improving the individual quality of life of chronically ill patients with osteoarthritis through the use of pharmaceutical care.

Materials and Methods: A total of 214 patients, 122 women and 92 men, aged between 54 and 72 years from Varna, are the subject of this study. They have already been diagnosed with chronic inflammatory or degenerative diseases of one or both knee, hip or shoulder joints.

Results and Conclusion: The use of pharmaceutical care through an individualized approach contributes to improving the individual quality of life of patients with degenerative and inflammatory joint diseases. The developed algorithm for consultation and prevention in patients with osteoarthritis can be successfully applied in the Bulgarian outpatient and hospital practice.

Keywords: *chronic inflammatory and degenerative diseases, chronic pain, joint pain, Master of Pharmacy, pharmaceutical care, quality of life*

ALTERNATIVES TO OPIOIDS FOR CHRONIC PAIN MANAGEMENT

Gabriela Tomova¹, Margarita Mihaylova¹, Iliana Lazarova¹, Mehmed Reyžov²

¹*Student, Faculty of Medicine, Medical University of Varna*

²*Department of Pharmacology and Clinical Pharmacology and Therapy,
Faculty of Medicine, Medical University of Varna*

Introduction: The rise in opioid abuse, leading to overdoses has increased the need of alternative ways for pain management, particularly medication that does not cause addiction and is abused less often. This would save many lives and make treating patients with chronic pain easier.

Aim: The goal of this scientific report is to present alternatives to opioid treatment.

Materials and Methods: There is no scientific consensus on how exactly chronic pain works, which has slowed down the development of pain management drugs. Alternative non-addictive painkillers are still being developed, such as tanezumab and BU08028. Tanezumab is a monoclonal anti-nerve growth factor antibody that prevents pain signals from reaching the spinal cord and brain. It is used to treat joint pain in patients with severe osteoarthritis and inadequate response to standard analgesics. BU08028 is a derivative of buprenorphine. It is a pan-opioid receptor agonist with partial agonist activity at the μ , δ and NOP receptors. Increasing the affinity for the NOP receptor reduces the addictive effects associated with buprenorphine.

Results: Among patients with chronic pain from osteoarthritis, tanezumab resulted in statistically significant improvements in subjective pain levels. BU08028 is a research compound that provides the pain relief of opiates, without being addictive. Mouse models prove that it effectively treats acute pain without creating dependence.

Conclusion: Pain management is a major clinical problem around the world. Researchers are working on figuring out the exact mechanisms of pain in order to create the best alternatives to opioids. The results so far are promising.

Keywords: opioids, overdose, alternatives, pain management, tanezumab, BU08028

FUNGOTHERAPY – THE LINK BETWEEN ALLOPATHIC AND HERBAL MEDICINE

Kalina Tzaneva¹, Elis Nasuf¹, Djeni Cherneva²

¹*Student, Faculty of Pharmacy, Medical University of Varna*

²*Department of Biology, Faculty of Pharmacy, Medical University of Varna*

Introduction: Fungotherapy is the science of treatment by mushrooms. The concept of this science came to existence and its name was officially introduced about 2,000 years ago. Medicinal mushrooms treat not the symptoms, but the causes of the illness. In contrast to allopathic medicine, the major aim of the fungotherapy is the overall recovery of the body by harmonizing its internal environment.

Aim: The aim of this article is to study the available in the literature information on clinical and pharmacological studies, which were conducted in the last decades, on the medicinal properties of mushrooms and their use in the medical practice.

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

Results: The studies conducted so far show that inside the medicinal mushrooms there is a complex of various BAS, among which are the most famous polysaccharides with antitumor activity - lentinan, gripholane, ganoderan and many others. Medicinal mushrooms have also antimicrobial, antiviral, antioxidant activity and have a protective effect on many of the organs and systems in the human body. In vitro and in vivo studies have been conducted in humans and animals to show that the immunomodulatory properties of medicinal mushrooms rank second after the antitumor ones.

Conclusion: The main idea of fungotherapy is not to act “against”, but “along with” the already known methods of the official medicine. In serious illness, the key to curing the patient lies between allopathic and natural medicine. Due to the increasing interest, the broad spectrum of actions and the lack of side effects, fungotherapy is developing at a rapid pace and can surely take a place in the integrative approach of medicine of the future.

Keywords: *fungotherapy, medicinal mushrooms, natural medicine, herbal medicine*

CHLORAMPHENICOL – IS IT WORTH IT NOT TO USE IT?

Ersin Ismail¹, Milena Georgieva¹, Veronika Gadzhovska², Diana Radkova²

¹*Faculty of Medicine, Medical University of Varna, Bulgaria*

²*Department of Infectious Diseases, Parasitology and Dermatovenereology,
Faculty of Medicine, Medical University of Varna, Bulgaria*

Introduction: Chloramphenicol is a synthetic bacteriostatic with a broad spectrum of activity against many Gram-positive and Gram-negative bacteria, anaerobes, rickettsiae, chlamydiae, and mycoplasmas. It is generally bacteriostatic but may be bactericidal, especially at higher concentrations. Since 1948, it has been used to treat severe infections in children and adults. However, its use is very restricted in developed countries due to numerous reports of severe adverse reactions such as agranulocytosis, aplastic anemia, leukemia, toxic hepatitis and gray baby syndrome.

Materials and Methods: A number of articles and scientific reports on the occurrence of severe and potentially fatal adverse reactions from the use of systemic and topical chloramphenicol have been reviewed. The frequency and severity of the reactions were compared based on the age, mode and duration of administration.

Results: The incidence of serious adverse reactions to chloramphenicol ranges from 1:1,000,000 in adults to 1:2400 in premature infants. However, in the developed world, this antibiotic is generally reserved for serious infections with limited alternative antimicrobial choices due to its well-known toxicities. Whilst, in the developing countries, it is still commonly used because it may be the only broad-spectrum agent available. Nowadays indications include bacterial conjunctivitis, severe typhoid fever, rickettsioses and serious infections caused by *H. influenzae*. Likewise, the Bulgarian Drug Agency approves 6 dosing forms – 250 mg tablets for systemic use, ear drops and 4 eye ointments.

Conclusion: Current drug monitoring capabilities, as well as rapidly evolving antibiotic polyresistance, are an opportunity to broaden chloramphenicol indications and reassess its undeniable benefits.

Keywords: *chloramphenicol, agranulocytosis, aplastic anemia, gray baby syndrome, antibiotic polyresistance*

ANTIBIOTIC RESISTANCE. MODERN PROBLEMS

Ivanina Dzhermova¹, Sevgi Yusein¹, Antoaneta Tsvetkova², Silvia Mihaylova²

¹Student, TRS Assistant Pharmacist, Medical College, Medical University of Varna

²TRS Assistant Pharmacist, Medical College, Medical University of Varna

Introduction: Antibiotics are products of the metabolism of various fungi and bacteria, or semisynthetic analogues of these products that act bacteriostatic or bactericidal. The widespread use of this class of drugs has led to the emergence of antibiotic-resistant pathogens. Antimicrobial resistance (AMR) severely limits the opportunities for managing infectious diseases and is a major problem for global health. New resistance mechanisms, which compromise the treatment of common infectious diseases, are being observed. A growing number of infections such as pneumonia, tuberculosis, gonorrhoea and salmonellosis become difficult to treat, as those mechanisms reduce the effectiveness of the antibiotics used.

Aim: The aim of this article is to raise awareness of the impact of the human factor as a reason for increasing antibiotic resistance, and to explore the possibilities of reducing the costs of treatment and overcoming this threat.

Materials and Methods: We have conducted a literature review and analysis of information from various electronic databases: Medinfo, antibiotic.ecdc.europa.eu, WHO (World Health Organization), Pubmed, Ministry of Health, ReAct and others.

Results: 1. The human factor as the reason for the growth of AMP:

- Improper use of antimicrobials in human and veterinary medicine;
- Poor hygiene conditions and practices in healthcare facilities, enabling the transfer of resistant microorganisms.

2. Antibiotic resistance extends hospital downtime and leads to higher medical costs and increased mortality. In the EU it is estimated that antimicrobial resistance will cost 1.5 billion per year in healthcare expenditure.

Conclusion: The discovery of new antimicrobial preparations against *Klebsiella pneumoniae*, and other pathogens developing resistance, is one of the greatest challenges in the fight against antibiotic resistance and protection of global health.

Keywords: antibiotics, antibiotic resistance, microorganisms

BIOCOMPATIBILITY AND CYTOTOXICITY OF SILICA-BASED BONE SUBSTITUTE MATERIALS

Tanya Dimova¹, Margarita Apostolova²

¹*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna, Bulgaria*

²*Institute of Molecular Biology, Bulgarian Academy of Sciences*

Aim: The aim of the study is to evaluate the biocompatibility and cytotoxicity of bioactive glasses (BGs) using the osteosarcoma cell line MG63. In this study, BG was used in the system 70SiO₂-25CaO-5P₂O₅ (BG0) with and without Ag₂O for bone tissue regeneration. BGs have been created as fillers for the treatment of bone defects in dental practice.

Materials and Methods: BGs in the SiO₂-CaO-P₂O₅ and SiO₂-CaO-P₂O₅-xAg₂O system (x=1.2 and 4wt%) were synthesized from TEOS, CaO, H₃PO₄, AgNO₃. Cell viability was measured by means of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Absorption was measured at 590 and 630 nm reference to ELISA-Reader. The statistical analysis of the results was carried out with an ANOVA test and Bonferoni procedure (p<0.05). The morphological alterations of the MG63 were observed directly by a phase contrast microscope.

Results: The synthesized silicate-based materials contain carbonate bound hydroxyapatite type B, silver and wollastonite (BG3). The relatively high content of 4 wt% Ag₂O incorporated in BG3 has an important effect in the improvement of the proteins for this type of material. The results of this study indicate that BG0 has no toxic effects, whereas BG1, BG2 and BG3 cause minimal toxic effects. BGs stimulate MG63 cells to differentiate into osteogenic media.

Conclusion: BG0 and BG containing silver have toxic effects on the cell line MG63. They cannot be used as biocompatible materials at concentrations higher than 1µg/cm². BGs containing up to 1 µg/cm² of Ag₂O stimulate cellular mineralization and osteogenic differentiation of MG63 cells.

Keywords: *bioactive glasses, bone substitute materials, MG63*

SIMPLIFIED SAMPLE PREPARATION OF NITROFURANTOIN ORAL SUSPENSION FOR HPLC ANALYSIS

Nikolay Adamov¹, Stefan Avramov², Svetlin Ivanov¹, Teodor Boyanov³,
Anton Valev³

¹*Student, Faculty of Chemistry and Pharmacy, Sofia University
"St. Kliment Ohridski", Bulgaria,*

²*Chromassist Ltd., Sofia, Bulgaria*

³*Bulgarian Scientific Pharmaceutical Laboratory to Erudita Pharmacy of Pediatrics,
Sofia, Bulgaria*

The extemporaneous compounding represents an individual preparation of a therapeutic product for patients in response to their specific needs. The preparation of this kind of product is frequently used, especially for children under 10 years of age, affected by the drug dose.

Nitrofurantoin is a drug substance from the pharmacological group of nitrofurans, which have a good antibacterial effect over infections of the urinary tract.

A specific therapeutic product for children under 10 years of age (nitrofurantoin oral suspension 10 mg/mL) has been successfully extemporaneously compounded in the Bulgarian Scientific Pharmaceutical Laboratory. Without any primary treatment, a macrocrystalline nitrofurantoin was introduced in the suspension. Aside from the main substance, various excipients including suspending agent, preservatives, flavoring agents, sweeteners, etc. were present in the suspension. Therefore, in order to control the assay of nitrofurantoin in the oral suspension we developed and validated new simplified and fast HPLC method.

The stability of the oral suspension nitrofurantoin 10 mg/mL was tested as well. The extemporaneous product showed only 3.7% deviation from the initial concentration (acceptance level <5%) after storage for 60 days at room temperature (22 °C). At elevated temperatures (50 °C for 48 h) only $\pm 0.5\%$ deviation was detected. The influence of pH on the oral suspension concentration after 60 days was also studied. The results revealed 4.4%, 6.99%, and 19.58% deviation from the initial concentration at pH 4, 7 and 10, respectively. The performed stress test allowed the formation of dynamic hydrogen bonding upon addition of o-phosphoric acid leading to initial decrease of the product concentration. However, after 40 days the o-phosphoric acid was released from the nitrofurantoin molecules due to weak hydrogen bonds, allowing the suspension to reach its initial concentration.

Keywords: nitrofurantoin, oral suspensions, stability test, pH stability

STRESS AT WORK AND THE RELATION WITH PUBLIC HEALTH

Emanuil Manasiev¹, Evgeni Grigorov²

¹*Student, Department of Health Technology Assessment, NCPHA, Sofia*

²*Department of Organization and Economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: Reviewing public health, as an aggregate of the health of each individual, we consider that the processes of enhancing the health level of each person, increase the public health level as a whole. Examining these processes and their implementation and management requires positioning them on a scientific foundation.

Materials and Methods: The research uses both primary and secondary data. The primary data are collected by using personal observation. Secondary data are collected from scientific articles, books, magazines and interviews from employees. Tools and techniques involve various data science techniques and statistical tools. All of them are applied to identify the employee satisfaction from the quality of the work and how the stress corresponds to their general feelings and work life balance.

Results: Employees shared that working tasks and employer policies are related to working stress. It included unrealistic deadlines, lack of support, unfair performance appraisal, lack of transparency and poor communication. The interventions were considered as effective if they enhanced management styles, and included physical exercise, breaks and ensuring fair time for planning the work flow.

Conclusions: It could be considered that satisfied employees are more productive at work, which makes them more adaptive to stress.

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

TOXICOLOGIC OVERVIEW OF GARDEN PLANTS

Stanislava A. Georgieva, Petko Marinov

*Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy,
Medical University of Varna*

Introduction: Virginia creepers (*Parthenocissus quinquefolia*, f. *Vitaceae*), wisterias (*Wisteria spp.*, f. *Fabaceae*), azaleas (*Azalea spp.*, f. *Ericaceae*) and rhododendrons (*Rhododendron spp.*, f. *Ericaceae*) are pleasant plants that can be found in gardens and parks around us. Are we aware of the dangers that they represent for human health?

Materials and Methods: Literature overview of toxic contents in the aforementioned species of plants was conducted.

Results: Rhododendrons and azalias are representatives of *Rhododendrons*, *Ericaceae* family. They are amongst the most widely spread garden plants. The dangers which they are hiding however are: abundance of grayanotoxins with effects on the central nervous system, as well as the gastrointestinal and cardiovascular system. The Virginia creeper is a creeping plant with long lifespan. There are observations of raphide crystals of calcium oxalate in its leaves and fruits, which cause skin irritations, gastrointestinal and neurological disturbances. Wisterias include a family of climbing plants. All parts of the plant contain a type of saponin called glycin, which is toxic when ingested and can cause dizziness, confusion, speech problems, nausea, sickness, stomach ache, diarrhea and collapse.

Conclusion: The most widely spread garden plants represent a potential health risk. Caution must be exercised especially to protect children from ingesting various parts of the plants.

Keywords: *toxic plants, Virginia creeper, wisteria, azaleas, rhododendrons*

BENEFITS AND APPLICATIONS OF CBD OIL

Maria Koleva

MEDUNIPHARM 2, Medical University of Varna

Introduction: Cannabidiol (CBD) is popular natural product which is used for a lot of diseases. CBD is not a psychoactive substance, so it is an alternative for those who are looking for a painkiller and relief of other symptoms of different diseases. Lately CBD has become most popular as a painkiller and against anxiety. CBD can relieve the pain when walking as well as muscle spasms related to multiple sclerosis and arthritis. CBD improves pain during movement, pain at rest and sleep quality in patients with rheumatoid arthritis. CBD reduces nausea and vomiting after chemotherapy. CBD has anti-inflammatory properties and ability to control the overproduction of sebum by the sebaceous glands so it can be successfully used against acne. CBD improves the quality of life and sleep in patients with Parkinson's disease. CBD positively affects the heart and circulatory system, including lowering high blood pressure.

Aim: The purpose of this development is to present some of the indications of CBD oil.

Materials and Methods: This article presents some of the researches and the potential role of CBD oil in the treatment of the most popular medical problems like anxiety, depression and cardiovascular diseases.

Conclusion: CBD can be used as a food supplement for a lot of diseases like multiple sclerosis and arthritis, anxiety and depression, epilepsy, Parkinson's disease, Alzheimer's disease, high blood pressure.

Keywords: *CBD, food supplement, medical application*

THE ACCESSIBILITY TO MEDICAL PRODUCTS OF PATIENTS WITH MULTIPLE SCLEROSIS AND THE MODIFICATION IN THE COURSE OF THE DISEASE

Maria Koleva

MEDUNIPHARM 2 Pharmacy, Medical University of Varna

Introduction: Multiple sclerosis (MS) is an autoimmune disease with genetic origin, which when combined with factors of the surrounding environment leads to a cascade of immune responses and upsets the blood brain barrier. This results in inflammatory demyelization of white brain matter in the central nervous system. It interferes with the conduction of impulses in the central nervous system and the result is neurological deficit.

MS is classified into three clinical forms: Relapsing remitting, Secondary progressive and Primary progressive

Aim: The purpose of this article is to summarize and present to patients with MS information on the access to medications modifying the course of disease, as well as to focus on the new requirements for reimbursements on the costly treatment of MS.

Materials and Methods: This article presents the new requirements of National Health Insurance Fund (NHIF) for the treatment of the relapsing remitting and the primary progressive form of MS with a modification of the course of the disease in outpatient care.

Conclusion: An opportunity for reimbursement of the treatment of the primary progressive form of MS including the medication ocrelizumab (Ocrevus) in the Positive Drug List at the moment is the only therapeutic alternative for this clinical form of the disease.

There is a change in the certification of the protocols for first-line medications - appointment is with 1C protocol instead of an 1A.

There is a new specialized commission in St. Anna University Hospital - Sofia.

Keywords: MS, NHIF, new requirements, reimbursement

MEDICATION USE REVIEW AS AN ESSENCIAL BACKGROUND FOR PHARMACOVIGILANCE

Galina Petrova¹, Bogdan Kirilov², Evgeni Grigorov^{1,3}, Anna Todorova¹

¹*Department of Organization and economics of pharmacy, Faculty of Pharmacy,
Medical University of Varna*

²*PhD Student, Faculty of Public Health, Medical University of Varna*

³*National Center of Public Health and Analyses, Sofia*

Introduction: The Medication Use Review (MUR) is a structured evaluation of drug use aimed at reducing the problems associated with the use and increasing the effectiveness of drug treatment. It is intended to assess the professional competence of community pharmacists in the monitoring of drug use and the impact of the MUR service on the patient's knowledge of drug use (administration, adherence to drug therapy, identification of existing problems related to drug use e.g. dysphagia, adverse drug reactions (ADRs), improving healthy lifestyles, giving advice, etc.). In Bulgarian pharmacies, MURs are not yet implemented.

Material and Methods: All scientific sources of current articles were identified mainly by research on the Internet. The keyphrase used in the search of materials is "Medication Use Review". A retrospective analysis of articles published from 2006 to 2016 was performed.

Results: It was found that there are various procedures for data collection around the different countries. We summarized 4 main groups of benefits of having an active pharmacovigilance process, and they are related to:

- Improving compliance;
- Minimizing ADRs resulting from misuse;
- Improving patients' awareness and knowledge of lifestyle changes in the context of specific chronic diseases;
- Adherence to therapy, etc.

Conclusion: MUR service can be provided by different healthcare professionals - GP, nurse and pharmacist, but in many countries MUR service is offered by master of pharmacy professionals. Best practices in MUR are carried out in cooperation with health professionals and patients.

Keywords: medication, use, review, service, pharmacist

APPROACHES IN THE TREATMENT OF SOCIALLY SIGNIFICANT DISEASES OF THE CENTRAL NERVOUS SYSTEM

Vladimir Damyanov¹, Plamena Petrova², Jivko Kolev³, Evgeni Grigorov^{3,4}

¹*PhD Student, National Center of Public Health and Analysis, Sofia, Bulgaria*

²*Student, Faculty of Pharmacy, Medical University of Varna, Bulgaria*

³*Department of Organization and Economics of Pharmacy, Faculty of Pharmacy,
Medical University of Varna, Bulgaria*

⁴*National Center of Public Health and Analysis, Sofia, Bulgaria*

Introduction: The diseases of the central nervous system are a major problem for the health systems in all European countries and also for Bulgaria. Achieving therapeutic goals also requires medical doctors and pharmacists to work together not only with other healthcare professionals but also with the patient to accurately assess his or her drug therapy needs. The patient should be an active participant in the pharmacotherapy. The mental state of the patient - depression, depression and a sense of hopelessness - also has an effect on the course of treatment.

Aim: The aim of the study is to present the major approaches in the treatment of socially significant diseases of the central nervous system and to analyze the role of generic products in the drug therapy.

Materials and Methods: The investigation was conducted on the base of the information listed in the Positive Drug List published by National Council on Prices and Reimbursement of Medicinal Products and the approved pharmacotherapeutic guidances and recommendations for algorithms for the treatment with medicines on the territory of Bulgaria.

Results: Taking into account the pharmacotherapeutic guidelines, we have analyzed the different medicine options available in Bulgaria for 4 major diseases of the central nervous system. The patients in our country have the access to all of the modern drugs and health technologies. Nevertheless, medical doctors prefer classical approaches and well established medicines.

Conclusion: There is a wide range of treatments for central nervous system diseases. In Bulgaria in the last years there has been an active process of generic penetration of cheap and effective drugs that are fully reimbursed by the National Health Insurance Fund (NHIF) according to the local legislation.

Keywords: *treatment, socially significant diseases, central nervous system*

3D PRINTING IN PHARMACY

Plamen Bekyarov¹, Boryana Mihaylova², Nadya Agova³, Desislava Aleksandrova⁴,
Momchil Lambev⁴

¹*Specialized Hospital for Active Treatment in Obstetrics and Gynaecology
„Prof. dr. D. Stamatov”, Varna*

²*Student, Faculty of Pharmacy, Medical University of Varna*

³*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna*

⁴*TRS Assistant Pharmacist, Medical College, Medical University of Varna*

Introduction: New technologies are increasingly used in every area of our lives, including pharmacy. This is largely determined by the ability to create medications and dosage forms that meet the individual needs of specific patient groups.

Despite the established production technologies, proven in quality and efficiency over time, there are difficulties in the treatment of some patient groups. A typical example is patients in pediatrics. They experience difficulty in taking the medication and in particular size and shape of solid dosage forms.

It is through 3D printing that the desired biopharmaceutical characteristics of the tablets can be achieved to facilitate and assist the treatment of these patients. Moreover, with this new technology, dosage forms can be created at the appropriate dosage for each patient. In this way it will be possible to avoid dosing by the patient and avoid the risk of overdose. Another advantage of the formulations obtained by 3D printing is the relatively low cost of producing them.

Aim: The purpose of the present work is to examine and summarize the possibilities for the application of 3D printing in the field of pharmacy.

Materials and Methods: This paper summarizes data from literature sources on the benefits of using 3D printed drug forms in pharmacy.

Results: Based on the analysis of the literature data, the benefits of using 3D printing in the treatment of patients in specific groups were confirmed.

Conclusion: 3D printing is an innovative approach to overcome the problems that accompany drug use. This approach can contribute to the better application of individualized therapy as appropriate to the needs and conditions of each patient.

Keywords: 3D printing, pediatrics, benefits

GUIDELINES FOR AUTHORS

GENERAL INFORMATION

Scripta Scientifica Pharmaceutica publishes articles aimed to provide the most current information in various medical fields. The following types of articles are approved for publication:

- ❖ Reviews
- ❖ Original articles
- ❖ Case Reports

The manuscripts can be submitted through the online submission system, which requires a registration in order to use it.

ONLINE SUBMISSION

1. Registered users can log in with the same username and password to all journals published by Varna Medical University Press;
2. After logging in to a given journal, the user can click on the “My Profile” link and self-enroll as an Author for that particular journal;
3. Then by following the “My Journals” link the user can see the journals in which he/she is enrolled as an Author;
4. Clicking the “New Submission” link for each journal of interest starts a new submission;
5. To complete the submission, the user must fill in the required fields of the article metadata – author(s), affiliation, bio-statement, e-mail, title, abstract, keywords, references, address for correspondence;
6. The text of the manuscript must be submitted as a file which does not contain any images, diagrams, graphs, author names, affiliations and references. The text of manuscript should be submitted in Microsoft Word .doc/.docx format;
7. The images, figures and tables are submitted as supplementary files.

METADATA

Author's names, primary affiliation, e-mail

Fill in the full first and last name of the author and the rest of the required metadata. If there are co-authors, the user should use the “Add Author” button to add each co-author, and fill the names, primary affiliations and e-mails of all co-authors).

Title

Title should be concise but descriptive.

Abstract

The abstract must be no longer than 250 words summarizing the essential new information communicated. The text of the structured abstract should contain the following four sections: Introduction, Material and Methods, Results and Conclusion.

Keywords

Please supply up to 6 keywords in English that reflect the content of the paper. It is recommended to consider the subject headings of Index Medicus.

BODY TEXT

The text of the manuscript must be submitted as a file which does not contain any images, diagrams, graphs, author names, affiliations and references. The structure of the body of the manuscript should include the following sections:

Introduction: Should concisely state the main objective of the study and should provide a background for the study.

Methods: Should describe the design of the study (randomization, cross-over, prospective or retrospective etc.), the setting (hospital, university or private practice, primary or tertiary care etc.) and the patients or participants in the study. Should also give details of the numbers and descriptions of patients, participants of samples in the study and detailed information about treatment, intervention, technique or procedure.

Results: should be summarized with relevant statistical indices, following the requirements for tables and figures.

Discussion: must review the relevant literature on the subject and discuss the findings of the current study in their differences and similarities.

Conclusions: that are directly supported by the data should be stated, with equal emphasis on positive and negative findings.

Pages should be single-spaced, Times New Roman should be used throughout, sized at 12 pt. Captions should be used within the body of the manuscript to outline important points. The text of the manuscript should be submitted in Microsoft Word .doc/.docx format.

REFERENCES

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develops, and currently include guidance for print documents (journal articles, books or other monographs); unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet (url, DOI, database).

References should each be numbered and ordered sequentially as they appear in the text. In the list of references, papers should be listed numerically.

The following basic examples illustrate the format to be used:

Journal article

Iwamoto Y, Koide H, Ogita K, Nishizuka Y. The protein kinase C family for the regulation of cellular functions. *Biomed Rev.* 1992;1:1-6.

Journal article with more than 6 authors

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res.* 2002;935(1-2):40-6.

Book

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. *Medical microbiology*. 4th ed. St. Louis: Mosby; 2002.

Book chapter

Thornton T. On the interface problem in philosophy of psychiatry. In: Broome MR, Bortolotti L, editors. *Psychiatry as Cognitive Neuroscience: Philosophical Perspectives*. Oxford: Oxford University Press; 2009. p. 121-137.

URL

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>

DOI, PMID

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

Abbreviations of journal titles should follow those listed in the Index Medicus (<http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng>). Responsibility for the correctness of the references lies with the author(s). After the manuscript revisions, authors should double check that all in-text citations are in the reference list and that all references on the reference list have at least one corresponding in-text citation.

NOTE: If there are any references the original titles of which are in a non-Latin alphabet, they should be translated or transcribed. At the end, in brackets, there should be the original language, e.g. (in Bulgarian).

IMAGES, FIGURES, DIAGRAMS AND TABLES

- ❖ Figures should be provided as separate files in TIFF, EPS, JPG, PNG, BMP or JPEG format and not embedded in the manuscript text file.
- ❖ All photos should be scanned at 300 dpi.
- ❖ Diagrams, drawings, graphs must be vector ones or saved at a resolution of at least 600 dpi. Diagrams should be in the original file format with data sheets. Their titles should obligatorily be provided within the text only.
- ❖ Tables should be provided on separate sheets and each table should have a title. No data reiterations in the text, tables, and figures are permitted. All tables must be cited in the text (e.g. "Table 1").
- ❖ Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi. They should be sufficiently contrasted and with a minimal size of 8 cm in width (1 column) or 16,6 cm in width (2 columns). The location of the photographs, diagrams, graphs, and tables should be indicated in the text (e.g., "Table 1" or "Fig. 1").

FIGURE LEGENDS

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).

PROOFS

For manuscripts accepted for publication, Galley PDFs will be produced by a Layout Editor and uploaded to the online manuscript tracking system. Once the Galley PDF is available, the authors will be informed by e-mail to log in to the system, download the Galley PDF, do proof-reading and return a list with corrections. No major changes in, or additions to, the edited manuscript will be allowed at this stage. Proofreading is solely the Authors' responsibility. Corrections to the proofs must be returned using the online manuscript tracking system within 72 hours after receipt. If the Publisher receives no response from the Author(s) after 10 days, it will be assumed that there are no errors to correct and the article will be published as it is.

SCRIPTA SCIENTIFICA PHARMACEUTICA, volume 6, 2019, supplement 1

Editor-in-Chief: Prof. Diana Ivanova, PhD, DSc

Co-Editor-in-Chief: Assoc. Prof. Svetlana Georgieva, PhD

Design and Layout Editing: Emilia Yordanova

Cover Design: Hristina Hristova

Proofreading: Yordanka Peteva

Publ. Lit. group: III-3

Sent to print: October, 2019

Print sheets: 13

Format: 8/60x84

Approved for print: October, 2019

Publisher: Medical University of Varna

55 Marin Drinov Street, Varna 9002, Bulgaria

www.mu-varna.bg

ISSN 2367-6000 (print)

ISSN 2367-5500 (online)

<http://journals.mu-varna.bg/index.php/ssp>

2019, Medical University "Professor Paraskev Stoyanov" of Varna