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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 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.

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No 11 (344) 2023

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MELANOMA AND DYSPLASTIC NEVI DEVELOPMENT AFTER RANITIDINE/ RILMENIDINE/MOXONIDINE, LERCANIDIPINE, ROSUVASTATIN AND VERAPAMIL/ TRANDOLAPRIL- NEW DATA/CASE SERIES. THE POTENTIAL ROLE OF NITROSAMINE/ NDSRIS CONTAMINATION IN POLYMEDICATION AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR

Georgi Tchernev[1,2], Naydekova N[2].

[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.

The idea of drug-induced/exogenic Nitrosogenesis is driven by the possibility of prolonged exposure of the human body to the influence of nitrosamines within the drug intake – substances or contaminants that have been proven to be carcinogenic or mutagenic one.

Until recently, there was a complete lack of data in the scientific literature on the relationship between cancer, polymedication and polycontamination with nitrosamines.

In the last decade, melanoma has been described repeatedly in the medical literature as a possible side-effect within the intake of possibly with nitrosamines contaminated medications such as: Valsartan, Hydrochlorothiazide, Amlodipine, Nebivolol, Bisoprolol and Perindopril.

However, the contribution of the currently presented new data (5 new patients) is also due to the establishment of the possible pathogenetic role (with respect to melanoma) of several completely new drugs, previously unknown to the scientific community (potentially/actually contaminated with carcinogens/nitrosamines), such as: Ranitidine, Rosuvastatin, Lercanidipine, Rilmenidine, Trandolapril, Moxonidine and Verapamil.

The leading and connecting link in shared new and old drug combinations of heterogeneous drug classes (polymedication) and melanoma development and progression remains again one and the same : the possible availability of nitroso component in the frame of exogenous nitrosogenesis according to the official FDA lists of 2023.

The number of drugs shared as contaminated with nitrosamines after whose intake melanomas occur is increasing.

Nitrosogenesis remains a new beginning, a new understanding and new interpretation of the carcinogenesis concerning melanoma, but probably also of cancer in general. Its further elucidation looks more than promising and is yet to come. More than worrying at the moment remains the fact that the scientific community has to clarify if : 1) peak concentrations of nitrosamines or NDSRIs within the framework of monomedication or 2) normal concentrations within the polymedication (catalogued in the list of FDA/ 2023 as potentially contaminated with hypothetical carcinogens), could hide relatively short-term risk of the development of real tumors: cutaneous melanomas and/or their precursor lesions.

The validation of the concept of Nitrosogenesis and its relationship to Carcinogenesis, is achieved in practice on the basis of the following facts: that it is the occurrence of the same monomorphic clinical pattern (melanoma/dysplastic nevi) , developing after the intake of drugs with different mechanism of action, contaminated with nitrosamines / NDSRIs. The unifying link between the intake of certain drugs and the development of certain tumours remains the presence of nitrosamines. Ingredients that are present in drug preparations, identified as availability and as carcinogenic potency, but not yet reflected in packaging or prescriptions. The question remains: why?

Key words. Nitrosogenesis, nitrosamines, NDSRIs, melanoma, dysplastic nevi, ranitidine, rosuvastatin, lercanidipine, rilmenidine, verapamil, trandolapril, hydrochlorothiazide, nebivolol, bisoprolol, amlodipine, valsartan, perindopril, polymedication, polycontamination.

Introduction.

According to a number of clinical observations, nitrosogenesis is a novel concept underlying the generation of cutaneous tumors, at least as a nonnegligible co-factor [1,2]. This concept or new model of interpretation concerns keratinocytic tumors as well as dysplastic nevi and melanoma in particular [3].

The FDA published in 2019 in its official bulletin all sartans that could be actually/potentially contaminated with nitrosamines/ NDSRIs [4].

By 2023, other drugs potentially/actually contaminated with nitrosamines of various classes are already on the FDA list - including ACE inhibitors Perindopril, Trandolapril/, beta blockers/Nebivolol, Bisoprolol/, calcium antagonists/ Amlodipine/thiazide diuretics/Hydrochlorothiazide and Ranitidine [5,6].

It sounds logical that the combined intake of several drugs contaminated with nitrosamines would correlate with the occurrence of multiple or `more severe' melanocytic tumors as pathology, regardless of the class of drugs in which the contaminants are found [3].

Not infrequently, however, monomedication can also lead to the concomitant development of cutaneous melanomas and/or their precursors [7]. In these cases, it is important to ascertain whether polycontamination with nitrosamines or monocontamination with peak concentrations is actually present: conditions previously uncommented upon.

Polymorbidity and polycontamination are now also clinically reported to be among the most significant triggers for the development and progression of cutaneous tumors, including melanomas [3].

In the context of the availability of nitrosamines as modulators of Nitrosogenesis/Carcinogenesis, we present 5 cases that demonstrate the real possibility of melanoma and/or dysplastic nevus development within the context of intake of potentially contaminated drugs from the sartans group, ACE inhibitors, beta blockers, calcium antagonists/ Verapamil, thiazide diuretics, centrally acting sympatholytics/ Moxonidine, Rosuvastatin and Ranitidine.

We describe once again the association between polycontamination with nitrosamines/NDSRIs/genome modifiers within polymedication and polymorbidity leading to the development of dysplastic nevi and cutaneous melanomas.

Case Series.

Case 1.

A 52-year-old patient reports the presence of two nevi in the abdominal area that he noticed about 10-15 years ago. The reason for his visit to the dermatology and dermatologic surgery outpatient clinic is that he has observed a change in size as well as intermittent bleeding from the lesion under his right mamilla for the past 1 year.

He reported arterial hypertension as comorbidities dating back to 2021 and started systemic therapy with Amlodipine 2x5mg; Moxonidine 1x0.2mg; Hydrochlorothiazide ½ tab. of 25mg for a total period of 2 years. From 01.04.2023 the previous therapy was changed to Valsartan 1x160mg, Rilmenidine 1x1mg and Hydrochlorothiazide ½ tab. of 25mg every other day, for a period of 8 months to date.

In childhood/youth he was treated long term with Ranitidine for gastritis and duodenal ulcer.

The dermatological status revealed an asymmetric lesion with irregular borders about 3.a 1.2 cm in size, with irregular dark pigmentation and elevation on palpation in the area below the right mamilla (Figure 1a). The lesion described was suggestive of cutaneous melanoma. In the area under the left mamilla, a lesion with a rounded shape and apparently clear borders, about 0.5 cm in size but with irregular pigmentation, was seen, which was suggestive of dysplastic nevus (Figure 2a).

An elliptical excision with an operative margin of 0.3cm in all directions was performed on the lesion suggestive of melanoma (Figure 1b) and an elliptical excision with an operative margin of 0.2cm was performed on the lesion suggestive of dysplastic nevus (Figure 2b). Histological verification showed: superficial spreading melanoma (Clark 3; Breslow 0.79mm) and a dysplastic nevus. Clean resection lines. Melanoma re-excision was followed by 1cm field of surgical certainty in all directions, histologically verified clean resection lines (Figure 1d).

A CT scan of the head, chest, abdomen, and pelvis with contrast was performed and showed -no evidence of metastatic spread. The staging was T1aN0M0. The patient was referred to the regional cancer clinic for follow-up.

Case 2.

A 71-year-old female patient in severe general condition was admitted to the outpatient dermatology and dermatologic surgery clinic for a tumor in the symphysis area. She first noticed a dark protrusion about 2 years ago (2021), which slowly grew to the size of a child's fist (6 by 3.5 cm), bled spontaneously,

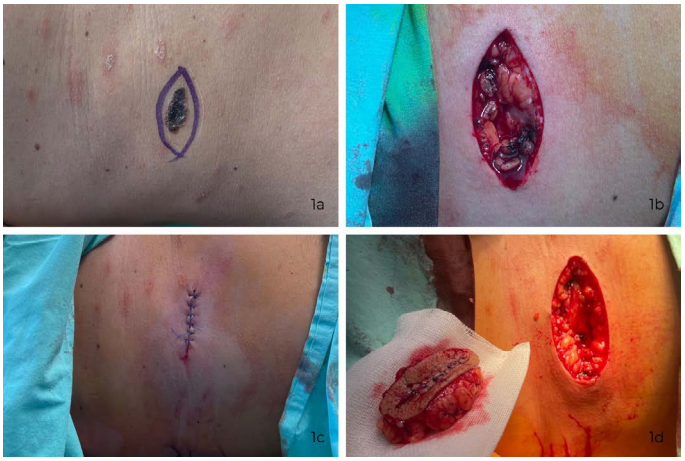

Figure 1. 1a: *Asymmetric lesion with uneven borders about 3 cm in size, with irregular dark pigmentation and elevation on palpation in the area under the right mamilla, suggestive of cutaneous melanoma.* ***1b:*** *Elliptical excision of the lesion with an operative margin of 0.3cm in all directions.* ***1c:*** *Postoperative image after the first excision.* ***1d:*** *Melanoma re-excision with 1cm operative margin in all directions.*

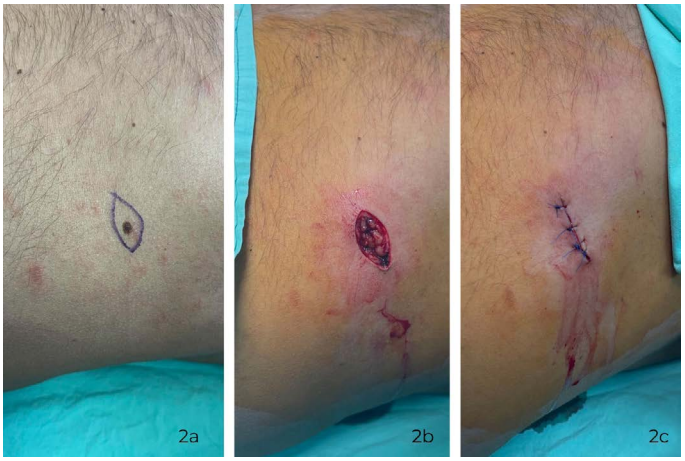

Figure 2. 2a: *A lesion with a circular shape and apparently clear borders, about 0.5cm in size, but with irregular pigmentation that is suggestive of a dysplastic nevus.*
2b: *Elliptical excision of the lesion with an operative margin of 0.2cm in all directions.*
2c: *Postoperative finding.*

and was sensitive to touch. In parallel, during the last half year she reported general weakness, loss of appetite, nausea and vomiting, pain along the course of the spine with numbness of the upper limbs.

As co-morbidities, she reported arterial hypertension dating back to 2018, for which she has been taking Nebivolol/ Hydrochlorothiazide therapy 5mg/12.5mg once daily in combination with Lercanidipine hydrochloride 10mg twice daily for 5 years.

During the dermatological status, a pedunculated tumor-like formation in the pubic area with a diameter of 6 cm by 3.5 cm and a tendency of spontaneous bleeding, with a smooth surface but irregular pigmentation was found (Figures 3a-b).

CT of the abdomen and pelvis was performed, and the process was shown to disseminate into the lung, liver and vertebrae. Treatment of the giant melanoma formation was planned with

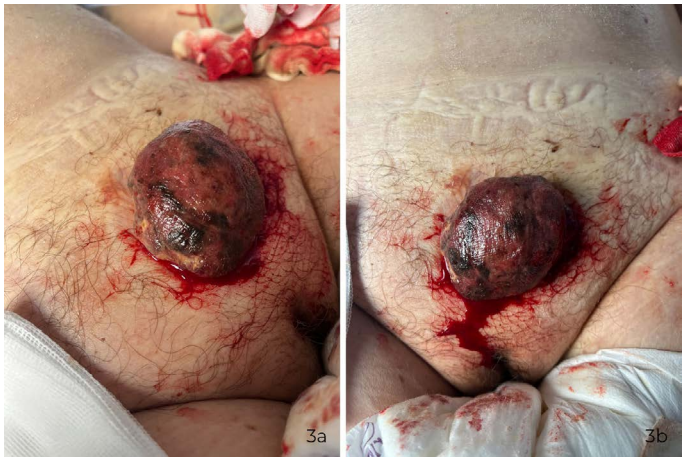

Figure 3. 3a-b: *Pedunculated giant cell melanoma, measuring 6/3.5cm, with irregular pigmentation and spontaneous bleeding.*

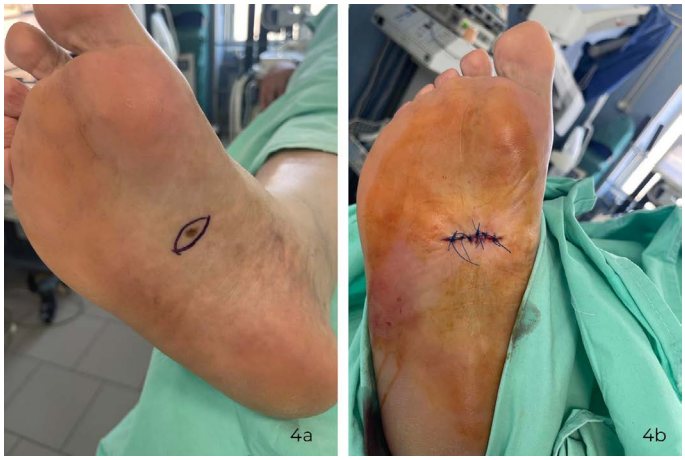

Figure 4. 4a: *Pigmented macule with irregular shape and indistinct borders, about 1cm in size, clinically and dermatoscopically suggestive of dysplastic nevus.*
4b: *Postoperative photograph after elliptical excision of the lesion.*

near-field of surgical security, BRAF testing and initiation of targeted therapy.

Case 3.

A 74-year-old male patient visits the dermatology and dermatologic surgery outpatient clinic for a slow-growing pigmented spot on his right foot that he first noticed about 10 years ago.

As a co-morbidity, he had a known history of arterial hypertension of about 26 years duration. He has been taking antihypertensive therapy for 25 years to date Nebivolol 2x5mg, Zofenopril 2x30mg, Spironolactone ½ tab of 50mg and Rosuvastatin 1x20mg.

During the dermatological status, a solitary macule with irregular shape and pigmentation, with indistinct borders and a size of about 1cm, clinically and dermatoscopically suggestive of dysplastic nevus, was found in the area of the right foot - (Figure 4a).

The lesion was removed by elliptical excision with a surgical margin of 0.3cm in all directions, and the material was sent for histological examination, which verified a borderline lentiginous nevus (Figure 4b).

Case 4.

A 61-year-old male patient visits the dermatology and dermatologic surgery outpatient clinic for a slow-growing formation on his left forearm that he first noticed 8 months ago.

He reported arterial hypertension and psoriasis vulgaris as comorbidities. He started systemic therapy in 2005 with Perindopril/Amlodipine 5mg/5mg, which he took for about 2 months. He then switched to therapy with Verapamil/ Trandolapril 2x180mg/2mg for a period of 18 years, which he still takes today.

From the dermatological status, a solitary, pedunculated, epidermal nodular formation with a depressed surface and pale pink colour, 1x1cm in size, suggestive of fibroma, was noted in the left axilla. Additionally, three nevi of 0.7- 1.1 cm in size, with heterogeneous pigmentation, irregular shape, and indistinct margins, suggestive of dysplastic nevi, were observed in the dorsal region (Figure 5b).

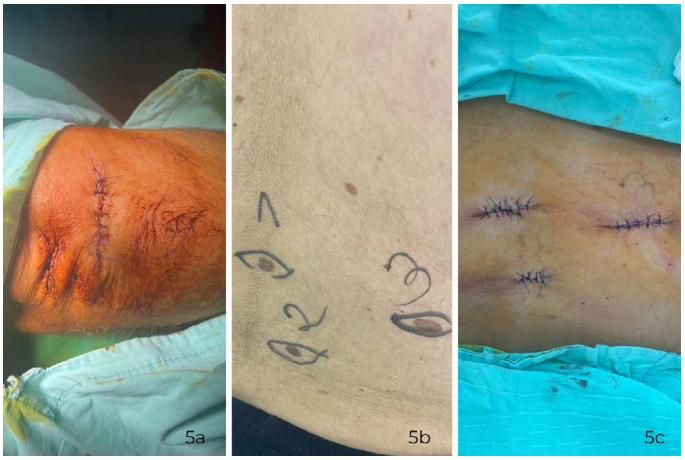

Figure 5. 5a: *Postoperative photograph after elliptical excision of a tumor lesion in the left axilla, suggestive of keratinocytic tumor.*
5b: *3 nevi on the back, 0.7-1.1 cm in size, with heterogeneous pigmentation, irregular shape, and indistinct margins, clinically and dermatoscopically suggestive of dysplastic nevi.*
5c: *Postoperative photograph after elliptical excisions of the three nevi.*

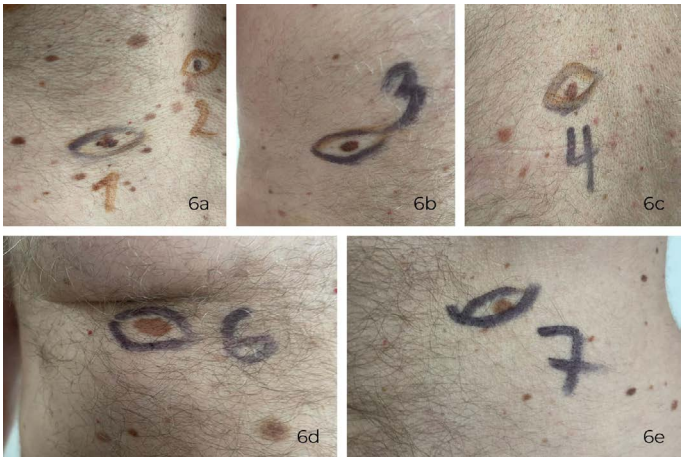

Figure 6. 6a-e: *Nevi on the patient's trunk with irregular shape, indistinct borders, and heterogeneous pigmentation, suggestive of dysplastic nevi.*

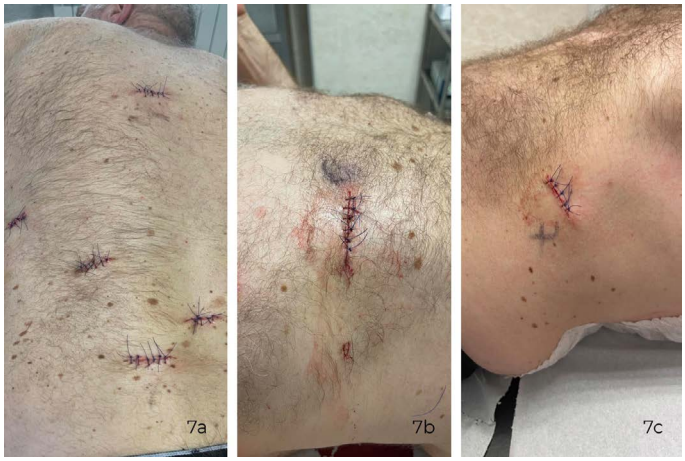

Figure 7. 7a- c: *Postoperative images after elliptical excision of the lesions.*

Four elliptical excisions were performed under local anesthesia (Figures 5a,5c). The materials were sent for histological verification, which showed that the nodular formation in the right forearm area histologically corresponded to a verruca with hyperkeratosis, nevus 1 corresponded to a dermal nevus with low-grade dysplasia, and nevi 2 and 3 corresponded to a dermal nevus with high-grade dysplasia.

Case 5.

A 63-year-old patient went to the dermatology and dermatologic surgery outpatient clinic for examination of moles he has had for nearly 30 years but has noticed changes in the color and size of some of them in the past 1-2 years.

He has arterial hypertension as a comorbid condition for which he has been taking Bisoprolol 1x5mg for 10 years.

During dermatological status, multiple nevi were found on the patient's torso. There were several irregularly shaped nevi with indistinct borders and heterogeneous pigmentation, suggestive of dysplastic nevi (Figures 6a-e).

Seven elliptical excisions were performed under local anesthesia (Figures 7a-c). Histological verification of the materials followed, the result of which showed: 1 seborrheic keratosis, 5 mixed melanocytic nevi with a marked degree of architectural and cytological dysplasia, and 1 mixed melanocytic nevus with a mild degree of architectural and cytological atypia.

Discussion.

The common feature between the presented cases is the intake of a heterogeneous class of drugs and the appearance of identical tumours or their precursors in the face of dysplastic moles and melanoma, which developed after a relatively similar period of drug intake. What has been shared helps to further clarify the ″last mysteries″, while also representing a direct logical answer to the latter: ″Are heterogeneous classes of drugs (with radically different mechanisms of action) a key factor with respect to the development of a monomorphic clinical finding, such as melanoma and dysplastic nevi in this case ? Is there any evidence for the availability or identification of a single potential (or multiple but synergistically acting), real or hypothetical inducer/contaminant that appears to be common to all classes of melanoma or cancer initiating drugs in general ? The answer is : Yes and that might be the nitrosamines.

The expert opinion on this was given in 2018 and reaffirmed in 2023 in the official FDA bulletins. It confirms the presence of carcinogens/mutagens/nitrosamines in Valsartan [4], Hydrochlorothiazide [8], Ranitidine [6] and Amlodipine [5] taken by our first described patient . For this reason, it is the combined (or subsequent) intake of these drugs in the context of polycontamination with nitrosamines that should not be surprising for the development of cutaneous melanomas and dysplastic nevi. Nitroso-Moxonidine, again taken by patient 1, has also been described as being available as a nitroso-compound but is not yet indexed in the FDA list of potentially/ really contaminated preparations [5].

Monomedication with Valsartan has been described as a possible inducer of cutaneous melanoma due to its possible contamination with nitrosamines [9]. Valsartan in combination with Hydrochlorothiazide has similarly been described as a melanoma and prostate carcinoma inducer in the context of potential nitrosamine contamination [10].

The most recent follow-up studies from the United States are once again confirmatory regarding the use of Hydrochlorothiazide as a monomedication and the development of cutaneous melanomas [11].

The role of amlodipine as an ″additional contribution″ to the cumulative daily intake of mutagens in the context of polymedication has already been discussed in relation to nitrosogenesis and skin cancer in other scientific works [1,2].

Rilmenidine taken by patient 1 is currently available in various databases for the determination of nitroso compounds and as Nitroso-Rilmenidine but has not yet been catalogued in the FDA list [5]. Its combination with Valsartan and Hydrochlorothiazide in our described patient 1 could have a synergistic effect in the context of polycontamination with nitrosamines.

For the first time in the world literature, prolonged (according to the history) administration of Ranitidine in childhood due to gastritis and duodenal ulcer and the subsequent development of cutaneous melanoma and dysplastic nevi (patient 1), (albeit after several decades) is also commented.

Due to the lack of clarity regarding the duration of intake and dose of ranitidine, at present the interpretation of the data appears to be also somewhat - speculative, but not rejecting the role of Nitrosogenesis in regarding melanoma pathogenesis. Whether prolonged Ranitidine treatment is relevant to melanoma and dysplastic nevus (initial malignant cell clone) generation remains unclear. However, the initiating point for initial cutaneous melanoma and dysplastic nevus generation within the potential contamination of ranitidine with nitrosamines in adolescence/ childhood could be quite possible , if not pivotal. Several decades later and after initiation of additional combination therapy for arterial hypertension with Amlodipine and Hydrochlorothiazide for a period of 2 years, followed by a change in therapy to Valsartan, Rilmenidine, Hydrochlorothiazide for 8 months, a change in the shape and size of the pigmented lesions was observed. Proceeding from the high carcinogenic potency of Valsartan contamination according to the 2019 FDA list [4], it would be more than logical to observe a short-term change in the evolution of lesions.

For the first time, the role of ranitidine in melanoma and dysplastic nevus generation is thematized worldwide in the context of its potential contamination with nitrosamines. Also new in this case is the calcium antagonist Rilmenidine, which has not been catalogued in the FDA list so far, but after whose intake (combined) could be associated with the generation of dysplastic nevi and melanomas in the context of nitrosogenesis. Nitroso-Rilmenidine is probably under evaluation for cataloguing in the FDA list.

The de novo occurrence of pedunculated advanced giant cell melanoma after Hydrochlorothiazide administration was presented in patient 2 and is entirely and strongly confirmatory, analogous to American data concerning heterogeneous collectives linking Hydrochlorothiazide monomedication to the occurrence of cutaneous melanomas [11,12]. Unfortunately, these data again do not comment on potential or actual nitrosamine contamination, which does not, however, exclude it as a cofactor in the induction of cutaneous melanomas [2,3].

To this intake could be added the intake of the beta blocker Nebivolol, already described as potentially contaminated with nitrosamines according to the April 2023 FDA list [5]. Beta blockers but in combination with Valsartan, Amlodipine and Hydrochlorothiazide have also been recently described as possible inducers of multiple cutaneous melanomas and dysplastic nevi within the nitrosamine contamination [3].

The fact that Nitroso-Lercanidipine is a reality , not a myth, suggests that its cataloguing in the new FDA list update is also likely to be short-term [13].

The concomitant use of 2 drugs officially declared as contaminated in the FDA list, repeatedly formalized in the scientific literature as possible melanoma inducers (Nebivolol/ HCT), in combination with Lercanidipine (potentially formalized as possibly contaminated/ Nitroso-Lercanidipine), could be risky in terms of generation and progression of pedunculated melanoma in the patient we described (case 2). Three years after taking potentially/actually polycontaminated with nitrosamines drugs, the patient developed a de novo advanced , metastatic giant pedunculated melanoma.

Systemic medication with beta blockers (in patient 3) with Nebivolol , could be critically considered and would also classify him as potentially risky with respect to melanoma pathogenesis and Nitrosogenesis , similar to patient 2.

Rosuvastatin is the other potentially nitrosamine-contaminated drug existing as Nitroso-Rosuvastatin [14,15], not yet catalogued in the FDA list [5], but possibly playing a role in terms of the so-called cumulative carcinogen intake (within the polymedication polycontamination framework) and subsequent melanoma generation. For Spironolactone and Zofenopril taken concomitantly, data on nitrosocontamination and FDA list presence/cataloguing are currently lacking [5].

In Patient 4, we describe the occurrence of dysplastic nevi after a short-term initial intake of Perindopril and Amlodipine for 2 months (combined preparation), followed by an irregular, but prolonged intake of Verapamil/Trandolapril (combined preparation) for 18 years. The following should be emphasized: the development of dysplastic nevi after taking amlodipine in combination with Perindopril is not new to the academic community and has been described in the literature, although it is not always reflected in the title of some published articles [16]. The occurrence of melanoma after Perindopril intake is also not new , and this intake could condition the staged occurrence of keratinocytic tumor such as BCC additionally [17]. International data from the United States in the recent past associate the risk of cutaneous melanomas (and logically their precursors) with the intake of ACE inhibitors [12], and the same is associated with the risk of basal cell carcinomas : for melanomas- adjusted OR (95%CI): 1.71 (0.97-3.00), i.e. about 171% risk (similarly, part of this risk concerns melanoma precursors in the face of dysplastic nevi). Amlodipine and Perindopril have been on the FDA list since 2023 as potential carcinogens with potencies of 5/FDA table [5], respectively.

Patient 4's therapy was changed to Verapamil/Tranodolapril for a period of 18 years. And while Trandolapril is available on the FDA list as of 2023 for ″hypothetical″ carcinogen-contaminated drugs [5], nitroso-verapamil is also now a reality and its cataloguing on the (FDA list) is probably forthcoming [18,19].

This in practice makes the combined intake of 2 potentially/ actually nitrosamine-contaminated drugs (Verapamil/ Trandolapril) over the years quite feasible. Hence, accordingly, the occurrence of dysplastic nevi after their administration should not be puzzling in the least.

The fifth patient described in the publication had a history of multiple melanocytic nevi since childhood, clinically and dermatoscopically suggestive of dysplastic ones, with a median age of 30 years, as well as a change in some of them dating back no more than 2 years.

He had been taking Bisoprolol for 10 years, and Bisoprolol was catalogued by the FDA list for 4 potentially carcinogenic drugs [5].

A number of publications in the world literature have thematized the positive role of beta blockers in patients with melanomas [20-22], but the fact that this information remains at present somewhat one-sided interpreted, manipulative, and speculative, but should not be downplayed because of the following few circumstances: 1) these articles thematize the role of the active substance in relation to (already) pre-existing melanomas, 2) interpretation of the data, which is to some extent unclear, finds, however, that patients were taking beta-blockers before the tumour/melanoma occurred, and 3) no one comments on the actual or potential role of beta blockers and their available contaminants in the form of nitrosamines in the generation of melanomas within the pre-manifestation drug intake [1-3].

In practice, the interpretation of the shared literature data [20-22] could also be the following: patients who took a beta blocker (contaminated with nitrosamines) subsequently developed cutaneous melanomas whose progression remained temporally delayed due to the action of the pure, active ingredient.

Beta blockers remain melanoma generators according to these data [20-22], however, the main pathogenetic inducer has not been thematized in the works, and this is only happening in 2023 through the formalization of the FDA list for nitrosamine contamination of beta blockers [5].

The three publications in question came out after 2018, or the year of the FDA announcement of valsartan contamination. There remains the logical question, with a slightly ironic note: ″Do I (or somebody) want to take a beta blocker that is contaminated with nitrosamines and leads to the formation of melanoma whose progression will be probably slowed down ″afterwards″ by the active ingredient of the same drug?″

The purposeful absence or underreporting of this information in the international articles [20-22] is certainly unable to shift the focus away from the role of beta blockers (nitrosamine contaminated) in relation to melanoma generation [1-3], and it is these articles – [20-22] that are indicative and confirmatory of the thesis of the importance of nitrosogenesis/its pathogenetic role in melanomas [20-22].

No one disputes that it is likely that the active ingredient in certain collectives of patients is able to (probably) slow the progression of melanomas that have already arisen [20-22], but these tumors arose within the context of already available intake of beta blockers [20-22] actually or potentially contaminated with nitrosamines.

This is where the indirect contribution of these papers lies- they focus attention on beta blockers intake and melanoma development as a topic [20-22], from which the thesis of Nitrosogenesis of melanoma, caused by the previous intake of beta blockers, potentially/actually contaminated with nitrosamines, emerges again.

Once again, the development of ″real tumors/melanomas″ after combined intake of ″hypothetical carcinogens″ within the framework of polymedication and polymorbidity is presented.

The occurrence of melanoma precursor lesions and lentigo maligna after the administration of sartans and hydrochlorothiazide has recently been described in the dermatological literature, discussing the role of polycontamination with nitrosamines within the framework of the combined drug administration [23]. International groups of experts consider polymedication with a heterogeneous class of medication within the framework of polycontamination with nitrosamines as extremely risky, at that - in the short term [24].

Conclusions.

1. The paper and data are confirmatory in nature regarding the already known hypothetical contamination (real/potential) of thiazide diuretics (Hydrochlorothiazide), ACE inhibitors (Perindopril) and calcium antagonists (Amlodipine) with respect to Nitrosogenesis and cutaneous melanoma development according to FDA.

2. The data are again confirmatory with respect to Nebivolol and Bisoprolol and their possible association for melanoma generation within the polymedication and polycontamination.

3. For the first time in the world literature, the role of calcium antagonists: Nitroso-Lercanidipine and Nitroso-Rilmenidine within polymedication as possible candidates for inclusion in the list of FDA , concerning the available potential/actual contamination with nitrosamines/NDSRIs is thematized. And the subsequent development of cutaneous melanomas.

4. The same applies to the intake of Nitroso-Moxonidine, so far absent from the FDA list , but possibly a preparation that could be included soon.

5. The contribution of the data presented here is significant and extremely important, describing for the first time in the world literature: a link between the intake of Ranitidine and the development (subsequently) of cutaneous melanoma and dysplastic nevi (in the context of subsequent polymedication and polycontamination of the drugs/ or the so-called nitrosogenesis). Ranitidine is catalogued in the FDA list as a potentially contaminated drug with a carcinogenic potency between 1 and 3, which undoubtedly confirms the role of nitrosogenesis in the generation of melanomas.

6. Analogous to the data for ranitidine are those for Rosuvastatin intake, currently uncatalogued from the FDA list but available as Nitroso-Rosuvastatin. And after whose intake in the framework of polymedication (Nebivolol/ Zofenopril (?))/ polycontamination and polymorbidity, developed a melanoma precursor lesion.

7. Combined administration of the ACE inhibitor Trandolapril and the calcium antagonist Verapamil within the context of nitrosamine contamination should also be regarded as potentially risky and as an innovative new idea concerning melanoma pathogenesis. Trandolapril has been catalogued in the FDA list since 2023 and nitroso-verapamil is currently a reality, and not a virtual one.

REFERENCES

1. Tchernev G. Nitrosogenesis of skin cancer: the nitrosamine contamination in the calcium channel blockers (amlodipine), beta blockers (bisoprolol), sartans (valsartan/losartan), ace inhibitors (perindopril/enalapril), tricyclic antidepressants (melitracen), ssris (paroxetine), snris (venlafaxine) and metformin: the most probable explanation for the rising skin cancer incidence. Georgian Med News. 2023;339:24-32.

2. Tchernev G. The nitrosamine contamination in beta blockers (bisoprolol/metoprolol), ace inhibitors (lisinopril/perindopril), thiazides diuretics (hct), calcium channel blockers (amlodipine/ felodipine), sartans (candesartan) and тhe subsequent skin cancer development and progression: apocalypse now. Georgian Med News. 2023;337:138-145.

3. Tchernev G. Nitrosogenesis of cutaneous melanoma: simultaneously development of primary cutaneous thick melanoma of the breast, thin melanoma/dysplastic mole of the back during parallel intake of bisoprolol, amlodipine and valsartan/ hct: nitrosamine polycontamination in the multimedication as the most powerful skin cancer trigger. Georgian Med News. 2023;339:83-88.

4. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

5. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

6. https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

7. Tchernev G. Neighbouring melanomas and dysplastic nevus developing simultaneously after candesartan intake: nitrosamine contamination/ availability as main cause for skin cancer development and progression. Georgian Med News. 2023;336:104-107.

8. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/pfizer-voluntary-nationwide-recall-lots-accuretic-quinapril-hclhydrochlorothiazide-quinapril-and
9. Tchernev G, Temelkova I. Valsartan Induced Melanoma?! First Description in Medical Literature! Open Access Maced J Med Sci. 2018;6:2378-2380.
10. 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.
11. Azoulay L, St-Jean A, Dahl M, et al. Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multisite population-based cohort study. J Am Acad Dermatol. 2023;89:243-253.
12. Nardone B, Majewski S, Kim AS, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. Drug Saf. 2017;40:249-255.
13. https://veeprho.com/impurities/n-nitroso-lercanidipine/
14. https://www.simsonpharma.com/product/n-nitroso-rosuvastatin
15. https://www.clearsynth.com/CSEO02715-N-Nitroso-Rosuvastatin
16. Kordeva S, Batashki I, Batashki A, et al. Multiple nevi development after valsartan/ amlodipine: pathogenetic mediated relationship or pure coincidence? J Meditsinski pregled. 2021;57:58-59.
17. Tchernev G. A flavour of death: perindopril induced thick melanoma and bcc of the back. Potential role of the generic substance or/-and possible nitrosamine contamination as skin cancer key triggering factors. Georgian Med News. 2023;336:123-125.
18. https://veeprho.com/impurities/n-nitroso-verapamil-impurity-1/
19. https://www.simsonpharma.com/product/n-nitroso-verapamil-ep-impurity-j
20. De Giorgi V, Geppetti P, Lupi C, et al. The Role of β-Blockers in Melanoma. J Neuroimmune Pharmacol. 2020;15:17-26.
21. Wrobel LJ, Gayet-Ageron A, Le Gal FA. Effects of Beta-Blockers on Melanoma Microenvironment and Disease Survival in Human. Cancers (Basel). 2020;12:1094.
22. De Giorgi V, Grazzini M, Benemei S, et al. Propranolol for Off-label Treatment of Patients With Melanoma: Results From a Cohort Study. JAMA Oncol. 2018;4:e172908.
23. Tchernev G, Kandathil LJ, Oliveira N. Insights into the development of lentigo maligna and dysplastic nevi: Spotlight on the possible relation with sartans, thiazides and nitrosamines. Port J Dermatol and Venereol. 2022;80:235-240.
24. 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.