GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 2 (335) Февраль 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 2 (335) 2023

Содержание:

Ahmad Ali Alrasheedi.
THE PREVALENCE OF COVID-19 IN THE COUNTRIES OF THE GULF COOPERATION COUNCIL: AN EXAMINATION AFTER THREE YEARS……..……..…6-12

Kordeva S, Cardoso JC, Tchernev G.
MULTIFOCAL FIXED DRUG ERUPTION MIMICKING ACQUIRED DERMAL MELANOCYTOSIS…….....……13-16

Oksana Matsyura, Lesya Besh, Zoryana Slyuzar, Olena Borysiuk, Olesia Besh, Taras Gutor.
ARTIFICIAL VENTILATION OF THE LUNGS IN THE NEONATAL PERIOD: LONG-TERM OUTCOMES.....17-21

Tchernev G, Kordeva S, Lozev I.
METATYPICAL BCCS OF THE NOSE TREATED SUCCESSFULLY VIA BILOBED TRANSPOSITION FLAP: NITROSAMINES IN ACES (ENALAPRIL), ARBS (LOSARTAN) AS POSSIBLE SKIN CANCER KEY TRIGGERING FACTOR…….....……..22-25

Zahraa M Alzubaidi, Wafaa M. A. Al-attar.
NURSES' KNOWLEDGE ABOUT HEPATITIS C VIRUS IN BAGHDAD TEACHING HOSPITALS: A CROSS-SECTIONAL STUDY...26-31

Theresa Semmelmann, Alexander Schuh, Horst Rottmann, Reinhard Schröder, Christopher Fleischmann, Stefan Sesselmann.
HOW TO AVOID FRACTURE OF THE LOCKING SCREW IN MODULAR REVISION ARTHROPLASTY OF THE HIP USING THE MRP TITAN REVISION SYSTEM…….....……...32-35

Siranush Mkrtchyan, Razmik Dunamalyan, Ganna Sakanyan, Hasmik Varuzhanyan, Sona Hambardzumyan, Marine Mardiyan.
EFFECT OF CHRONIC PERIODONTITIS ON HEALTH-RELATED QUALITY OF LIFE AND ANXIETY AMONG PATIENTS IN YEREVAN,ARMENIA…….....……..36-40

Raghad O Aldabbagh, Marwah abdulmelik Alshorbaji, Yahya Mohammed Alsabbagh.
THE PHYSICAL AND PSYCHOLOGICAL EFFECTS OF MOBILE GAMES ON CHILDREN IN MOSUL/IRAQ……41-45

Bukia N.G., Butskhrikidze M.P., Machavariani L.P., Svanidze M.J., Nozadze T.N.
ELECTRIC-MAGNETIC STIMULATION PREVENTS STRESS-INDUCED DETERIORATION OF SPATIAL MEMORY….....……46-53

Marko Kozyk, Adam Wahl, Kateryna Strubchevska, Kolosova Iryna, Shatorna Vira.
CHRONIC EFFECTS OF CADMIUM CHLORIDE ON RAT EMBRYOGENESIS…….....……54-59

Labeeb H. Alsadoon, Kassim Salih Abdullah.
COMPARATIVE EFFECT OF INSULIN, GLIMEPIRIDE, AND METFORMIN ON INFLAMMATORY MARKERS IN TYPE 2 DIABETES MELLITUS…….....……60-63

Miloslav Doul, Philipp Koehl, Marcel Betsch, Stefan Sesselmann, Alexander Schuh.
RETURN TO SPORT AFTER SURGICAL TREATED TIBIAL PLATEAU FRACTURES…….....……64-68

Zaid Saaduldeen Khudhur, Uday Hani Mohammad, Nooman Hadi Saeed.
HAEMATOSPERMIA: CAUSES AND ASSOCIATED CHANGES IN SEMEN ANALYSIS IN NORTH OF IRAQ……..…69-72

Prots H, Rozhko M, Paliichuk I, Nychyporchuk H, Prots I.
STUDY OF BONE RESORPTION AS A RISK FACTOR IN DENTAL IMPLANTATION IN PATIENTS WITH GENERALIZED PERIODONTITIS…….....……73-78

Teimuraz Lezhava, Tinatin Jokhadze, Jamlet Monaselidze, Tamar Buadze, Maia Gaiozishvili, Tamar Sigua, Inga Khujadze, Ketevan Gogidze, Nano Mikaia, Nino Chigvinadze.
EPIGENETIC MODIFICATION UNDER THE INFLUENCE OF PEPTIDE BIOREGULATORS ON THE "OLD" CHROMATIN.…….79-83

Mudrenko I.G., Kolenko O.I., Kiptenko L.I., Lychko V.S., Sotnikov D.D., Yurchenko O.P.
THE PROGRAM OF THE COMPLEX DIFFERENTIATED MEDICAL AND PSYCHOLOGICAL REHABILITATION OF THE PATIENTS WITH SUICIDAL BEHAVIOUR IN DEMENTIA…….....…….84-89

Tchernev G, Kordeva S.
MULTIPLE BCCS AND DYSPLASTIC NEVI AFTER ACE INHIBITORS (ENALAPRIL/PERINDOPRIL): THE ROLE OF NITROSAMINE CONTAMINATION/AVAILABILITY AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR…….....……90-94

Lyazzat T. Yeraliyeva, Assiya M. Issayeva.
CHANGES IN DEATH RATES FROM LOWER RESPIRATORY INFECTIONS BETWEEN 1991 AND 2019 IN THE REPUBLIC OF KAZAKHSTAN…….....……..95-98

Rocco De Vitis, Marco Passiatore, Giovanni Barchetti, Isabella Ceravolo, Luigi M. Larocca, Marta Starnoni, Francesco Federico, Federica Castri, Giuseppe Taccardo.
PATTERN OF A PRIMARY B-CELL LYMPHOMA IN ULNAR NERVE: INTRANEURAL OR EXTRANEURAL…….....……..99-103

Bazargaliyev Ye, Makashova M, Kudabayeva Kh, Kosmuratova R.
EPIDEMIOLOGY OF GENES ASSOCIATED WITH OBESITY IN ASIAN POPULATION. LITERATURE REVIEW……...……104-110

Samsonia M.D, Kandelaki M.A, Baratashvili N.G, Gvaramia L.G.
NEUROPROTECTIVE AND ANTIOXIDANT POTENTIAL OF MONTELUKAST-ACETYLCYSTEINE COMBINATION THERAPY FOR BRAIN PROTECTION IN PATIENTS WITH COVID-19 INDUCED PNEUMONIA…….....……111-118

Condé Kaba, Carlos Othon Guelngar, Barry Souleymane Digué, Keita Karinka, Diallo Mamadou Hady, Keita Fatoumata Binta, Cissé Fodé Abass.
ALZHEIMER'S DISEASE, AN ASSOCIATION OR A COMPLICATION OF PAGET'S DISEASE? STUDY OF AN OBSERVATION IN GUINEA…….....……119-120

Condé Kaba, Keita Karinka, Carlos Othon Guelngar, Diallo Mamadou Hady, Keita Fatoumata Binta, Cissé Fodé Abass.
CLINICAL AND IMAGING ASPECTS OF TALAR OSTEOCHONDRITIS: A CASE REPORT FROM GUINEA…….....……121-123

Fishchenko Iakiv, Kravchuk Lyudmila, Kormiltsev Volodymyr, Saponenko Andrey, Kozak Roman.
THE USE OF RADIOFREQUENCY NEUROABLATION IN THE TREATMENT OF OMALGIA IN PATIENTS WITH SHOULDER JOINT ARTHROSIS…….....……124-128

V.V. Talash, I.P. Katerenchuk, Iu.A. Kostrikova, T.I. Yarmola, G.L. Pustovoit, L.A. Tkachenko.
TERATOMAL NEOPLASMS OF THE PERICARD: THE PROBLEM AND REALITIES (CLINICAL CASE)……..129-136

GEORGIAN MEDICAL NEWS
No 1 (335) 2023

MULTIPLE BCCS AND DYSPLASTIC NEVI AFTER ACE INHIBITORS (ENALAPRIL/ PERINDOPRIL): THE ROLE OF NITROSAMINE CONTAMINATION/AVAILABILITY AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR

Tchernev G[1,2]*, Kordeva S[1].

[1]*Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria.*

[2]*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, General Skobelev 79, 1606, Sofia, Bulgaria.*

Abstract.

Nitrosamines as contaminants in a wide variety of drugs are also found to be one of the most likely causes of skin cancer. A detailed analysis of this contamination could in the near future solve to a large extent the puzzle of carcinogenesis concerning the keratinocytic forms of cancer and melanoma. But also, probably cancer in general.

Over 80% of skin cancer is due to acquired mutations, and nitrosamines, which are contained as contamination in certain batches of the most commonly distributed drugs worldwide (such as sartans, ACE inhibitors, ranitidine, metformin, hydrochlorothiazide, rifampicin, and a number of others.) are considered among the most powerful external mutagens, carcinogens. Carcinogens that until 2021 were not supposed to be present in medicines and carcinogens for which it was subsequently decided to create a regulatory regime for permissible availability.

Regardless of whether these contaminants are applied within the so-called daily acceptable intake dose or many times above it, the problem with the availability of nitrosamines continues to be present. It is also caused by the lack of reflection of the concentration of the corresponding nitrosamine in a certain drug. Thus, it is impossible to calculate the ″permissible daily intake of the total number of mutagens and their concentration based on polymedication″.

In practice, drug manufacturers distribute nitrosamines in parallel with drugs, although they are not listed as a component of the product but are identified and allowed as contamination or substances with permissible availability by the EMA/FDA.

From another point of view, the fact that is not commented on is also of interest, namely that not all batches are affected by this contamination. This suggests that the contamination may have been controlled, since in a manufacturing error the contamination should be widespread.

The registration of the potential contamination of a heterogeneous type of medicinal products on the European market to the executive agencies for drug control in certain geographical areas has remained for years without any answer and opens a number of questions.

The problem with ACE inhibitors is similar to that with sartans, hydrochlorothiazide, metformin, and ranitidine. The ″special impression″ of the clinicians is determined by the fact that the patterns of manifestation of the skin tumors during the administration of a heterogeneous class of medications are similar to completely identical. From this it could be concluded that the unifying factor between the pattern of occurrence could not be based on the action of the main substance of each drug class, since it remains to be radically different.

The unifying link remains the sole and only contamination or the permissible already availability of a new ingredient known as nitrosamines. We present cases of multiple basal cell carcinomas and dysplastic nevi following enalapril and perindopril administration. The role of potential contamination of ACE inhibitors with nitrosamines for the development of skin cancer is discussed.

Key words. Enalapril, Nitrosamines, skin cancer.

Introduction.

The pathogenesis of the keratinocytic forms of skin cancer remains a mystery. Besides the genetic factors (xeroderma pigmentosum, Goltz Gorlin syndrome), congenital or acquired immune deficiencies, systemic immunosuppressive therapy (in transplant patients), light skin (Fitzpatrick type 1), painful sunburns and etc. [1-3], there are other factors such as the presence of certain or multiple mutagens in some medications (the so-called nitrosamines) which are able to potentiate the skin cancer development [4,5].

The controversy with the regulatory authorities and their limitations remains relevant at the moment, however at the end of 2022, the results of an extremely important retrospective large-scale study by a French team, concerning the mentioned issue, was announced [6]. The purpose of the study is to clarify the overall cancer risk in patients taking nitrosamine-contaminated valsartan in comparison with those taking uncontaminated valsartan for a certain period of time [6]. Statistically significant risks were found only for melanoma and liver cancer; therefore it should be noted that the scientific work was focused on the presence of a single nitrosamine contamination without specifying whether it has exceeded the acceptable daily dose (ADI) or not [6].

The terms "availability", "availability above the daily acceptable dose" or "200 times above the daily acceptable dose" was not taken into account, but in all likelihood play a key role in the generation of certain or multiple types of cancer.

Although the data are not conclusive, it remains indicative that even the presence of a single mutagen/nitrosamine in valsartan as contaminant is capable of causing melanoma and liver cancer even in small percentage of the patients [6].

With the problem arising in 2022, a famous pharmaceutical company withdrew from the market a large number of antihypertensive drugs containing hydrochlorothiazide and quinapril due to the increased concentrations of another type of nitrosamine [7]. Because of this confession by the pharmaceutical giant Pfizer (for periods between 20 and 30 years ago) ACE inhibitors (and the possible development of skin cancer) were brought to the attention of the clinicians.

Therefore, the nitrosamines should be the possible cause of the same cancer development, regardless of whether they are present in sartans or ACE inhibitors, smoked meats, or beer [4].

We present two unrelated cases of patients receiving ACE inhibitors for arterial hypertension, subsequently developed multiple basal cell carcinomas, some of which located in areas never exposed to solar radiation. One of the patients also developed a dysplastic melanocytic nevus.

The potential role of nitrosamines in officially announced drug classes (including ACE inhibitors) as potential carcinogenic inductors, in particular keratinocytic types of cancer and melanoma precursors (in the dysplastic nevi), is discussed.

Case report 1.

A 72-year-old male reported to the dermatology department (2023) with primary complaints of multiple tumorous lesions located behind the neck, left ear, on the forehead, under the right eye and on the upper abdominal region. The lesions are from about no more than 2 years. In recent months the patient noticed the lesions changing in size and color.

Comorbidities: duodenal ulcer and past ischemic stroke for which he takes systemic medications: vinpocetine 10mg twice a day, enalapril 10mg once in the morning (since 2008), flupentixol/melitracen 0.5mg/10mg once in the morning, acetylsalicylic acid 100mg once in the evening and piracetam three times a day.

In 2010 a basal cell carcinoma was removed from the patient's right nasolabial fold via followed single surgical excision and undermining approach for defect closure. The histology showed Basal cell carcinoma, incomplete, so that radiation therapy followed with good final results and no clinical signs of disease progression over the years.

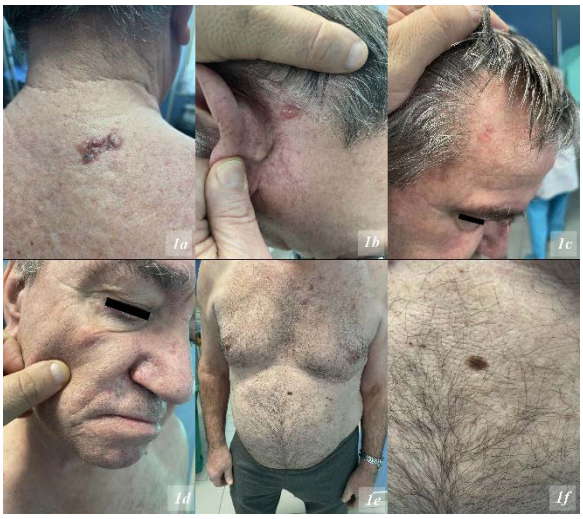

Figure 1a-f. *Nodular formations with a pearly surface located on the skin of the neck (a) and behind the left ear (b). The lesions on the forehead (c) and under the right eye (d) were hardly defined, erythematous and with visible teleangiectasias (c). A pigmented macule with uneven pigmentation is observed on the skin of the abdomen (e,f).*

Current dermatological examination 12 years later showed nodular formations with a pearly surface located on the skin of the neck (Figure1a), behind the left ear(Figure 1b). The lesions on the forehead(Figure 1c) and under the right eye (Figure 1d) were hardly defined, erythematous and with visible teleangiectasias (Figure 1c). The formations were all suspected clinically and dermoscopically for basal cell carcinoma. Additionally, a pigmented macule with uneven pigmentation is observed on the skin of the abdomen, suspected of dysplastic nevus (Figures 1e,f).

Under local anesthesia the patient underwent surgery for four of the suspicious lesions – on the neck (Figure 2a), behind the left ear (Figure 2b), on the forehead (Figure 2c) and for the lesion on the abdomen (Figure 2d). Within one surgical session each lesion was removed with an elliptical excision. The remaining defects were closed by single interrupted sutures (Figure 2a-d). Outpatient follow-up and removal of the sutures were done 10 and 12 days after the surgery. Histology showed three basal cell carcinomas, staged pT1N0M0 and one dysplastic nevus with clear resection lines.

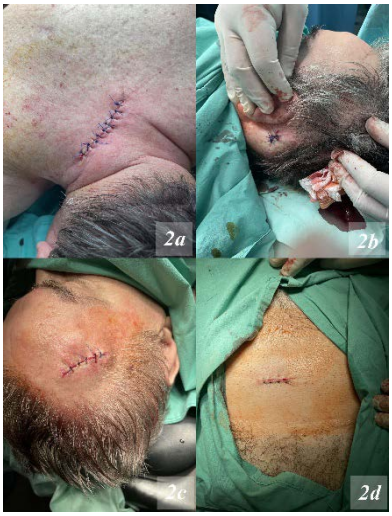

Figure 2a-d. *Intraoperative view: Surgical excision of the lesions: on the neck (a), behind the left ear (b), on the forehead (c) and on the abdomen (d). The remaining defects were closed by single interrupted sutures (a-d).*

A change in the patient's medication therapy was suggested – enalapril was recommended to be switched to amlodipine.

Case report 2.

An 87-year-old female reported to the dermatology department with primary complaints of a tumorous lesion located above the right upper lip and reddish plaque on the left cheek and forehead from 3-4 years.

Comorbidities: past Covid-19 infection, arterial hypertension, congestive heart failure, ischemic heart disease, bilateral macular degeneration of the retina. Systemic medication: since 10 years (2012/2013) perindopril/indapamide 10mg /2.5 mg once in the morning, Lercanidipine hydrochloride 10 mg once daily and latanoprost 50 micrograms/ml eye drops.

In 2017 the patient reported a lesion which later on and after removal was verified as basal cell carcinoma 0.6/0.4 cm in size, stage T1N0M0 with clear resection lines. The procedure was surgically removed with an oval excision under local anesthesia and the defect was closed with an island flap.

The current dermatological examination (2023) in the policlinic showed several raised lesions with a firm consistency, an erythematous base and a pearl-like edge with crusts located above the left eyebrow (Figure 3a,b), under the left eye (Figure 3c) and above the right lip (Figure 3d). The lesions were suspected of basal cell carcinoma.

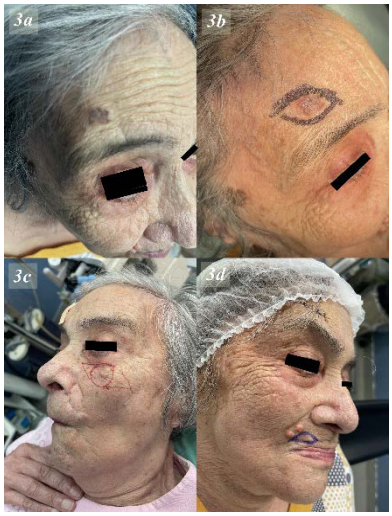

Figure 3a-d. *Raised lesions with a firm consistency, an erythematous base and a pearl-like edge with crusts located above the left eyebrow (a,b), under the left eye (c) and above the right lip (d).*

Under local anesthesia the lesions located on the left eyebrow (Figure 4a,b), under the left eye (Figure 4c,d) and right upper lip (Figure 4e) were removed with an elliptical excision.

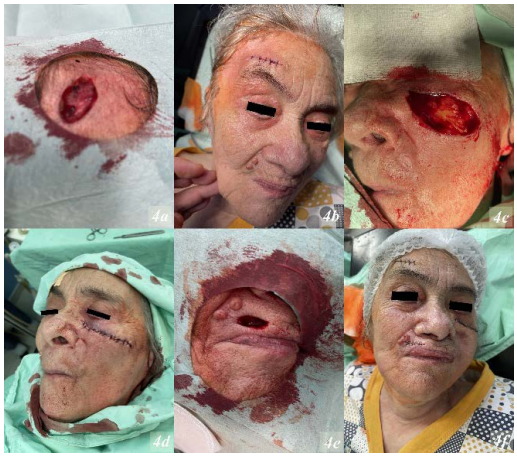

Figure 4*. a,b: Intraoperative view: Elliptical excision of the lesion located on the left eyebrow(a). The remaining defect is closed by single interrupted stitches (b).*
c,d: Intraoperative view: Elliptical excision of the lesion located under the left eye (c), closed by single interrupted stitches (d)
e: Intraoperative view: Elliptical excision of the lesion located on the right upper lip (e)f: Postoperative view of the patient. Defects closed by single interrupted stitches.

Smooth postoperative period (Figure 4f). Outpatient follow-up and removal of the sutures were done 10 and 12 days after the surgery. Histology showed three basal cell carcinomas, staged pT1N0M0 with clear resection lines.

A change in the therapeutic regimen was done - Chlorthalidone 25 mg, Lercanidipine hydrochloride 10 mg, Moxonidine 0.2 mg once in the evening. The medication with perindopril/ indapamide was stopped.

Discussion.

The analysis of the scientific data from the recent past [8-10] is often ignored by current meta-analyses and retrospectives studies. However, connecting the past and present studies [6,8-10], is capable of providing answers to many remaining unresolved dilemmas and could help resolve future problems (for example the problem with the nitrosamines in high blood pressure drugs (but not only in them).

The value/ paramount importance of the retrospective studies from the recent past lies entirely in their lack of observation of certain external factors [8-10] that were not known at that (past) time—namely, the availability of nitrosamines, which was revealed in 2018 by the FDA [6]. Therefore these ″unknown″ events are guaranteeing the absolute neutrality and objectivity of the final results of the study, due to the fact that they could not be influenced by nonexistent (at least at that moment) facts or data [8-10].

Prospective analyzes are accepted as absolute proof of a causal or pathogenetic relationship in medical science and data evaluation. However, at the moment their importance seems minimal or difficult to implement because it would not be possible from an ethical point of view to start prospective studies, which would track the side effects of the nitrosamines in certain medications.

It would be also difficult (from a moral and practical point of view) to persuade the patients to voluntary sign the consent documents in order to take the nitrosamine-contaminated drugs at concentrations between 20 and 200 above the acceptable daily limit (ADI) or the recently (20-30 years) distributed medications by the pharmaceutical companies themselves [7]. These facts are contributing to the thesis about the significance and neutrality of the retrospective/prospective case reports. The information in those is also confirmed by recent meta-analyses and large-scale retrospectives studies [8-10].

Long before the results from the large-scale French study confirming the link between the nitrosamines and melanoma [6], this connection had already been published many times based on single clinical cases [11-18]. Regardless of this fact, the French study re-emphasizes the link between the intake of nitrosamine-contaminated valsartan and the development of melanomas [6]. Similar observations are being made for the simultaneous appearance of melanocytic and keratinocytic tumors after oral intake of potentially nitrosamine-contaminated sartans, thiazide diuretics or combination of the above mentioned [19-21].

These cases are indicative and alarming regarding the potential role of nitrosamines in the keratinocyte cancer development [19-21]. Proceeding from the thesis/"hypothesis" that nitrosamines present a key role in the skin cancer development in general, it would be wise to say that their presence in the ACE inhibitors

(officially announced only by Pfizer at the moment) would cause equivalent to analogous types of cancer (analogous to those registered after oral intake of contaminated sartans and thiazide diuretics).

The potential presence of nitrosamines in sartans also appears to be a possible cause for the development of dysplastic nevi and basal cell carcinomas [20,21].

Their potential presence in ACE inhibitors would in all likelihood lead to the progression of the same lesions (Patient 1 presented with multiple basal cell carcinomas and dysplastic nevus after oral administration of enalapril).

Based on the fact that it is unlikely that two different types of skin tumors (or tumor precursors such as dysplastic nevi) can be induced after oral administration of antihypertensive drugs with different mechanisms of action, then the unifying factor for this induction remains only the nitrosamines? These data have been supported today only for melanoma or melanocytic skin tumors [6].

Back in 2017, Nardone B et al. established a relationship between the intake of ACE inhibitors and the development of basal cell, squamous cell carcinomas and melanomas [10].

1) BCC- unadjusted OR (95% CI): **2,09** (1,87-2,34) / adjusted OR (95% CI): **2,23** (1,78-2,81)

2) SCC- unadjusted OR (95% CI): **2,53** (2,07-3,08)/ adjusted OR (95%CI): **1,94** (1,37-2,76)

3) MM- unadjusted OR (95% CI): **2,42** (2,00-2,95)/ adjusted OR (95 % CI): **1,71** (0,97-3,00)

Similar are their observations regarding the intake of ARB blockers [10].

1) BCC- unadjusted OR (95% CI): **2,16** (1,85-2,52) / adjusted OR (95% CI): **2,86** (2,13-3,83)

2) SCC- unadjusted OR (95% CI): **2,50** (1,93-3,23)/ adjusted OR (95%CI): **2,22** (1,37-3,61)

3) MM- unadjusted OR (95% CI): 2,25 (1,73-2,94)/ adjusted OR (95 % CI): 1,24 (0,54-2,85)

As well as after taking thiazide diuretics [10].

1) BCC- unadjusted OR (95% CI): **1,73** (1,49-2,02) / adjusted OR (95% CI): **2,11** (1,60-2,79)

2) SCC- unadjusted OR (95% CI): **2,97** (2,33-3,79)/ adjusted OR (95%CI): **4,11** (2,66-4,35)

3) MM- unadjusted OR (95% CI): 2,06 (1,59-2,66)/ adjusted OR (95 % CI): 1,82 (1,01-3,82)

As for keratinocytic skin tumors, it is striking that the risk of developing basal cell carcinoma after taking ACE inhibitors is doubled, and after stratification of the data, this risk is even slightly increased, which in practice largely excludes a sporadic relationship between the two events [10].

Similar are the data for squamous cell carcinoma after administration of ACE inhibitors [10].

The relationship between the use of ARB blockers and the development of basal cell carcinoma is even more pronounced, to an extent similar to that after taking ACE inhibitors, with an almost threefold risk after stratification (unadjusted/adjusted OR) [10]. For squamous cell carcinoma, the risk remains double, and relatively constant after stratification.

The data are also convincing for keratinocyte tumors arising after the administration of thiazide diuretics: an almost twofold and constant risk of developing basal cell carcinoma, as well as a 3- to 4-fold increased risk of developing squamous cell carcinoma [10].

The link between taking the three types of antihypertensive drugs and the development of keratinocyte types of cancer may be from:

1) The batches from the three drug classes have been withdrawn from the market due to the repeatedly elevated concentrations of nitrosamines.

2) The risk of developing keratinocytic types of cancer and in particular basal cell carcinoma being doubled and relatively constant.

We can conclude that the nitrosamines may be, or in fact are the missing piece of the puzzle in the carcinogenesis of the keratinocytic forms of skin cancer and basal cell carcinomas especially.

Regardless of whether the nitrosamines occur as an impurity in any of the three drug classes (ACE inhibitors/ARB blockers or thiazide diuretics), in practice they are the most likely substances with a potential procarcinogenic effect, causing this persistent and relatively even distributed risk.

Analogous and indicative are the data on the appearance of melanomas after taking ACE inhibitors - an almost or approximately two-fold increase [10]. This could also explain the reason for the parallel appearance of 1) multiple keratinocyte tumors in the two described patients and 2) the dysplastic nevus presented in patient 1 [20,21].

Conclusion.

It can be concluded that the pathogenesis of keratinocyte cancer and melanomas remains a mystery to this day. However, the curtain on this mystery appears to be slightly lifted following the FDA's 2018 release of nitrosamine contamination's data in valsartan. This provided a closer monitoring of the actual patients followed by retrospective analyses/meta-analyses of large databases worldwide.

The relationship between the intake of different types of potentially contaminated drugs and the development of skin cancer (but also other types of cancers) is found to be significantly increased.

For the first time in the world literature, 2 cases of patients with skin cancer after long-term intake of ACE inhibitors, potentially contaminated with nitrosamines, are presented. A thorough analysis of the available literature was made.

The differences in the statistics across the geographic regions may be due to:

1) The different genetic sensitivity or predisposition of the population regarding the development of a certain type of cancer in certain geographical regions.

2) The quality of the different drugs that are distributed in a certain geographical area by certain manufacturers and their suppliers.

3) The possible presence/ availability of different nitrosamines as mono- or polycontamination in the presented drugs.

The companies and the regulatory authorities in the form of the FDA/EMA have a unique opportunity to bring this sensitive information to the public: Which and how many nitrosamines are in these medications? At what concentration levels? Period

of administration? In which medications exactly ? What are the results of the intake: single or multiple cancers that are developed?

Still, these are unanswered questions or perhaps delayed responses?.

REFERENCES

1. Hernandez LE, Mohsin N, Levin N, et al. Basal cell carcinoma: An updated review of pathogenesis and treatment options. Dermatol Ther. 2022;35:e15501.
2. Bauer A, Haufe E, Heinrich L, et al. Update on occupational skin cancer-basal cell carcinoma and solar UV exposure. Hautarzt. 2021;72:484-492.
3. Juan HY, Zhou AE, Hoegler KM, et al. Overview of familial syndromes with increased skin malignancies. Arch Dermatol Res. 2022.
4. Tchernev G, Kordeva S, Marinov V, et al. Nitrosamines in antihypertensives, metformin and ranitidine as cofactors for melanoma and development of other cancers. Expert Group opinion. Port J Dermatol and Venereol. 2022;80:332-334.
5. Tchernev G, Oliveira N, Kandathil LJ, et al. Valsartan (and/or Nitrosamine) Induced BCC and Dysplastic Nevi: Current Insights. Clin Res Dermatol Open Access. 2021;8:1-6.
6. Mansouri I, Botton J, Semenzato L, et al. N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 million Valsartan Users. J Am Heart Assoc. 2022;11:e8067.
7. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretictm
8. Sipahi I. Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: Meta-regression analysis of randomized trials. PLoS One. 2022;17:e0263461.
9. Sipahi I, Debanne SM, Rowland DY, et al. Angiotensin-receptor blockade, and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010;11:627-636.
10. Nardone B, Orrell KA, Vakharia PP, et al. Skin cancer associated with commonly prescribed drugs: tumor necrosis factor alpha inhibitors (TNF-αIs), angiotensin-receptor blockers (ARBs), phosphodiesterase type 5 inhibitors (PDE5Is) and statins -weighing the evidence. Expert Opin Drug Saf. 2018;17:139-147.
11. Tchernev G, Temelkova I. Valsartan Induced Melanoma?! First Description in Medical Literature! Open Access Maced J Med Sci. 2018;6:2378-2380.
12. Tchernev G, Temelkova I. Drug-Induced Melanoma: Irbesartan Induced Cutaneous Melanoma! First Description in the World Literature! Open Access Maced J Med Sci. 2019;7:114-116.
13. Tchernev G, Temelkova I. Irbesartan Induced Cutaneous Melanoma! Second Case in the Medical Literature! Open Access Maced J Med Sci. 2019;7:121-123.
14. Tchernev G, Temelkova I. Additional 4 cases of valsartan/irbesartan-induced melanomas? J Biol Regul Homeost Agents. 2019;33:911-912.
15. Tchernev G, Temelkova I. Olmesartan/valsartan induced giant achromatic cutaneous melanoma: "modified" one-step surgical approach with favourable outcome. J Biol Regul Homeost Agents. 2019;33:1775-1777.
16. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. Expert Rev Clin Pharmacol. 2021;14:1075-1080.
17. Tchernev G, Temelkova I. Valsartan/hydrochlorothiazide induced prostate carcinoma in a patient who subsequently developed melanoma. J Biol Regul Homeost Agents. 2019;33:1125-1127.
18. Tchernev G, Patterson JW. Telmisartan/hydrochlorothiazide-induced nevus-associated cutaneous melanoma: first report in the medical literature. Expert Rev Clin Pharmacol. 2021;14:289-293.
19. Tchernev G, Poterov G, Patterson JW, et al. Sartans and cancer: Multiple verrucous carcinomas and giant acral melanoma developing after antihypertensive therapy with valsartan and olmesartan. Journal Medical Review (Bulgarian) 2020;56:58-60.
20. Tchernev G, Oliveira N, Kandathil LG, et al. Valsartan (or/and Nitrosamine) induced BCC and dysplastic Nevi: Current insights. Clin Res Dermatol Open Access. 2021;8:1-6.
21. Malev V, Tchernev G. Dysplastic nevus, and BCC development after antihypertensive therapy with Valsartan and Hydrochlorothiazide!? Clin Res Dermatol Open Access. 2019;6:1-2.