

# GEORGIAN MEDICAL NEWS

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии  
საქართველოს სამედიცინო სიახლენი

## GEORGIAN MEDICAL NEWS

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**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 ВИНТИ 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 ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

### WEBSITE

[www.geomednews.com](http://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](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. Корректур авторам не высылаются, 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 computer-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.nlm.nih.gov/bsd/uniform_requirements.html)  
[http://www.icmje.org/urm\\_full.pdf](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 საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ 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 შედეგის 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 ფხიხლებში 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.

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## THE NITROSAMINE CONTAMINATION IN BETA BLOCKERS (BISOPROLOL/ METOPROLOL), ACE INHIBITORS (LISINAPRIL/ PERINDOPRIL), THIAZIDE DIURETICS (HCT), CALCIUM CHANNEL BLOCKERS (AMLODIPINE/ FELODIPINE), SARTANS (CANDESARTAN) AND THE SUBSEQUENT SKIN CANCER DEVELOPMENT AND PROGRESSION: APOCALYPSE NOW!

Georgi Tchernev<sup>1,2</sup>.

<sup>1</sup>Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior, General Skobelev 79, 1606 Sofia, Bulgaria.

<sup>2</sup>Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria.

### Abstract.

The problem of contamination of the most commonly used medicines with nitrosamines is worsening worldwide. According to recent literature data, this "contamination" is the cause not only of skin cancer (keratinocytic/melanoma) but also of gastrointestinal neoplasms, brain tumours, neuroblastoma, rectal carcinoma, acute lymphoblastic leukaemia, and many others. It is these clinical manifestations that are associated with/ or already directly linked to the nitrosamine content of drugs and food products used by patients in previous periods. And it is this permissive availability/contamination that could prove to be the most likely, powerful inducer of acquired mutations underlying the worldwide cancer pandemic.

Of further concern is the evidence of contamination of newer classes of medications by nitrosamines- namely: beta blockers, calcium antagonists and selective serotonin reuptake inhibitors (SSRIs). In practice, mankind faces the problem of certainly over 1 billion patients taking nitrosamine-contaminated drugs: 280 million patients with depression (antidepressants), over 1 billion patients with arterial hypertension (antihypertensive drugs), over half a billion patients with type 2 diabetes mellitus (oral antidiabetic drugs/metformin/ sitagliptin), over 4 billion patients with gastritis (ranitidine), over 5 million with tuberculosis (rifampicin), and probably a number of others. The calculations are apocalyptic, since even if only 20-30% of the groups were affected, the number of patients taking these drugs would, by a rough calculation, currently amount to over 1 billion. And there are certainly other classes of drugs yet to be announced.

It is for this reason that we should not be surprised that the data on the development of keratinocyte cancer after intake of nitrosamine-contaminated preparations is growing at a breakneck pace. This data indirectly but strongly confirms the importance of a newly introduced concept in the medical science : Nitrosogenesis of skin cancer.

A concept, until recently unknown, incomprehensible, but at the same time frightening and gradually accepted, imposing itself and which with each passing day is gaining more and more scientific significance and "visibility", "scientific tangibility, receptivity, and acceptability."

This article presents, for the first time in the world literature, patients who developed single/multiple forms of keratinocytic cancer (partly in combination with melanoma precursors-dysplastic moles) after administration of two new classes of potentially nitrosamine-contaminated antihypertensive drugs: beta blockers (bisoprolol, metoprolol) and calcium antagonists

(amlodipine, felodipine).

For the first time in the scientific literature, the contributory pro-carcinogenic role of another potentially nitrosamine-contaminated ACE inhibitor- lisinopril , as well as that of candesartan: in the development of keratinocytic cancer is also discussed.

For the first time in the world literature, the conclusion regarding the pathogenetic relationship between the intake of potentially contaminated drugs (from different drug groups) and cancer development is based on the model of the equivalent clinical manifestation of skin tumors (rather than on controlled long-term prospective analyses). Nitrosamine contamination in these drug groups appears to be the sole and major unifying factor or causative agent for these manifestations.

**Key words.** Nitrosamines, contamination, Candesartan, bisoprolol, metoprolol, amlodipine, felodipine, lisinopril, perindopril, Skin cancer, BCC, melanoma, apocalypse.

### Introduction.

The issue of nitrosamines and their availability in a number of medicinal products is still far from a definitive solution or a solution for the benefit of the end users - the patients.

An avalanche of new data and scientific papers on the subject have been published, linking the intake of nitrosamine-contaminated medicinal products to the development of various cancers.

Recently, a worrying significant risk of developing brain tumours, neuroblastoma, and acute lymphoblastic leukaemia after intake of nitrosamine-contaminated drugs during pregnancy has also been identified [1].

Importantly, another newly published prospective observational study associated intake of nitrosamine-rich food with a significant risk of developing a particular form of cancer, namely rectal cancer [2].

The so-called "dietary component" currently remains an unclear factor in the development of skin cancer, and certainly plays an additional role in the body's nitrosamine load.

A new, "fresh meta-analysis" links/associates increased intake of nitrate, nitrite and nitroso compounds contaminated foods, drinking water, cigarette smoke, work environment and the indoor air again with the occurrence of gastrointestinal neoplasms [3].

The development of melanomas after intake of nitrosamine-contaminated sartans or sartans in combination with hydrochlorothiazide are not exceptions in this respect, but on the contrary confirm the thesis of the role of nitrosogenesis in the development of melanomas [4-6].



The association between intake of nitrosamine-contaminated antihypertensive drugs from the ACE inhibitor group and the development of keratinocytic cancer and/or keratinocytic cancers in combination with melanoma precursor lesions appears to be similar to completely analogous [7,8].

We present 4 cases of patients with keratinocytic tumors occurring concomitantly or in parallel with melanoma precursors (dysplastic nevus) within the context of the intake of various antihypertensive drugs actually/potentially contaminated with nitrosamines.

For the first time, keratinocytic cancers occurring after, during, or within the intake of beta blockers (bisoprolol/ metoprolol) and calcium channel blockers (amlodipine/ felodipine) are presented in the world literature: two new classes of drugs for which nitroso contamination is known but has never been thematized towards drug side effects and skin cancer [9-11].

The nitrosogenesis of skin cancer appears to be, in effect, a key new, so far unexplored element of its pathogenesis, however unpleasant this may sound to regulators in the face of the EMA and FDA.

#### Case 1.

We report an 85-year-old patient who visited the dermatologic surgery outpatient clinic for a complaint of a bleeding skin neoplasm localized 2 cm below the medial orbital angle (Figure 1a). The lesion was no more than 2 years old. On dermatologic examination, a tumor-like, rounded lesion, approximately 1.4 cm in diameter, partially pigmented, with central necrosis, clinically and dermatoscopically suggestive of basal cell carcinoma was observed (Figure 1a).



**Figure 1.** 1a: Drug-induced basal cell carcinoma (Bisoprolol/ Lisinopril) in the area under the left eyelid and immediately above the nasolabial fold.

1b: Oval excision of the tumor.

1c & 1d: Conduction of an island flap to cover the resulting defect.

The patient's known comorbidities included: arterial hypertension and heart failure since 2010; diabetes mellitus since 2010; gout; and benign prostatic hyperplasia.

Patient's concomitant medications include: Colchicine 0.5 mg -one tablet every 12 hours; Bisoprolol fumarate 5 mg half tablet in the morning (from 2015 to present); Torasemide 10 mg- 1 tablet in the morning from 2014 ; Lisinopril 10 mg- 1 tablet in the morning/ from 2020 to 2023; clopidogrel 75 mg- 1 tablet in the morning from 2019; solifenacin succinate/ tamsulosin 6/ 0, 4 mg - once daily from 2021/3; atorvastatin 10 mg once daily from 2013; isosorbide mononitrate 20 mg once in the evening from 2011, human insulin 100 IU/ml - 8E in the morning and 4E in the evening.

A cardiology consultation was conducted to change medication, and bisoprolol 5 mg and lisinopril were stopped, with amlodipine 5 mg prescribed if needed.

Clopidogrel was stopped preoperatively and switched to nadroparin calcium for 4 days, and nadroparin was not administered on the day of surgery. Surgical removal of the tumor under local anesthesia was performed as follows: the primary was initially excised as an oval excision (Figure 1b), and the defect was closed by island plasty (Figures 1c-d). The postoperative course was without complications. Histological findings were suggestive of nodular type basal cell carcinoma with tumor size less than 2cm and central ulceration of 1 to 2mm. Screening showed no evidence of metastasis. The patient was referred to the regional cancer hospital for follow-up.

Medication with bisoprolol and lisinopril was stopped during the inpatient stay. The case could also be considered as the first case of basal cell carcinoma after taking a potentially nitrosamine-contaminated beta blocker, bisoprolol (Both drugs are in the group of drugs declared by regulatory authorities or potentially nitrosamine-contaminated ones).

#### Case 2.

We report a 74-year-old female patient with a history of complaints of approximately two years in the form of a rapidly growing tumor localized in the medial orbit. Dermatological examination revealed a nodular lesion elevated above the skin level, measuring 1.7 cm by 1.6 cm, circular in shape and indistinct from the surrounding tissue, suggestive of nodular basal cell carcinoma (Figure 2a).

The patient's known comorbidities were arterial hypertension in 2013, status post partial cervical resection in 2016 , status post laparoscopic cholecystectomy in 2021, Hashimoto's thyroiditis.

Patient's concomitant medications include: euthyrox 75 micrograms once daily; hydrochlorothiazide 25 mg - ½ tablet daily in the morning / since 2015; felodipine 5 mg once daily, in the morning / since 2018.

Surgical excision of the tumor was performed (2b), and the defect was closed using an island flap (2c-d). Smooth postoperative period, no complications occurred. Histopathological findings were suggestive of nodular basal cell carcinoma with tumor size of less than 2 cm, clean resection lines/ histology: A well-demarcated dermally located epithelial lesion represented by orthohyperkeratosis, epidermal atrophy, proliferation of atypical basaloid keratinocytes forming heterogeneous nests and pseudofollicular structures with a palisaded periphery,

demarcated by a retraction phenomenon, and fibrinous, well-vascularized stroma. Perineural and lymphovascular infiltration is absent. Clean resection lines.



**Figure 2.** *2a:* Drug-induced (Hydrochlorothiazide/ Felodipine) basal cell carcinoma in the medial orbital angle. Toxic antihypertensive drug combinations containing nitrosamines.  
*2b:* Removal of the defect by oval excision.  
*2c:* Conduction of an island flap to cover the defect.  
*2d:* Postoperative photograph immediately after covering the defect by island flap.

No evidence of process dissemination within the staging. The patient was referred to the regional cancer hospital for follow-up.

In view of the difficult control of blood pressure values during the inpatient stay, a change of systemic treatment for the arterial hypertension to hydrochlorothiazide and felodipine (announced potential availability of nitrosamines as early as 2022) was recommended by the attending cardiologist in the outpatient setting.

### Case 3.

We report an 89-year-old female patient with complaints (according to history) of several months' duration in the form of tenderness and bleeding in the nasal area and left eyebrow (Figure 3a). Clinical and dermatoscopic attention during the dermatological examination focused on an endophytic

growing verruciform lesion localized in the apex of the nose (subsequently identified histologically as squamous cell carcinoma of the skin with intracellular keratinization, 3/2 mm in size and free resection margins of 5 and 2 mm) (Figure 3a). Lesion diameter of 1.3 cm, relatively clear demarcation from healthy tissue, hyperkeratotic surface, clinically suggestive of spinocellular carcinoma (Figure 3a).

A second lesion, exophytically growing, with a diameter of no more than 0.4 cm, bleeding and painful, suggestive of basal cell carcinoma (verified histopathologically postoperatively as nodular type basal cell carcinoma measuring 2 by 2 mm and free resection margins of 1.2 and 5 mm) was found in the nasal area again and adjacent to the medial orbital angle on the right (Figure 3a).

A third lesion was found above the left eyebrow-hyperkeratotic, dense in consistency, painful and bleeding, with a diameter of 1.5 to 0.7 cm (relative horizontal to vertical direction), (Figure 3a), suggestive of hyperkeratotic actinic keratosis/seborrheic keratosis (histopathologically verified postoperatively as seborrheic keratosis). A pigmented lesion, clinically and dermatoscopically suggestive of dysplastic melanocytic nevus, was found in the dorsal region (Figures 3f, 3f).

As comorbidities, the patient had arterial hypertension, gastritis, colitis, and ischemic heart disease.

The patient's current medications at the time of hospitalization included: amlodipine 5 mg/half a tablet per day, intake since 4 years; bisoprolol fumarate 2.5 mg-one per day, intake since 3 months; molsidomine 2 mg-intake since 6 years, one tablet per day; piracetam 1200 mg-one per day since 3 months; vinpocetine 10 mg-one per day since 6 years.

The lesions above the left eyebrow and near the medial orbital angle on the right were removed by elliptical excisions, and the defects were covered by using single skin sutures (Figure 3b). The lesion at the apex nasi was excised in depth to the cartilage by means of oval excision. The defect was covered using a full thickness mesh graft with skin taken from the neck area (Figures 3b-d). A compression dressing was made with sterile compression, fixed with diametrically placed sutures (left intraoperatively deliberately longer for the purpose) to better fix the graft and avoid possible hematoma (Figures 3b). The patient refused excision of the dysplastic nevus in the dorsal area.

Due to the potential availability of nitrosamines officially announced by the regulatory authorities for the two drugs (bisoprolol, amlodipine), it was recommended that in the outpatient setting the medication should be substituted after assessment by a cardiologist.

### Case 4.

We report a 62-year-old patient with complaints of approximately one year's duration, localized in the right temporal area as a raised neoplasm above the skin level with a diameter of 0.6 cm, central necrosis, and a pearly rim, suggestive clinically and dermatoscopically of basal cell carcinoma (Figure 4a).

The patient's known comorbidities included dyslipidemia, hypertensive heart with congestive heart failure, tricuspid insufficiency, hypercholesterolemia, aorto-coronary bypass graft, hypertensive heart disease/grade III, left ventricular



**Figure 3.** **3a:** Drug-induced (Amlodipine/ Bisoprolol) basal cell carcinoma of the nose and spinocellular carcinoma of the nose after amlodipine and bisoprolol administration. Nitrosamine contamination in Amlodipine and Bisoprolol as substantial skin cancer trigger.  
**3b:** Postoperative findings after skin grafting in the form of full thickness mesh graft from the neck to the tip of the nose. There were 2 elliptical excisions of the tumors above the eyebrow and to the right of the dorsum of the nose.  
**3c/d:** Free skin graft from the neck and its subsequent adaptation in the nasal area. Closure of the neck defect using single skin sutures.  
**3e/ 3f:** Drug-induced dysplastic nevus in the dorsal area after Amlodipine and Bisoprolol administration. Nitrosamine contain in commonly prescribed antihypertensive medication seems to have a key role in the pathogenesis or Skin cancer and skin cancer precursor lesions.



**Figure 4.** **4a:** Drug-induced (Metoprolol/ Perindopril/ Candesartan) basal cell carcinoma localized in the right temporal region. Nitrosamine contamination in beta blockers seems to have the same procarcinogenic effect as Perindopril and Candesartan preparations.  
**4b:** Preoperative marking of the resection lines.  
**4c:** Postoperative findings after successful surgical excision.

diastolic dysfunction, and status post mitral valve annuloplasty (performed for prolapse and high-grade mitral insufficiency in 2019).

Concomitant medication within the hospitalization included: metoprolol 25 mg once daily in the morning from 2009 to present; perindopril arginine 5 mg once daily for the period between 2009-2019, subsequently replaced by candesartan cilexetil 16 mg once daily to present; acetylsalicylic acid 100 mg once daily in the evening from 2009; rosuvastatin 10 mg once daily in the evening (from 2019).

Surgical elliptical excision of the tumor under local anesthesia was performed. The defect was closed using single skin sutures (Figures 4b-c). The histological finding was suggestive of basal cell carcinoma, stage 1. The postoperative period was uneventful.

Outpatient drug switch with candesartan and metoprolol was recommended by the supervising cardiologist after benefit/risk assessment.

The case could be considered as indicative of a first case related to the development of basal cell carcinoma occurring after the combined administration of a potentially nitrosamine-contaminated beta blocker (metoprolol), an ACE inhibitor (perindopril) and subsequent replacement of the ACE inhibitor with SARTAN (Candesartan).

### Discussion.

The presentation of this scientific work aims to focus the attention of clinicians on the role of nitrosogenesis in the development of keratinocytic/melanocytic skin cancer.

A case of basal cell carcinoma of the face occurring after combined administration of bisoprolol and lisinopril (patient 1) is also presented for the first time in the world literature, commenting on the influence of the nitroso component in both drugs on the potential generation of a malignant cell clone.

The mechanism of development of cutaneous tumours after amlodipine and felodipine should be similar.

The problems with the mutagenic/clastogenic action of nitroso derivatives formed within the *in vitro* reaction of beta blockers with sodium nitrite have been known not since today or yesterday, but since as far back as 1994 [12]. The clastogenic/mutagenic activity of N-nitroso derivatives of 5 beta adrenergic blocking drugs was then demonstrated in partially hepatectomized rats, finding that: all 5 N-nitroso derivatives of beta blockers induced a statistically significant increase in the frequency of hepatocyte micronuclei, the mutagenic action of NO-propranolol, NO-metoprolol and NO-nadolol being slightly stronger than that of NO-atenolol and NO-sotalol [12].

Within the two models tracking the mutagenic effect (after administration/application) of different doses of nitrosode derivatives in beta blockers (*in vivo/in vitro*), it was found that the clastogenic/mutagenic effect was also present in the *in vitro* experiments: it was definitely stronger than that in the *in vivo* ones conducted [12].

Consideration must also be given to the fact that there are significant differences in the calculation/estimation of *in vivo* mutagenic effects in experimental animals and human subjects who are not /or have been subjected to randomization within

some studies relative to the prospective/retrospective follow-up model (our submitted 4 patients), namely: In retrospective/prospective follow-up and subsequent analysis of patients (such as the 4 cases or part of them we presented), contamination of concomitant medication with nitrosamines or their derivatives is taken into account. On the other hand, we also follow the cumulative total potential/actual mutagenic effect of the concomitant medication over the years, which is essential for the generation of a malignant cell clone or a given cancer form.

These factors have not been calculated in comparative analyses of the clastogenic effects (*in vivo/in vitro*) of nitrosopyridine in beta blockers described in the past [12]. Nevertheless, both phases of the experiment do not reject but confirm the thesis that a clastogenic/mutagenic effect is present: both *in vivo* and *in vitro* [12].

Would it be reasonable to assume that the effect of bisoprolol taken by our patient would be similar to analogous, to that described in the shared data (patient 1) [12]? Especially when combined and with the intake of another class of drugs, the so-called ACE inhibitors, lisinopril, also catalogued as actually/potentially contaminated [13].

Monomedication with ACE inhibitors has in turn been described as risky in terms of generating keratinocytic cancers due to its potential/actual contamination with nitrosamines [7,8].

This medication has also been shown to be risky with respect to the development of keratinocytic cancers such as basal cell carcinoma of the skin in combination with melanoma precursors- dysplastic nevi [14].

Regarding the presented patient number 2 and the intake of hydrochlorothiazide and felodipine, the following could be mentioned: hydrochlorothiazide has a photosensitizing effect, which according to the latest literature data suggests or predisposes patients taking it to keratinocytic but also melanocytic skin cancer [15].

However, should not precisely "this one-sided interpretation [15]" of its action shift the focus away from the role of nitrosamines in thiazide diuretics as an additional, if not even more potent, inducer of the development of keratinocytic but also melanocytic skin tumors? Because precisely:

1) hydrochlorothiazide or certain batches of it have been withdrawn from the market due to elevated doses of nitrosamines [16].

2) the data on nitrosation of hydrochlorothiazide have been known since as far back as 1977 [17] but have been studiously ignored until now.

3) there are dozens of publications that "suggest" that the clastogenic/mutagenic action of the nitrosamines in hydrochlorothiazide is present and quite real with respect to the development of diverse cancers (not just skin cancer) [5,18-21].

Even this interpretation of the data/facts alone points clinical thought in the direction of a strong general pro-carcinogenic effect (based on the presence of carcinogenic impurities in the drug) and against the thesis/hypothesis of a "one of a kind" photosensitizing effect and subsequent development of skin cancer [18-21]. Recent follow-up studies in the literature have associated specifically hydrochlorothiazide monomedication (high cumulative daily dose/daily intake) with a significant

association in terms of generating the most common forms of skin cancer seen by clinicians: basal cell carcinoma and squamous cell carcinoma [22]. Future analyses should in all likelihood also focus on the aforementioned nitrosamine issue, rather than "disregarding" and ignoring it as a topic for discussion and subsequent detailed analysis. Otherwise, we risk facing the wave of side effects again, this time also caused by monomedication with hydrochlorothiazide.

The synergistic additive mutagenic effect (due to reported nitrosocontamination and of combination preparations containing calcium antagonists as well) of the addition of felodipine medication over time probably does not require detailed analysis. The role of calcium antagonists in relation to skin cancer nitrosogenesis will be discussed in more detail in patient number 3.

The third case we presented was of an elderly patient who developed 2 epithelial tumors in the facial area (Figure 3), as well as a dysplastic nevus in the back (Figure 3). The lesions occurred after 4 years of taking amlodipine, and a beta blocker was taken additionally- bisoprolol fumarate for the last months before the hospitalization (case 3). Starting from 1) official bulletins/data on possible potential contamination also of calcium antagonists with nitrosamines (nitroso-amlodipine) [22], and 2) the recall of batches of nitrosamine-contaminated combination antihypertensive drugs, containing amlodipine and sartans [23], the hypothesis/thesis of possible contamination of monomedication with amlodipine or analogues of the same drug group could also be expressed. This should be prioritized as a future follow-up and goal.

Preliminary, as yet unpublished (our) data on side effects are indicative of just such a relationship. The clinical manifestation of these 4 tumor lesions does not exclude the potential/actual mutagenic influence of a beta-blocker or N-Nitroso-Bisoprolol taken in parallel, albeit for a short period [24].

Supporting these claims are a number of other clinical observations reported over the years as publications in the world literature such as : 1) the development of basal cell carcinoma and dysplastic nevus after systemic administration of valsartan in combination with hydrochlorothiazide [25]. 2) the development of basal cell carcinoma and dysplastic nevus after starting treatment again with valsartan and bisoprolol [26]. 3) the occurrence of melanoma of the heel in combination with 3 verrucous carcinomas within the intake of valsartan and olmesartan, as well as a short-term intake of the amlodipine/valsartan combination, subsequently eliminated from the drug market because of nitrosamine contamination above the permissible daily limits [27], development of basal cell carcinoma and dysplastic nevi after a potentially nitrosamine-contaminated ACE inhibitor-ramipiril [28].

What all of the above and previously published data have in common is : 1) the development of similar to completely identical clinical combinations of keratinocytic cancers in combination with melanomas or melanoma precursor lesions, and 2 ) the development of these combinations following administration of radically different classes of drugs that have been declared as potentially/actually nitrosamine contaminated.

And for those who have difficulty understanding "pathogenetic relationships", the following anecdote could be shared: "If a

young and beautiful lady walks in 4 different city/suburban parks and is "attacked each time", then in all likelihood the attacks are not determined by the parks, the alleys, the flowers, the weather, or the atmospheric pressure (as well as random association/sporadicity)-they would be determined by a common, unifying factor, and that could be one party: 1) either the lady's challenging attire/behavior, or 2) someone following her to all four parks. " Similar is the case with the presence of nitrosamines (in the park) and the pattern of manifestation of skin tumours (in the lady).

Interesting how and why, but these data of ours overlap completely with the statistics of Beatrice Nardone's data from 2017, which remain enigmatic and up to date at the moment-namely that: the risk of developing basal cell carcinomas, spinocellular carcinomas and cutaneous melanomas is present after taking all three classes of drugs: ACE inhibitors, ARB blockers-Sartans and HCT- Hydrochlorothiazide [29]. It should not be overlooked that batches of all three classes of the mentioned groups of drugs have been declared as potentially/actually contaminated and withdrawn from the market due to elevated concentrations of nitrosamines above the permissible levels. However, the same pattern of manifestation of skin tumours after taking amlodipine can be added to these groups of drugs. Which in turn would be a logical rationale for amlodipine monomedication (but also felodipine case 2) to be checked for nitrosamine contamination and new batches of medication withdrawn from the market! The difference in these cases is that the starting point is back to front- namely: the clinical picture, from which conclusions are drawn about the potential contamination of the currently or formerly administered medications. And this in turn is a good reason for checking previously unpublicised and in all likelihood nitrosamine-contaminated medications.

Absolutely analogous and completely overlapping considerations are the development of skin tumors and their precursor forms after the administration of beta blockers contaminated with nitrosamines described in patient number 1, for example, as well as after the administration of ACE inhibitors [7,8].

In the fourth patient we described who developed basal cell carcinoma, his medication included metoprolol for a total of 14 years in combination with perindopril for 10 years. Perindopril was subsequently replaced by candesartan for a period of 4 years - until the time of hospitalization (see exact data for patient 4). The availability of nitrosamines has been reported and described in the literature for each of the drug classes described.

Large-scale studies from the recent past have found (analogous to the case presented) a significantly significant association between monomedication with ACE inhibitors and Sartans with the development of basal cell carcinomas (more than twofold increased risk for both classes of drugs) [29]. These significant associations have been confirmed in recently published analyses regarding the role of ACE inhibitors in the development of keratinocytic cancer [30]. However, it is a great pity that both publications do not find what the likely cause of these relationships might be [29,30], in contrast to the very well presented new and detailed data published recently [31], it is these that etablate the role of nitrosamines in ACE inhibitors

in relation to keratinocyte cancer development [8,31], but not only [8].

Sartans in general, and eprosartan (contaminated with nitrosamines) in particular, are similarly associated with the development of keratinocytic cancer [29,32].

The indifferent, somewhat "gentlemanly role" of regulatory entities with respect to the regulation and elimination of carcinogenic substances in pharmaceuticals certainly does not contribute to the elucidation of ubiquitous nitrosamine contamination nor to the containment of the cancer pandemic [33].

Conducting certain mutation tests in the form of the so-called AMES Test (but not only) in order to prove their mutagenic/carcinogenic effect (OF NITROSAMINS), the subsequent accurate identification/elimination from the "drug menu" of patients, should be a priority [34].

Because "permissive availability" allows cancer to occur in practice, it does not restrict it. It only distances it in terms of time relative to the intake of the relevant amount of carcinogen. And this amount is not constant and can be increased from 20 to 200 times—a fact that turns out, however, to be unregulatable. Similar to the manifestation of skin cancer.

### Conclusions.

The contributions of the presented scientific work consist mainly in the formalization of two completely new classes of drugs: beta blockers (bisoprolol, metoprolol) and calcium antagonists (amlodipine, felodipine), actually/potentially contaminated with nitrosamines and after whose administration the development of keratinocytic skin tumors or keratinocytic tumors in combination with precursor lesions of melanoma (dysplastic nevi) is observed.

For the first time, the role of a new potentially nitrosamine-contaminated ACE inhibitor, lisinopril, in skin cancer/keratinocytic cancer nitrosogenesis is described and commented upon, as is that of candesartan.

Considering that candesartan has been described in the literature as a generator of multiple melanomas and dysplastic nevi [6], its actual role in practice represents: an overlap of its pro-carcinogenic effect in the direction of keratinocytic cancer as well. This combination has been described by us repeatedly with respect to other classes of contaminated drugs.

Clinical patterns of manifestation in the form of the same combinations of cutaneous tumors could be considered as indicative or at least suggestive of their possible common pathogenesis.

The commonality in all the described classes of drugs could be only one: the presence of the same unifying component known as NITROSAMINE.

The nitrosogenesis of skin cancer opens doors that lead to unraveling the puzzle of carcinogenesis worldwide.

A carcinogenesis that is opening a business for billions and a carcinogenesis that is costing human lives or put another way: Apocalypse now!.

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