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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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NITROSOGENESIS, ANTIDEPRESSANTS AND THE SERTRALIN INDUCED NEVUS ASSOCIATED CUTANEOUS MELANOMA: THE NDMA/ NNK (NDSRIS) CONTAMINATION AS MOST POTENT MELANOMA INDUCTORS: ALEA IACTA EST

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Abstract.

The purposeful oblivion of the objective truth, the disregard of scientific reality, the denial of the contributions and successes of surrounding researchers, the substitution of priorities in clinical routine and the unwillingness to reason in the right direction often lead to disastrous consequences in the field of public health.

Controlled projects almost never lead to a significant contribution or breakthrough in medicine that will be remembered by future generations.

Another illustrative example in this regard is the link shared above to the saga of the worldwide cancer pandemic and its possible real cause: the contamination of drugs with nitrosamines/NDSRIs.

The carcinogenic action of nitrosamines in rats under experimental conditions was demonstrated as early as the early 1960s (1954) by Barnes and Magee.

The series of subsequent experiments in their numerous research studies was strongly indicative of a pathogenetic role of nitrosamines / dimethylnitrosamine / in the development of liver cancer and kidney cancer. Starting from the fact that contact with nitrosamines is of primary importance for the development of tumours in animals, there is practically no circumstance that would lead us to believe that the intake of the same mutagens in man would have a different carcinogenic effect from that already known to us (as was found under experimental conditions as early as 1954, but in animals).

On the contrary, to this day the incidence of cancer is increasing every year and, according to global statistics, it is projected to increase by nearly 50% or 18 million new cases by 2040. The intake of (un)identified nitrosamines found in drugs as contaminants is increasing analogously to the shared breakneck cancer incidence.

In addition to the number of identified carcinogens or NDSRIs , the number of affected drug classes is also progressively growing and in mid-2023 this number amounts to over 250 drugs according to the official data of the FDA bulletin of 08.04.2023.

In practice, the population/patients have been in a continuous, still ongoing, multicentric prospective study since 1954.

The parameters of the ″experiment″ are probably pre-set, crystallizing gradually over time and imposed forcefully in the form of hypnotic suggestions and directives by regulators. Encouragingly , the results of the prospective study are also available, are not one-sided and have been published in dozens of international journals as well as in part in the well-known Cancer Journal of the clinicians / Impact factor 254,7.

The bad news is that in most of these observations and results, there is no correlation of what is shared between, say, 1) mandatory alternative-free intake of mutagen-contaminated drugs and 2) the breakneck development of heterogeneous cancers/including melanomas, and the scientific vision of the studies is currently rather one-sided.

Cancer incidence is skyrocketing (according to Globocan/ Cancer Journal for the Clinicians), and not a single worldwide study has commented on its potential link to actual contamination of the most commonly used drugs worldwide with nitrosamines/ NDSRIs.

For the past 5 years, the team of the Bulgarian Society of Dermatological Surgery has been committed to formalizing the final results of these prospective nationwide observational studies and providing full transparency on the relationship between the intake of actual/potential nitrosamine-contaminated drugs and the development of skin cancer. Over 95% of newly reported skin cancers during this period (2016-2023) were associated with prior intake of drugs listed in the 2023 FDA as potentially nitrosamine/NDSRIs contaminated or carcinogens.

Melanoma is one of the most significant patterns of tumor arising after contact of the human body with nitrosamines. Whether the drugs affected by the contamination are from the group of sartans, beta blockers, hydrochlorothiazide, calcium antagonists, ACE inhibitors or antidepressants- the ultimate side effect remains the same and is known to the scientific community as or by the frightening and loud name : melanoma. We report the occurrence of another case of nevus associated cutaneous melanoma and multiple dysplastic nevi after taking the antidepressant Sertraline. A drug declared according to the official FDA bulletin of 08.04.2023 as potentially contaminated with class 2 nitrosamines/ NDSRIs: having similar to completely identical carcinogenic potency as that of NDMA and NNK. Or reciprocal to that in valsartan, irbesartan, olmesartan, repeatedly described already as possible melanoma inducers.

According to the literature search, this is also the first case in the world of Sertraline-induced nevus associated cutaneous melanoma, and we share the view/ thesis that the real inducer of the tumor is in fact the impurities in the medication in the form of contaminants or nitrosamines: the so-called NDSRIs.

The nitrosogenesis of skin cancer is a more than significant concept that has been cleverly concealed by the scientific community until recently. The reason for this concealment could be sought in the paramount importance or central role that the nitrosogenesis occupies at the base of the ″pyramid″ guaranteeing billions of dollars of monthly revenue to the regulators of globalism.

Key words. Sertraline, NDSRIs, melanoma, dysplastic nevi, dermatologic surgery, nitrosogenesis, NDMA, NNK.

Introduction.

The year 2023 should definitely go down as a memorable one in terms of the FDA update/regulation on 1) the 250 drugs originally announced as potentially/actually contaminated with nitrosamines/NDSRIs/potent carcinogens , and 2) the identification of the five classes of carcinogens (according to their potency) that could be identified as contamination in the drugs themselves [1]. This is in effect a kind of self-recognition , but also a telling example that polycontamination worldwide is/ could be of ″monstrous proportions″ and that the intake/problem of contaminated drugs in polymorbid patients could hardly be limited or overcome [2,3].

Analogous to what has been shared- Nitrosogenesis in melanoma is or remains to be a fact that should not be questioned in the context of polycontamination and polymedication in polymorbid patients [4]. A number of data are available describing the occurrence of, for example, multiple melanomas after concomitant/simultaneous administration of valsartan, amlodipine, hydrochlorothiazide, and bisoprolol [4]. And looked at in detail and in line with the newly introduced information according to the official FDA bulletin of 2023 (1)- what does this mean in practice:

Bisoprolol has a potential carcinogenic potency of class 4 or 1500 ng/daily tolerable dose [1], amlodipine is classified as a class 5 NDSRIs or a daily tolerable dose of 1500 ng/day according to the official FDA bulletin of 2023 [1]. Valsartan should have been classified as containing class 1 or class 2 carcinogens / NDSRIs due to its repeated contamination with NDMA or NDEA over the years [5], but interestingly why- it is not listed in the current FDA list of contamination with potent/ potent carcinogens potentially present in valsartan as of 2023 [1]. Whether the reason therefore is due to an imminent halt in its production in the near future- remains at present unclear. Similarly, batches of hydrochlorothiazide have been withdrawn from the market [6], for which the FDA also does not mention in its official bulletin of 2023-which class of potential carcinogens the NDSRIs found in hydrochlorothiazide belong to [1]. And these were identified as early as 2022, which was (self-) acknowledged by Pfizer.

The creation of reference limits for carcinogens in medicines is a paradox that is likely to remain unparalleled in the world history of medicine: overlooked by regulators but skillfully exploited by manufacturers for over 50 years, generating billions a month for the pharmaceutical industry.

In 2023 we are effectively talking about forced tolerance available to polycontaminants/ in the form of ″hypothetical″ mutagens, carcinogens/nitrosamines or NDSRIs due to the lack of alternative at the time ?

Parallel to the above, it should not be overlooked that by 2040, scientists expect or predict an increase in the incidence of cancer worldwide of about 47% or 28.4 million cases per year compared to 2020, for example [7]. And with all this data, scientists are perplexed as to what is the cause of this skyrocketing cancer incidence.

No less puzzling is the absence of any data worldwide thematizing the incidence of cancer in general/generally and its relation to the mono- or polycontamination of the already mentioned recently officially declared nitrosamine-contaminated drugs. These analyses would provide some extremely quick answers that could be revealing but also sobering to the ″leaders of globalization processes″. It is in this way that the link between the generation of cancer and the intake of already ″hypothetical carcinogens″ [1] with ″predicted carcinogenic potency″ [1] through polymedication in polymorbid patients could ″be shine in its full glory″.

We present a patient taking the antidepressant sertraline, potentially and now officially designated by the FDA as possibly contaminated with class 2 nitrosamines/NDSRIs such as NDMA and NNK , who subsequently/ within this intake developed nevus-associated cutaneous melanoma/multiple dysplastic nevi, treated successfully surgically within 2 surgical sessions.

Case report.

He was admitted to the department of skin diseases and dermatological surgery because of the presence of a pigmented lesion localized in the back area, which had increased in size over the last year, while becoming slightly sensitive and painful to touch (Figure 1a). The duration of the complaints is (according to rough anamnestic data) of about 1 year, and the date of presence of the lesion is generally unclear or difficult to determine within the patient discussion. In parallel, multiple dysplastic nevi were found on the back, trunk, and under the right breast (Figures 1b and 1c).

The patient's known comorbidities include: a condition following surgical removal of colon cancer in 2012, tachycardia dating back to 2023, and endogenous depression (dating back 3 -3.5 years).

A patient’s systemic medication includes sertraline 50 mg once daily for 3 years: quetiapine 100 mg once daily for 3 years. Perindopril 8mg/amlodipine 5mg/indapamide 2.5mg/twice daily, assigned within the patient's hospitalization.

Within the dermatological examination in the dorsal area, at the level of Th12 at 5.5 cm to the right, a pigmented lesion with an asymmetric, elliptical shape, 2.5 cm in diameter by 1 cm, heterogeneous in coloration, caused by a central, tumor-like achromatic zone, overlying a grayish pink plaque-like base, was found to extend between 15:00 and 9:00 (Figure 1a). Dermatoscopically, there was a disrupted to completely absent melanocytic network in places, intense areas of regression with a pale pink to gray hue. Clinically and dermatoscopically, the lesion is suspicious for cutaneous melanoma.

In the area under the right breast - multiple melanocytic nevi with clinical and dermatoscopic signs of dysplasia (Figures 1b and 1c). Age of lesions unclear overall. Age of change in colour and size: about 2 years.

An elliptical excision was performed for the lesion suggestive of melanoma with a surgical margin of certainty of 0.2 cm (Figures 1d and 1e), and the histopathological verification of the lesion was as follows: evidence of a well-demarcated melanocytic lesion represented by Ortho hyperkeratosis, irregular acanthosis, proliferation of large fusiform melanocytes, and well-formed heterogeneous nests obturating the dermoepidermal border and projecting into the papillary dermis. Prominent angiofibroplastic stroma with multiple melanophages distally dermocarcinated by dermal melanocytic nevus. Clear resection lines. Perineural and

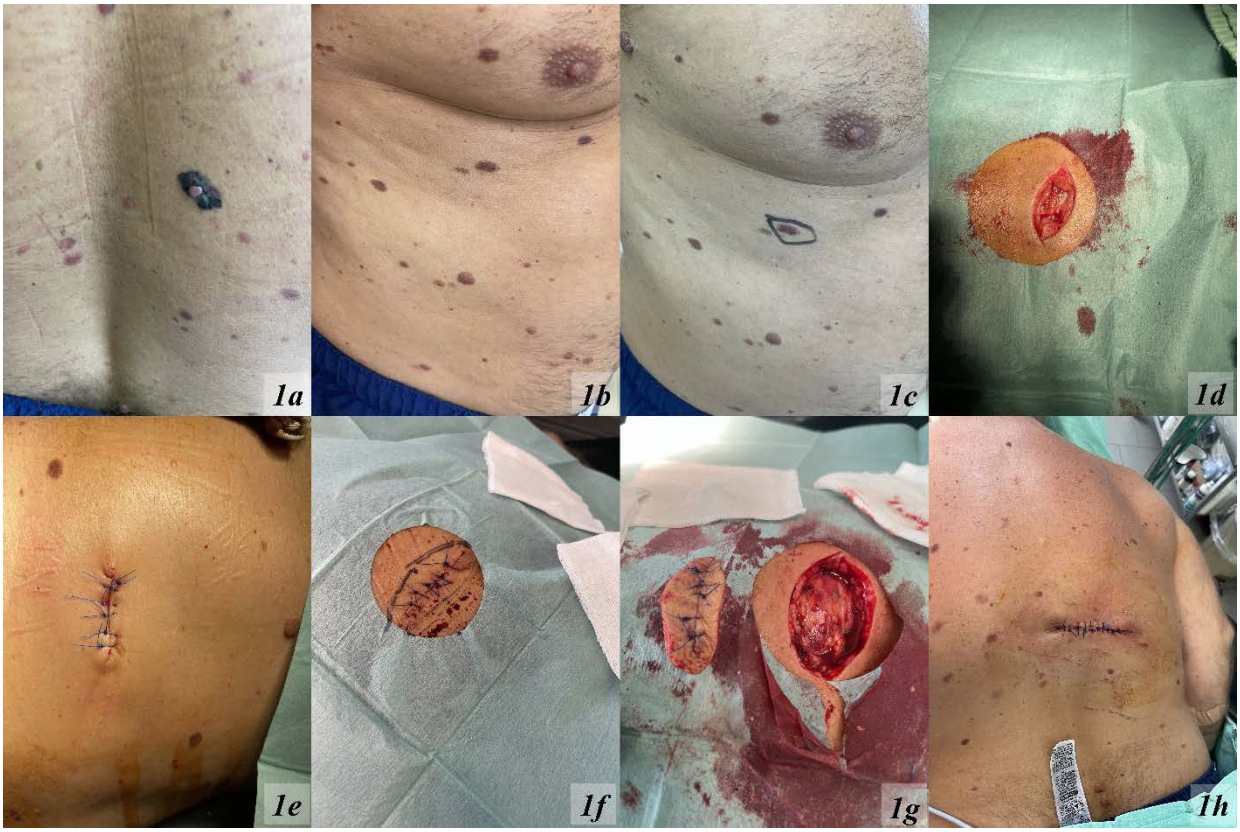

Figure 1.
1a: *Clinical findings in a patient with subsequently histopathologically proven nevus-associated cutaneous melanoma.*
1b: *Multiple dysplastic nevi within concurrent intake of nitrosamine contaminated drugs.*
1c: *Marking of resection lines in a dysplastic melanocytic nevus scheduled for removal.*
1d: *Removal of a cutaneous melanoma with near surgical margin of safety within the first excision.*
1e: *Postoperative clinical findings after defect closure.*
1f: *Marking the second resection field according to the tumor thickness found after the first excision/ according to the AJCC/ EJC recommendations for surgical treatment of cutaneous melanomas.*
1g: *Intraoperative finding. Tissue resection next to the muscular fascia.*
1h: *Postoperative finding after closure of the defect.*

lymphovascular invasion absent. Clark 2, Breslow 0.58 mm.

On the occasion of the histopathologically thin melanoma, re-excision was performed with an additional surgical margin of 1 cm, with no evidence of residual cells in the re-excision (Figures 1f-1h). Screening was also performed and was not indicative of metastasis, with final staging of the lesion determined at stage 1a (T1aN0M0).

A second melanocytic lesion located under the right breast was surgically removed (Figures 1b and 1c) , with histopathological evidence of: an extensive, asymmetric melanocytic lesion represented by ortho- and follicular hyperkeratosis, irregular acanthosis, proliferation of large fusiform melanocytes , obstructing the dermoepidermal border and with solitary ascending migration, demarcated by matted nevo-melanocytes located among fibrous stroma. Clean resection lines. The histological picture corresponds to a mixed dermal melanocytic nevus with marked architectural cytological atypia. The patient was sent for registration and follow-up to the regional cancer hospital.

Discussion.

The link between melanoma and nitrosamines dates back to 2018, when in fact the first case of melanoma was described, followed by a lethal outcome that developed after taking two preparations of a well-known pharmaceutical company containing valsartan in combination with amlodipine [8]. In practice, the patient described involved the intake of potentially nitrosamine polycontaminated class 1 and/or class 2 drugs in combination with class 5 / according to the 2023 FDA categorization (Figure 1) [1].

Similar cases of melanoma development are not lacking after taking irbesartan in combination with hydrochlorothiazide [9] or irbesartan in combination with amlodipine [10]. Polycontamination or the intake of drugs contaminated with nitrosamines remains the only constant link between these cases, concerning of course again the development of melanomas.

Similar reasoning could be applied to systemic treatment of arterial hypertension with nitrosamine-contaminated olmesartan and valsartan and the subsequent development of giant achromatic melanoma [11]. Contamination of these drugs is predominantly or mainly with class 1 to 2 (strong/potent) carcinogens/NDSRIs according to FDA data from 2023 (Figure 1) [12].

Multiple melanomas have also been observed after intake of the drug candesartan [13], for which the FDA sets tolerance

concentrations for daily intake of NDEA, NDMA and NMBA: potential class 1 or class 2 carcinogens (Figure 1) [12].

In the shared cases, the following link is indicative: between the occurrence of melanomas and the intake of a heterogeneous class of drugs, which only in 2023 have been declared by regulators (FDA) as actually affected by contamination with carcinogens/ nitrosamines/ NDSRIs of a heterogeneous class or ingredients with potentially carcinogenic activity [1,12].

Melanomas have also been described in the scientific literature after administration of potentially nitrosamine-contaminated telmisartan [14] or telmisartan in combination with potentially/ actually contaminated hydrochlorothiazide [15].

Patients' intake of actual/potential nitrosamines/ NDSRIscontaminated mono- or polymedication, in practice, has been shown to be crucial or indicative of melanomas [4,8-11,13-15].

It is unclear why, until recently and currently, the message from regulators to end-users has been or remains: medicines should be accepted and patients ″not to worry″, while at the same time medicines are quietly withdrawn from the market and some are stopped from production altogether/ without any explanation.

Another official message from the regulatory authorities concerning mutagen/carcinogen contamination is that nitrosamines do not cause cancer if taken for prolonged periods and in certain doses. However, regulatory bodies do not thematize the issue of carcinogen intake within the framework of polymedication and polycontamination [2-4]?

It is interesting how nitrosamines in cigarettes have been identified as carcinogenic to the human race in terms of lung cancer, for example [16], nitrosamines in food have been identified as carcinogenic in terms of the development of gastrointestinal or urogenital forms of cancer [17,18], but nitrosamines in medicines were not dangerous and should not be feared within their intake ? Although this intake is indicative of the development of melanomas and keratinocytic forms of cancer [2,3,4], but not only. It remains an open question: are these compounds in practice analogous to completely overlapping in structure and mechanism of action ? Is end-user confidence generally lost?

The carcinogenic effects of nitrosamines on the human body have been known since 1977 and have been associated with the induction of gastrointestinal cancer [19].

But it was only 46 years later that the FDA reacted "adequately" and stated that there was a problem and it needed to be solved [20]. This partial solution concerns/restricts to some extent the intake of carcinogens as monomedication (but does not guarantee the absence of tumors after intake of preparations contaminated with nitrosamines), while at the same time it does not solve the problems of polymedication and polycontamination in polymorbid patients [2-4].

It is here that the reason for the exponentially increasing incidence of cancer worldwide should be sought [7].

The nitrosogenesis of skin cancer is a fact and a phenomenon that cannot, should not and cannot be ignored, as the data continues to be available: it is established by the dozens of daily registrations of the occurrence of skin cancer after simultaneous intake of contaminated with nitrosamine preparations, such hat the dose-dependent time intervals for the development of cancer match perfectly, and the availability of real carcinogens/ nitrosamines/NDSRIs has already been officially initialed by regulators as a permissible availability [1,12].

The only missing piece of evidence at present remains the monthly/daily sampling of drug batches to prove the permanent presence of mutagens in single or multiple preparations taken by patients. This unit could clarify another thesis/hypothesis: that of the controlled or sporadic spread of carcinogens.

With widespread pollution, the so-called manufacturing error comes to the fore.

In case of sporadic pollution (peak pollution, time-limited pollution, or pollution of production only in certain geographical regions), other reasons could be sought.

Sleeping on the truth - intentional or not, leads (according to official statistics) to a jump in new cancer registrations by about 50% over a predictable period covering the next 20 years (2040) - damage for which the regulators should be held accountable and mutagen producers [7]. And damage that has been presented by these same units until now as insignificant, harmless, and as something normal: like the concept of hypothetical carcinogens?

As far back as 1981 Valda Cradock’s important reflection echos in The Nature: ″Tumours have now been shown to be induced by a wide variety of N-Nitroso compounds in many species of animal and there is no reason to believe that man will prove to be an exception. There is also no doubt that man is exposed to these potent carcinogens [21].″

Although the toxic effects of nitrosamines on the human body have been known since 1954 [22], this has been skillfully, diligently, and purposefully ignored and neglected by regulatory authorities and drug manufacturers for nearly 80 years [12]. Interesting as fact, this data has not deterred regulators, in tandem with pharmaceutical industry representatives and their political lobbyists, from officially parroting the availability of carcinogens in drugs through the 2023/FDA 08.04, 23 [12] regulatory decree on permissible concentrations.

This action could at the same time be announced as the most powerful blow to public health worldwide, allowing pharmaceutical companies to make trillions a year on account of the ″free spread″ of carcinogens in drugs taken by over 5 billion patients every day [23].

Carcinogens that have so far been deliberately overlooked and carcinogens that have turned out to be an integral part in more than 95% of the most widely distributed preparations worldwide [1,5,6,12].

Barnes and Magee continued in 1956 with their experiments and demonstrated that oral or parenteral administration of dimethylnitrosamine in rats was associated with the generation of liver tumors , which showed a propensity to metastasize/ aggressive character [24].

Barnes and Magee's experimental studies, enigmatic for their time, did not stop in 1959, proving again that nitrosamines/ dimethylnitrosamine/ caused tumours in rats under experimental conditions [25].

Only 3 years later (1962) the same two experimenters proved that the substance dimethylnitrosamine also caused tumours of the kidney/ again in rats [26].

It was not until 2022 (or 60 years later) that someone tried to look for an analogue of their reasoning in real patients/ retrospective analysis and so came the ″revolutionary discovery by French scientists″ (confirming over 20 international scientific papers by Bulgarian dermatologists) who found a link between NDMA-contaminated valsartan and the risk of melanoma and liver cancer, but this time in humans [27]. Clearly the analogy is there , and the results are more than shocking.

It seems that it has taken mankind 77 years to ″peel back the veil of truth″ and rethink and re-read data already made public long ago, but this time through the prism of the 1954 experimenters: Barnes and Magee [22,24-26].

Strangely why and strangely how, it took the pharmaceutical companies, in all likelihood, an extremely short time to discover that 1) one of the most potent human carcinogens, nitrosamines/ NDSRIs, are found in 99% of the most widely distributed drugs worldwide [1], and that 2) for these carcinogenic/mutagenic substances, a forced regulatory tolerance regime/ ″regulatory umbrella″ has been secured, providing a definite correlate/ increasing incidence of cancer in general [7]?

Parallel to the 2 circumstances mentioned, looking back retrospectively or over a period of about 50 years, it appears in practice that a trouble-free intake of mutagen-contaminated drugs by billions of patients was available or ensured. The pathogenetic role of NDEA and NDMA in the generation of melanomas was described by Bulgarian dermatologists for the first time in the global scientific literature in 2018 and precisely concerns the relationship between contamination with class 1/ 2 nitrosamines/ NDSRIs with class 5 (of valsartan and amlodipine) and the occurrence of cutaneous melanoma, subsequently leading to a lethal outcome [8].

Contamination of antidepressants with nitrosamines should not be seen as novel. This year, batches of the antidepressant amitriptyline have been withdrawn from the pharmaceutical market precisely because of nitrosamine contamination [28].

Diverse classes of antidepressants such as melitracene, paroxetine and venlafaxine have been described in the literature as possible triggers of skin cancer within the framework of polymedication and polycontamination [2].

Amitriptyline has also been described as a drug with possible contamination with class 1 potent carcinogens/nitrosamines/ NDSRIs , analogous to the potent nitrosamine NDEA [1,2].

The situation is similar with the use of the antidepressant Venlafaxine, potentially/actually contaminated with class 1 potent NDSRIs according to FDA data from 2023/official bulletin [1,2]. For class 1 and class 2 carcinogens, contamination within the polymedication is not a prerequisite for cancer generation, as these classes are in fact potent carcinogens with proven clinical relevance/significance (Figure 1)[1]. When such a combination/accumulation or concurrent, simultaneous intake of nitrosamine/NDSRIs contaminated drugs is present, it could correlate with the severity of clinical symptomatology [2,4].

The Nitrosogenesis of skin cancer is a process that is confirmed directly or indirectly through the daily observations of clinicians [2-4], referenced and aligned with the data officially published by regulatory authorities on available contamination with potent carcinogens (Figure 1)[1,5]. This ″inseparable relationship″ could not go unrecognized for much longer, as it has already been repeatedly resolved and officially documented [29].

In support of the thesis/ of pathogenetic relevance (between nitrosamines and the generation of skin cancers or melanomas in particular), the following analogous publications on the occurrence of nevus-associated cutaneous melanomas after ingestion of class 1 or 2 potent nitrosamines/NDSRIs are indicative: references [8,11,15,30]. The similarities between them are determined by 1) the intake of potentially/actually class 1 NDSRIs-contaminated heterogeneous drugs and 2) the development of nevus-associated cutaneous melanomas [8,11,15,30].

The drug sertraline does not make an exception in terms of contamination with potent / ″hypothetical″ according to the FDA bulletin of 2023 NDSRIs/ carcinogens, being assigned to group 2 NDSRIs , whose carcinogenic potency is attributable to that of NDMA and NNK (Figure 1) [1].

Since the presence of nitrosamines/NDSRIs has been identified in over 95% of the most used drugs worldwide, regulatory authorities in the face of the FDA have also now defined some of the most potent carcinogens and mutagens as: compounds with ″predicted carcinogenic potency″ [1]. And the reference tolerable intake limits for carcinogens have been relaxed to the concept of : ″FDA recommended AI limits for certain hypothetical NDSRIs″ [1].

The ″speeches″ in the official bulletins of the regulators [1] have a clear , pronounced protectionism (general opinion) and make us wonder whether patients around the world are not currently under a large-scale prospective follow-up concerning the potentially controllable intake of carcinogens and mutagens in the framework of polymedication and polymorbidity?

The predicted intake parameters for carcinogens are now officially set by the FDA, and the estimate of global cancer incidence also relative to 2040 is more than clear and frightening [7]?

The most powerful regulatory body, the FDA, betones the availability of ″hypothetical″ carcinogens in drug preparations, and according to the companies themselves, this concentration has at times been overstated by up to 200 times over the past 30 years.

And the journal with the highest global impact factor of 254.7/ Cancer Journal for Clinicians [31] gives its estimate of a global increase in overall cancer incidence of nearly 50% from 2020 to 2040 [7].

The prospective study of the role of nitrosamines/NDSRIs and the generation of melanomas and cancers in general (but also of the skin and worldwide) was probably started long ago (in the 1960s?), but until recently this was not clear to either patients or the academic community.

Its start was in all likelihood given short term after the discoveries of Magee and Barnes in the early 60's [22,24,25,26]?

Presumably, too, much of its results were reported before the end of 2018, or the year that regulators in the face of the FDA began declaring valsartan's contamination with nitrosamines as problematic. In parallel with this, the permanent removal of a number of preparations) from certain pharmaceutical companies and in certain geographic regions) from the drug market was

launched. Hypothetically speaking- it was these results (on cancer incidence) that were alarming or startling, necessitating their stepwise disclosure and stepwise removal. Apparently, in this period and with regulatory institutions, social responsibility was in a phase of perhaps temporary activity towards objectivity.

The only priority goal at the moment for clinicians with ″at least residual semblance of moral″ would be to report the final results of this ″inappropriately launched and currently still ongoing prospective study″ (concerning the permanent intake of hypothetical carcinogens/ NDSRIs/ nitrosamines/ within this extremely unpleasant experiment.

This ″reporting of results″ does not require informed consent from patients, but only the social responsibility of the therapist. A responsibility that has been mentioned by our ancestors and proven authorities [32].

The Nitrosogenesis of melanoma appears to be more than an undeniable fact! The depression and sertraline in the patient described are in fact ″secondary and insignificant availabilities″ or ″decors″ that do not need any kind of interpretation or analysis.

The preservation of 1) pure, well-intentioned clinical thought, 2) the social responsibility of physicians, 3) absolute reliability/ accuracy in the interpretation of actual clinical results, and 4) full transparency and accessibility of the latter to the public, regulators, and the scientific community from: 1) the influence of globalization processes, 2) the forced or spontaneous mediocrity of the individual (group mediated or congenital), 3) lobbying interests and 4) commercialism- this is what would guarantee a better survival and a better quality of life. Categorically and for every single patient.

Sic parvis magna! Or perhaps it would sound better: Alea Iacta Est!

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