Academic Criticims: Antihypertensives, Nitrosamines And Melanoma- Beyond The Medical Aspects of The Socially Significant Human Problem. Current State and Future Directions

*Georgi Tchernev1,2, Lyudmil Ivanov1,2, Simona Kordeva1, Valentina Broshtilova2, Shafali Khanom1, Casey Sabrina Henry2, Jenisa Mary Joseph1

1Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria
2Department of Dermatology and Venereology, Military Medical Academy, 1606, Sofia, Bulgaria

Abstract

The rapid reversal of the direction of thought, of the general attitude, focus and vision on a problem or task, is not new and has been known since biblical times, the Middle Ages or the recent past, but in various forms, such as: “The King is dead, long live the King!” It is for this reason that abrupt shifts of perception and behaviour or receptor sensitivity in a cell or tissue should not be seen as unusual for the human race either.

Similarly, the moral and ethical behavior of the scientific community at the moment has suddenly announced an abrupt change in its outlook, interpretation, and interpretive attitudes-namely: it had another point of view concerning the pathogenesis of skin cancer in general (but so also for prostate cancer, lymphomas, etc.). And the reason for this was the medication intake for high blood pressure. On the intake of the pure medications. Also defined as cancer associative pathogenetic intake.

This change, or total metamorphosis, concerning the academic insight, growth, and awareness, is occurring massively and universally only in 2024, linking thiazide diuretic use (according to the most recent German study) to the occurrence of at least 4 heterogeneous forms of skin cancer: basal cell carcinomas, squamous cell carcinomas, atypical fibroxanthoma, and dermal pleomorphic sarcoma.

“The understanding turns out to be even quite contagious”, encompassing in parallel an American study (published in the form of a meta-analysis/2024), which announces that there is a change of everything mentioned so far as understanding (or concerning Oncopharmacogenesis) and there is a significant association between the intake of most of the known worldwide antihypertensive drugs and the occurrence of keratinocytic tumors and melanomas subsequently.

A third study, again by an American collective (2024), linked the intake of photosensitizing drugs in postmenopausal women, again with the development of keratinocytic tumors and melanomas, and found a definite association with the patients’ exposure to solar radiation as well (photocarcinogenesis/nitroso-photocarcinogenesis?).

And calcium antagonists are associated once again (2024) with the potential generation of prostate cancer, while renin angiotensin antagonists: rather with a lower risk or better prognosis of patients, however, already developed this type of tumor. But let us note that this type of carcinoma occurs within the already mentioned antihypertensive medication, which has been available for years (on sartans or on calcium antagonists) before the tumor even arises! And whether the prognosis of patients is better afterwards depends rather on other factors. Interpretation of clinical as well as certain prognostic data is and remains in practice a play on words or refraction through a particular (different) mental, ideological or “light prism”.

But the most general thesis is and remains the following: the intake of these two classes of medication (sartans and calcium antagonists) is followed by the subsequent occurrence of prostate cancer, although this is not clearly expressed in any line of the referenced work.

Interesting how even the academic community in Taiwan, only now, in 2024, is “suddenly impressed” that taking antihypertensives/ and diuretics during pregnancy is associated with a rather high, significantly associated risk of developing acute lymphocytic lymphoma and non-Hodgkin's lymphoma in newborns.

Refracting all the mentioned scientific information through the prism of Oncopharmacogenesis and drug-initiated Nitrosogenesis, the following could be shared: it is unlikely that these follow-ups (formalized in 2024) are random, episodic and manipulated. But everything formalized so far finds its reasonable explanation in the following: 1) there is no way that a single drug in the form of a pure/active substance can lead to the development of heterogeneous forms of cancer: be it skin, prostate, blood, lymph gland or a number of others. These drugs are described by regulators as containing...
heterogeneous nitrosamines/carcinogens or mutagens, each one individually or in combination, capable of inducing heterogeneous cancers! And 2) There is no way that in Germany, France, America and Bulgaria for example, the same tumours can be registered after taking the same drugs and this not be catalogued as a carcinogenic side effect for years. Regardless (or even dependent) of whether it is caused by the contaminant in the form of a particular nitrosamine or the active ingredient, the generic. And 3): the unifier in these publications (concerning cancer) remains to be the one and only or rather: the drug related Nitrosocombination, the Oncopharmacogenesis/Pharmacooncogenesis. Or the contamination with a heterogeneous/monomorph type of carcinogens in the form of nitrosamines and their derivatives, which remain, however, completely uncommmented as a cause of cancer and melanomas in particular, and that too, and very unfortunately, in none of the international publications presented.

Nitrosamines could also be considered as bicarcinogens or polycarcinogens. A typical example therefore remains NDMA: it activates RAS oncogens before its metabolism, and its metabolites after metabolism in the liver, are in fact other, radically different mutagens. From another point of view, contamination of certain preparations is possible with up to several nitrosamines or NDSRIS at the same time (in the context of mono or polycontamination of one or more drugs).

Precisely because of the above-shared facts, the association between the intake of a particular contaminated antihypertensive drug and the subsequent development of melanoma or other cancers does not require such in-depth analyses or future, prospective follow-up. Polycarcinogenic intake could also lead to the development of melanomas, even if this intake is not formally indicated on drug packaging worldwide. It is this lack of formalisation that casts serious shadows of doubt over the pure substance and could prove to be a subsequent or relatively short-term deterrent to the spread of even uncontained drug production and the resulting global drug shortage. The labelling of the Nitroso-component and its complete elimination afterwards, remains the only guarantee for: 1) the protection of the health of patients worldwide, 2) the guarantee of their legal right to be informed of what products they consume as final consumers and 3) the guarantee of the survival of companies in the conditions of reasonable and fair competition and not on the basis of a hidden distribution of nitrosamines in medicines ensuring 3. 1) the development of melanomas (but also a high incidence of cancer in general) but also 3.2) government subsidies in the billions by law. Crossign this "devil's circle" would ensure that the "much desired progress" is achieved: a rapid and explainable decrease in cancer incidence in general, but also in melanoma incidence in particular.

In this context, we report on another or next two patients who were taking a particular antihypertensive medication and developed melanomas again subsequently. In patient 1 we discuss the role of beta blockers in the face of bisoprolol and the subsequent development of cutaneous melanoma, and discuss the weakness/manipulative aspect of certain international data on the subject: such as a protective effect of beta blockers in melanomas, for example, which does not exist, but is rather attributable. In the second patient described, a nevus associated melanoma developed on the basis of multimedications with perindopril, amlopidine and monoamidine. Modern scenarios of cancer generation in the context of Nitrosogenesis, Oncopharmacogenesis and Nitroso-pharmacogenesis are commented. Clearly defined new concepts in medicine would be able to rewrite soon the history and textbooks concerning skin cancer and melanoma in particular. The vision of new horizons, however, requires a rapid rethinking and imposition of new concepts and standards based on a new perspective rather than on lobbyist, inadequate in action and design coercive regiments for universal tolerance of carcinogens in the most commonly distributed antihypertensive (but no only) drugs worldwide. The scientific worldview and insights remain, to date, the only guiding but also saving light in that direction.

Keywords: perindopril; amlopidine; monoamidine; bisoprolol; NDMA; nitrosogenesis; oncopharmacogenesis; photonitrosogenesismelanoma

Introduction

The vision of melanoma pathogenesis is about to be completely changed, and possibly finally unraveled (1). Drug-induced Nitrosogenesis appears to be part of the newly introduced concept of Oncopharmacogenesis of skin cancer in the scientific literature (and perhaps also a concept concerning cancer worldwide) (2,3).

Nitroso-pharmacogenesis is another specific, innovative concept due to the fact that some of the nitrosamines identified so far in drugs could also be classified as pharmacocarcinogens or substances with genotoxic effects: such as the nitrosomorpholine in molsidomine, for example (4).

There is a lack of data on the phototoxicity of the other nitrosamines (NDMA, NMBA, NDEA, but also for all NDSRIS) identified as contaminants in the most commonly distributed drugs worldwide (5).

There is also a lack of data on the presence of DNA adducts in tumour tissue (in particular in the skin) that arise after metabolism of nitrosamines in the liver and exert their genotoxic, carcinogenic but also organ-specific effects.

The problematic issue is that there is no official data on the presence of carcinogens in the drugs, but there is serious evidence of the subsequent development of skin cancer after their administration (and a permissive/enforced unofficial availability declared by regulators) (6-8).

It is the opinion of the regulators that, at present, although these carcinogens are demonstrably present in drugs and their numbers are increasing daily, they do not need to be formally declared by the manufacturers.

The question remains: who is protecting whom by not declaring mutagens as available in drugs? And why? And at the expense of whom and to what does it do so?

However, there is no lack of documented evidence of the $250 million recently paid by the Pfizer company, as well as the $100 million paid by the Sanofi company for claims of more than 14,000 forms of cancer resulting from the intake of NDMA-contaminated drug products containing ranitidine (9,10). Claims for which the court effectively acquitted both companies (11,12). Hence the reasonable question: "Who pays 350 million when acquitted by the court or found not guilty?"

Or: What are the two pharmaceutical giants actually paying for: 1) for the lack of carcinogens in the drugs? Or for 2) The presence of carcinogens that are not dangerous to those taking them, but would be better left hidden? Or about 3) cancer for example that has developed accidentally in 14000 human after taking a
single drug that contains a potent, potential carcinogen - NDMA. But the carcinogen is not responsible for the cancer? What stronger proof does the scientific community expect? Someone is paying 350 million soon to have NDMA not declared as a real carcinogen but remain a potential one? And the regulators are silent! And what does the scientific community have to say about this - why are these 14,000 patients not formalized in scientific journals, nor thematized at congresses? There is only a single publication concerning the worldwide melanoma and dysplastic nevus development, described by a Bulgarian team. Data on post-irradiation cancers remain largely classified.

And NDMA in practice appears to be or could be considered as a bicarcinogen activating in parallel the processes of metabolic reprogramming of the tumor cell: 1) one pathway directly by activation of RAS oncogenes, but also 2) by undergoing methylation through the liver and the emergence of a radically different mutagenic metabolite such as methylidyazonium for example (13).

I wonder how and why regulators and companies do not consider to label the presence of these carcinogens in drug leaflets and prescriptions, but are willing to keep silent about their side effects such as cancer (of the skin, but not only), while paying 350 million for the silence of those affected? Will buying silence for $25,000 per patient go unpunished? An assessment that gives an accurate insight into the globalization and demoralization of living matter or material in the 21st century, the robotization, aphorization and soullessness of our surrounding aggressive environment. An environment conditioned by quick profits or profits at any price! Globalisation!

What is left for the polycontamination of certain drugs with several similar to completely analogous carcinogens - already a well-known and officially published fact in the scientific literature (4) (NDMA) and NDEA in losartan for example)?

Beatrice Nardon and colleagues previously hinted (although not in detail) at the possibility of pro-carcinogenic effects of antihypertensive drugs in 2017 in their enigmatic paper linking the most commonly distributed anti-hypertension drugs to a monomorphic clinical picture; melanoma and keratinocytic cancer? Does it not confirm everything she has shared so far? This is a very interesting and internationally worthy question, which will in all likelihood again remain largely secret but also rhetorical: the interpretation of the significance of certain data, their scientific weight over the years.

It's also interesting how life-shortening carcinogens are found in 300 of the most widely distributed drugs worldwide? And even multiple carcinogens at the same time? Which cannot even at the moment even be officially eliminated?

One also wonders how long the regulators worldwide have to play mankind with yet another fraudulent but enticing offer to test for carcinogenic and mutagenic activity of a given carcinogen under static, experimental conditions? With mutagenicity tests in bacteria and rodents? Given that, in the context of polymedication/polycontamination, patients have been in yet another and currently still ongoing prospective follow-up of carcinogen intake with drugs for nearly 40-50 years?

Are not the final epidemiological results of this prospective follow-up, which are more than indicative, reported to date: 20 million new cancer cases by 2022 (16), and projected - by 2050 (relative to polydrug intake worldwide): 35 million new cancer cases overall (16), sufficient. Despite medical breakthroughs and modernisation? And this particular article topics polymorbidity, infections, overweight, obesity, and smoking, but not the polymedication/polycontamination with nitrosamines needed to overcome these conditions (16). Restructuring the already available data and statistics from this work (16), would immediately answer the questions: is potentially contaminated drug production related to a skyrocketing global cancer incidence! And the answer is: DEFINITELY YES!

New and/or future analyses are clearly unnecessary. There is simply the chance to suddenly free ourselves from the congenital or regulatory-imposed enforced blindness that has existed since 1956, right up to the present. To impose a new line of purification to start, to at least give the chance of a new, cathartic beginning. Real progress in medicine remains to be linked to the loss of capital in monetary form. The progress and profit, derived from taking a new path of purification, they can bring to humanity something greater, incommensurable with money and material values. And these are concepts such as health, longevity and improved quality of life. These concepts cannot be valued monetarily.

The processes of carcinogenesis are multifactorially determined especially in the context of polymedication/polycontamination (17). These are dynamic processes that are not amenable to static, piecemeal interpretation or the interpretation of static mutagenic assays currently proposed by the EMA or FDA. The idea or thesis of so-called metabolic reprogramming of the tumor cell explains precisely this complexity of the parallel action of carcinogens on a given structure in the human organism-the cell (18): be it melanocyte, keratinocyte, or enterocyte. The nitrosamines in tobacco smoke are known and largely studied human carcinogens (19) that induce mutations in the human genome. What makes us think that ingesting analogous carcinogens, but this time with drugs, would be safe for human DNA remains unclear!

In practice, it appears that the tests of the regulators in the face of the EMA and the FDA were made to initiate and secure precisely the so-called forced or currently alternative-free availability of carcinogens in medication. These tests do not comment in detail on the "complexity" resulting from the parallel intake of
nitrosamines and the consequent complex carcinogenic action. They provide an episodic, static assessment of an effect or lack of effect at a given time, while not excluding the same carcinogenic effect or lack thereof but under different conditions. These tests are unnecessary.

Based on the above, could it be concluded that these mutagenicity tests are available solely or primarily to generate profits for manufacturers to legitimately condition the availability of something that is not even officially declared on the packaging? A greater health but also moral catastrophe has not existed since concepts like MEDICINE and healthcare were introduced through the ages!

But clinically and scientifically -this "lack of formal availability", paraphrased by regulators, remains a guarantor of a slow and painful, programmed (human/cell) death. While the positions of regulators and manufacturers are being clarified.

None of the regulatory units commented on so far recommend a full elimination regime against carcinogens? And that is practically the only sure step or guarantor for the health of end consumers.

This particular situation is comical and remains without analogue, even anecdotal: "The shepherd keeps the sheep with his dogs, so that they will not be eaten by the wolves. Or the wolves that the sheep never meet in their lives! The reason for the lack of such an encounter is also the fact that 99.99% of sheep are short- to the slaughterhouse or livestock market. But not by the wolf, but by the shepherd - the guardian not of their cherished but anyway "sheep lives", but by the guardian of his own profit derived from their sale or death."

The demagogy in the diverse types of business worldwide is uniform, analogous- to completely identical. The creation of illusory fear is one of the most effective weapons of the regulators of globalization/ drug regulators/ so that the masses can be manipulated: from the moment of their birth- to the moment of their programmed (cellular) death!

The dilemma is still relevant today: are not nitrosamines the genetic weapon for localized or mass death regulation?

And finally: How long will the majority of human race continue to be intelligent at the level of Paramecium caudatum and Entamoeba histolytica, also remains unclear?

Precisely because of this fact, our team is or was committed to the short-term task of demonstrating what has already been repeatedly proven (not only by us), namely: 1) that polymedication with potentially nitrosamine-contaminated medication carries the short-term risk of developing skin cancer or melanoma in particular (1-3,7,8) and: 2) this could occur even when the carcinogens in question in the drugs are thus also in minimal concentrations (although to date no one has dared to declare their real availability), in the context of metabolic reprogramming of the tumor cell by the administration of even a single nitrosamine such as NDMA, for example, also known as bi-carcinogen or bi-mutagen (13).

Another interesting fact and not unimportant fact that accompanies 1) polymedication and 2) the cancer pandemic globally- it is also 3) the skyrocketing revenues of Big Pharma: in billions for single companies and trillions overall (4.7 trillion for 2024) (20).

And let's leave the questions open:

Is it these breakneck profits that determine the forced tolerance of nitrosamine medication?

And does this oblige end-users to accept them as “alternativeless” at the moment?

Not only do regulators create frameworks that are "allegedly salvageable", but they also create frameworks from which there really is "no way out"; the alternativeless framework of forced tolerance of carcinogens and subsequent death. This is precisely the framework of nitrosamines around human fates. A frame that must be finally broken, and broken into very small pieces.

We present 2 new patients with once again developed short term melanomas within the mono and polymedication/potential contamination concerning arterial hypertension. Potential links to drug-mediated nitroso/photocarcinogenesis and oncopharmacogenesis are commented (17).

Case report 1

We present a 49-year-old female patient with a history of complaints of 2-3 years, presenting as new-onset pigmentation in the upper lip area, laterally (Fig 1a). Arterial hypertension with a history of 5 years. On treatment with bisoprolol 10 mg once daily for 5 years.

The pigmentation is asymmetrical in shape, with indistinct borders in the area of the passage on the skin, elevation in its lower part in the form of a small nodule, and different diameter different directions (fig 1a). Clinically and dermatoscopically, the lesion is suggestive of a nevus-associated melanoma or lentigo maligna melanoma. An ellipsoidal excision of the lesion was performed with maximal near field surgical margin of safety (Figs. 1b-1d), and the histopathologic findings were in favor of: Extensive, asymmetric, poorly demarcated melanocytic lesion, represented by a parakeratotic crust overlying focal epidermal necrosis, proliferation of atypical epithelioid melanocytes with prominent superficial pagetoid spreading, consuming the overlying epidermis and a dense conglomerate with artificial acantholysis projecting into the papillary dermis among a lichenoid, lympho-plasmacytic stroma. Perineural and lympho-vascular infiltration is absent. Clean resection lines. Ulceration, low mitotic index. (figs 2a, 2b) Clark 2, Breslow 0.46 mm. Histologic picture consistent with lentigo maligna melanoma. Screening without evidence of metastasis.

According to the recommendations for surgical treatment of melanoma, the patient was referred for re-excision with a surgical margin of safety of at least 0.5 cm.
Figures 1a: A pigmented lesion, localized in the area of the transitional mucosa, showing infiltrative nodular growth towards the inner side of the upper lip. A suspicious for lentigo maligna melanoma.

Figures 1b: Clinical status after surgical eradication of a pigmented malignant lesion with a surgical margin of 1-2 mm.

Figures 1c: Clinical picture after closure of the defect with single skin sutures, first postoperative day.

Figures 1d: Clinical picture on postoperative day 7 after suture removal.
Case Report 2

We report a 41-year-old man with multiple melanocytic nevi from childhood, localized on the torso and so far according to the shared anamnestic data- unchanged (fig. 3a-3c). The patient has arterial hypertension diagnosed 2 years ago and has been on treatment for 2 years with: 1) a combination drug containing Perindopril 10 mg/ Indapamide 2.5 mg/ Amlodipine 10 mg, once daily/ in the morning and 2) Moxonidine 0.4 mg once in the evening. The patient noticed changes in the mole 15 months after starting this concomitant intake, and the last 2 months the changes worsened and he was seeking dermatological help. Clinically, the lesion was suspicious for nevus-associated melanoma and surgical treatment was recommended, which he refused at first (fig. 2a-2b).
Discussion

General picture and introspection against the background of academic sarcasm: time to laugh or time to cry, or maybe time for both?

The academic critique should differentiate itself from and strongly disapprove of the generalised lobbying leading to real, actual observations, and subsequently to a global health cataclysm, also known as a cancer pandemic. Academic criticism should be the most powerful corrective to bring about changes in favour of public health. At any time and at any level.

It is for this reason that objective truth should and presumably could be discussed at least occasionally in detail. These details include the untold, unspoken truth, based on others’ or one’s own observations, uninfluenced by the pharmaceutical lobby’s “magic wand”.

Although it remains hidden for a long time, there comes a point when confronting it becomes an inevitable part of our daily lives, even if we do not want it ourselves. Initially, a part of our grey and boring everyday life, which then takes on the colours of the rainbow. But, in parallel, it is also part of the universal, globalised everyday life, which greys and fades, if only briefly, but deservedly.

The association of antihypertensive drugs taken worldwide with heterogeneous forms of skin cancer is becoming increasingly tangible and recognisable. The reason for this tangibility remains a voltage in the atmosphere around us that has risen to over 1000 degrees.
And this pressure stems from the lack of ability to formalize the truth about cancer in general/skin cancer or the truth that guarantees trillions a year. These trillions have regulated, like a steel ring, public sentiment through mass misinformation until now, guaranteeing the well-being of demoralization and concealment of truth for the past 50-60 years. The success of this exercise has been guaranteed thanks to the artificially created general psychosis and widespread conformity that have flooded the "material" on a daily basis through the news media with data such as: "Take your blood, diabetes and stomachache medication regularly! Nitrosamines have been identified as a constituent of most common drugs! Nitrosamines are potential carcinogens and mutagens! Let companies eliminate them as quickly as possible! But let patients not worry and continue to take them!"

It leaves open the question: how can patients not be bothered by something that is practically unavailable? But is it carcinogenic? And according to claims by thousands of patients, is associated with cancer? But also there are thousands of patients who developed cancer after taking a substance officially missing in the drugs?

Not dissimilar are the claims of the cardiology guild, which fully support(s) the link between taking a nitrosamine-contaminated mono- or poly-medication and the subsequent development of skin cancer: "Let patients drink carcinogen-contaminated drugs because there are two possibilities: 1) they may develop short-term stroke, diabetes, gastritis, ulcer; rhythm disturbances or heart attack, but of course: 2) they may also develop cancer, but that is only after a few years. at least!"

The general attitude of regulators and manufacturers is no different: "Nitrosamines do not need to be formalised on the internet/ probable human carcinogens: it would definitely be better to take them apocryphally with the drugs or without the knowledge of the end users!"

These suggestions by regulators and manufacturers sound like the call of the Jedi (or directly from the mediclornians) from the "Star Wars" series in cases where the latter influence with their power the behaviour of mentally, spiritually and physically weaker individuals. And their message would be similar: "Take nitrosamines. They will help you especially when you do not know where they are and in what concentration! Never mind that they cause cancer - it is irrelevant to you. It's only and especially important in the context of polymedication and metabolic reprogramming of the tumor cell. But that's science! You don’t understand it, but it’s not important! Just drink them! May the force be with you. These are potential, not actual/ real carcinogens! You think you've developed cancer, but in practice, you haven't! Forza!"

The opinion of other scientists/international teams on the topic of skin cancer and antihypertensive medication in 2024.

A recently published meta-analysis/multicentre study from America, found a significant association between the use of a heterogeneous type of antihypertensive medication and the development of skin cancer (21): 1) and this association was found to be statistically significant for the development of basal cell carcinomas after the intake of calcium antagonists, diuretics and in particular thiazide diuretics; 2) for the development and of squamous cell carcinoma after intake of calcium antagonists and thiazide diuretics, and for 3) the development and of melanoma after intake of calcium antagonists, thiazide diuretics, and ACE inhibitors (21). Although the significance level of these associations is not high, the authors define it as a causal association (21).

However, the article does not address whether the drugs taken are from the group of potentially nitrosamine-contaminated or NDSRIs, or what exactly might underlie the phototoxicity/ photosensitivity (21). Nitrosamines are again not on the agenda as a topic.

A multicenter follow-up of skin cancer patients from Germany found a significant association between hydrochlorothiazide intake and the development of 4 types of skin cancer subsequently, namely: a significantly higher incidence of hydrochlorothiazide intake in patients with atypical fibroxanthoma/dermal pleomorphic sarcoma (44.5%) compared with those who developed squamous cell/basal cell carcinoma (25.3%), (22). Strangely, here again, no comment is made on who might in fact be responsible for the so-called photosensitivity, nor whether concurrent or co-medication was available that might fall under the heading of: potentially affected by (hypothetical) nitrosamines. The authors refer only briefly and generally to the concept of phototoxicity (22).

The awakening of scientific consciousness is again giving calls to activity, but this time from the territory of "Today's America" and focused on the use of antihypertensive drugs in, unknown to us, postmenopausal women (23)? The colleagues’ findings are more than suggestive regarding the development of heterogeneous forms of skin cancer- melanocytic and keratinocytic (23), and remain in full agreement with the data we have shared to date regarding antihypertensive medications and the development of heterogeneous forms of skin cancer over the years (2018-2024). Namely, the development of non-melanocytic forms of skin cancer are significantly or within monomedication with the intake of: ACE inhibitors, calcium antagonists, diuretics, loop diuretics and thiazide diuretics (23). The risk of NMSC increased linearly with the use of multiple antihypertensive agents (p-trend = 0.02) and with longer duration of use (p-trend < 0.01) (23). In practice, polymedication or polyclotamination with nitrosamines (increased, albeit hypothetically but also significantly), the risk of this development (23). Similar to everything we have shared over the years (6-8, 24-28).

Separately, the authors found an extremely strong or significant association between taking sartans and diuretics as monomedication and subsequent development of melanomas: for sartans, (1.82 [1.05-3.15]) , and for diuretics, (1.34 [1.13-1.59])
Only their formalisation could lead to the official clearance of preparations from mutagens.

In this way, companies could regain at least part of their reputation with patients, while retaining a certain market presence in terms of pure production. This can only be achieved through formal and frequent inspections and the public announcement of their results in order to achieve self-discipline.

**Have there been adequate decisions from regulators so far?**

What is tragic in this case is that neither the regulators in the form of the FDA, EMA, etc., nor the National/ International Court systems, are in a position to oblige the manufacturers to make this essentially life-saving formalisation of carcinogens a reality. What results directly from the lack of an adequate approach to date uncontrolled polycontaminated drug intake and a breakneck rising, astonishing incidence of cancer worldwide (includes melanoma and non-melanocytic cancers) (16).

**Weaknesses of international follow-up and the other point of view on the topic of beta blockers and protective effect in melanoma patients**

We next focus on the presented patient with melanoma of the transitional mucosae that developed after short-term administration of the beta blocker bisoprolol. Whether photocarcinogenesis or nitroso-photocarcinogenesis was the leading cause in this patient is difficult to determine. But these variants will be considered from a different starting point, which will also allow/assume a radically different interpretation of the pathogenesis of cutaneous tumors.

It is strange how and why a number of publications in the world literature have focused on the protective or beneficial effect of beta blockers in advanced melanomas, for example (39-41). Perhaps the purpose of these works is to focus clinicians’ attention on the fact that these patients were taking beta blockers before these tumors arose? And they certainly succeeded in achieving the desired effect in this regard.

None of these publications focuses on any of the following facts:

1) patients who developed advanced melanomas were also taking beta blockers before these melanomas occurred, but these data are lacking in the above 3 publications (39-41); 2) data are lacking on whether these beta blockers were contaminated with nitrosamines/NDSRIs; 3) data on comedication and comorbidities that might discuss polycarcinogen-contaminated multimedicine are also lacking in most cases.

The strength of the above three papers (39-41), their worldwide contribution, could be defined basically and relative to the information that they conceal or do not comment, namely:

1) Beta blockers were taken before melanomas appeared.

2) Beta blockers could be contaminated with nitrosamines/ according to the official FDA list of 2023, but this is not indicated on the prescription of the drug itself.

3) This contamination could occur both within mono but also polycarcinogen-contaminated polymedication with carcinogens/ again unclear; information is only known to regulators/ manufacturers.
Aspects of The Socially Significant Human Problem. Current State and Future Directions

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The hidden part of the unshared truth opens the door for new horizons and a new perspective this time as well, which is taken as the starting point of our new observations:

Starting from the thesis of possible polycontaminated multimedication in certain patients, our team considers that the cumulative drug intake/ total intake of carcinogens/ over a certain period/, has the potential to overwhelm/disturb the balance of the "ONLY experimentally proven effectiveness" of beta blockers (which should also be considered as conditioned by the pure substance, for example/possible but not certain), and this is what could lead to the clinical manifestation of melanomas.

The medicament consists of 1) a pure, formal part and 2) a carcinogenic, informal, non-figureg part or (probably) (un)desired part. The second one being the determinant of carcinogenic efficacy in vivo, in real patients.

The in vitro proven effectiveness of the pure substance on the occasion of a beneficial effect, relative to real patients, is highly manipulative as a statement and finds no applicability in clinical practice.

Under experimental conditions, the complexity of reality or the complexity of the surrounding environment is lost. And this remains a determinant of cancer development and progression. This invalidates mutagenic tests and necessitates something much simpler as a general concept of behaviour: elimination of contamination.

What conclusions can be reached on the thesis of Nitrosogenesis and Oncopharmacogenesis, also related to our 2 new patients presented?

**Beta blockers and melanoma/patient 1:**

Potentially or actually contaminated combined intake of bisoprolol with valsartan/hydrochlorothiazide and amlodipine (again contaminated with nitrosamines) could be associated, according to literature data, with subsequent development of 2 melanomas and dysplastic nevi (1). In all likelihood, the clinical presentation corresponds with the severity of nitrosamine contamination within the polycontamination (1).

The potential contamination of bisoprolol with another, possibly/ actually contaminated agent such as furosemide, for example, could be associated with the simultaneous development of melanoma and two keratinocytic tumors (3). Nitrosamines in this case also remain in sight as a possible/potential pathogenetic inducer (3).

Beta blockers (bisoprolol/ nebivolol) in combination with the ACE inhibitor perindopril, are also associated with the development of metastatic melanoma based on nevus spilus (42).

The development of nodular melanoma in the dorsal area has also been observed after the intake of potentially/actually nitrosamine-contaminated Valsartan/hydrochlorothiazide and bisoprolol (43).

In addition to polymedication in the context of potential polycarcarcinogenesis, it could also be considered that the contamination of monomedication of beta blockers and bisoprolol in particular, could be risky in terms of melanoma development. Or the lentigo maligna melanoma that we describe. At least as a cofactor.

**Moxonidine, amlodipine and perindopril and melanoma: patient 2**

Moxonidine is not listed as a potentially nitrosamine-contaminated or NDSRIs drug on the 2023 FDA list (5) but is available as nitroso contamination 1 to 3 (44-46). Its future categorization in the nitroso-contamination list cannot be ruled out.

Calcium antagonists, such as Rilmenidine and lercanidipine, in the context of polymedication and possible polycarcarcinogenesis, are generally associated (regarding some new data) with the possibility of playing as a cofactor role in the development of cutaneous melanomas and dysplastic nevi (47).

Our clinical observations regarding amlodipine administration and subsequent development of melanomas against the background of concurrent polymedication and possible nitrosamine contamination are similar (1).

Similar and complementary observations regarding monomedication with calcium antagonists and the development of melanomas have been recently published by an American collective in the form of a meta-analysis (21). Although percentage-wise this relationship is not strong, it remains present or causally associative (21).

Finally, it would be appropriate to shed some light on the ACE inhibitor perindopril taken by our second patient and its association with melanoma.

The intake of ACE inhibitors and subsequent development of melanomas was described as early as 2017 in an enigmatic article by Beatrice Nardone and colleagues (14), which subsequently became the occasion for many of our subsequent prospective analyses and follow-ups over the years, most of them confirmatory in nature. Seven years later, another American meta-analysis was confirmatory again regarding the intake of ACE inhibitors and the subsequent development of melanomas (21). Percentage differences of these confirmatory data could also be explained by different degrees of contamination of the drug production over the years and in the respective geographical regions (14, 21). Contamination is not a constant but a variable.

The dilemma for ACE inhibitors remains to be determined - is the active substance responsible for the procarcinogenic effect or the so-called nitroso component (in contaminated preparations) Or maybe both?

As data are not lacking in both directions.

While some authors are of the opinion that, under experimental conditions, treatment of already present melanoma cells with lisinopril could potentiate their aggressive behaviour (48), the administration of potentially nitrosamine-contaminated...
perindopril in real patients could (according to other authors) be the cause of melanoma development and progression (49). Experimental results should not be regarded as absolutely conclusive because of the loss of complexity of the ‘environment’. They could be indicative, guiding.

The data on the use of tramadol in the context of polymedication/polycollaboration with nitrosamines are analogous, although cataloguing of this agent in the FDA list is probably still pending (47). Melanoma precursor lesions and basal cell carcinomas have also been described after receiving Ramipril and bisoprolol (50). According to the authors, the link here is again or could be seen as the result of the availability of teh so called nitrosamines (50).

Conclusions

Old but also multiple new analytical data from the international medical literature link the intake of ‘pure’ antihypertensive drugs of a heterogeneous class to the generation of skin cancer and melanomas in particular (14, 21-23). However, they do not thematize so-called nitroso-contamination (14, 21-23), which does not rule it out in practice. Lack of thematization is very often a cause of estabilisation of significance and is an unfortunate attempt to dull the attention in a radically different direction.

Precisely because of this fact, the thesis of drug-induced Nitrosogenesis in the context of Oncopharmacogenesis and Photo(nitroso) carcinogenesis, remain to be the only ‘life jackets’ for pharmaceutical companies and patients: formalizing the real concentrations of carcinogens and striving for their complete elimination.

Companies and regulators will be forced to label available carcinogens and their real concentrations on drug packaging, as this will be the only opportunity to clean up their subsequently badly damaged “contamination image” and regain the trust of the patients. This would not be possible by establishing daily acceptable doses for a given carcinogen, but only by eliminating it completely from the drug menu.

This safety door would help create parallel regulatory sites in each nationally responsible institution or country to confirm or reject the presence of these carcinogens as contaminants in each and every drug. Elimination regimes for carcinogens will be enforced by the scientists of the world in a coercive manner, but with a non-profitable goal: by formalizing the objective, purifying truth. This truth is binding, not coercive. Therefore, it will impose itself.

Failure or delay in introducing elimination regimes will leave the shadow of carcinogenicity hanging with full force over pure substance.

Shifting the blame to its true causative agents is proving extremely difficult in practice due to the fact that their official availability (of nitrosamines) has been hidden for decades.

Even more unfavourably, calcium antagonists for example are also associated with the development of other types of carcinomas such as that of the prostate for example (51). The nitrosocomponent could again be seen as probably the leading one.

Analogous and even more interesting are recently formalized results observed in the treatment of pregnant mothers with antihypertensive drugs that link the postpartum period (up to 13 years of age) with the occurrence of acute lymphocytic lymphomas and non-Hodgkin lymphomas (52). The significance of this medication and subsequent neoplasm development was nearly two fold: acute lymphocytic lymphoma [hazard ratio (HR) = 1.87, 95% Confidence Interval (CI) 1.32 - 2.65] and non-Hodgkin’s lymphoma (HR = 1.96, 95% CI 1.34 - 2.86) (52).

The Era of Nitrosamines in medicine has been relevant for years, but even more relevant today. Its detailed decoding is under constant update. The undertaking of this long, hard and painful journey has the goal of finding and validating the right solutions that would lead to a drastic decrease in the incidence of melanomas, but also of cancer in general, worldwide. It is a matter of desire and of perspective.

The activation of carcinogenesis in the context of metabolic reprogramming of the tum or cell is a complex multi-step process. This process could also be activated in the context of contact with carcinogens/nitrosamines in the form of drug intake, possibly also at low doses or doses that are defined by regulators as daily acceptable intake doses. The assays recommended by the regulators could not be considered as an adequate model for assessing carcinogenic activity under real conditions, in vivo and in patients. They are based on a static assessment of a given condition and do not comment on complex action, so in practice, they remain completely redundant.

Will anyone take responsibility at all?

So far, 75,000 patients after “various classified” forms of cancer after taking a certain single drug containing NDMA are apparently not convincing enough evidence for the courts of the world.

It is strange how verdicts of acquittal in court are reached on the basis of the same conclusions, namely that: “Following the 16 epidemiological studies looking at human data regarding the use of ranitidine, the scientific consensus is that there is no consistent or reliable evidence that ranitidine increases the risk of any cancer (53)”. But apparently the court decisions also remain mixed, as there is another decision on June 6, 2024 regarding carcinogens or NDMA in ranitidine, for example, and that is: “June 3, 2024: In the best news in this litigation in a long time, a Delaware judge ruled that GSK, Pfizer, and other pharmaceutical companies must face state court trials for claims that their former heartburn drug Zantac causes cancer. Superior Court Judge Vivian Medinilla determined that the evidence presented by consumers is valid and warrants a jury’s assessment. Again, this impacts about 75,000 lawsuits that have been filed in Delaware following the federal case dismissals (54).”

Suddenly, data emerge, unclear, previously unknown, until recently denied completely, but in fact emanating both from the
academic and medical community to the executive drug agencies of the world, but also to law firms: about a new 75,000 tumors, conditioned by the intake of a single drug contaminated with NDMA (54)? And this substance is still classified as a "potential human carcinogen" (55)? The question remains open: are 75,000 cancer claims after intake of a single NDMA-contaminated drug sufficient to turn it into an actual human carcinogen? The United States Environmental Protection Agency would certainly have to rethink the categorizations in question very seriously in order to, or if it wants to, maintain the confidence of end users.

These decisions should not be made on the basis of static tests such as the Ames test, CPCA test and others, but also on the basis of clinico-pathological correlations and dose-dependent time intervals, which remain for the time being the most objective criteria for establishing causal relationships concerning melanomas and contaminated drug intake. The reason therefore remains the complexity of carcinogenesis in real-life settings and its consideration of factors such as metabolic reprogramming of the tumor cell-again an interesting, multi-step, multifactorial process.

Following science-based logic, regulators should be aware that the only sure step to solve the problem globally is and remains elimination regimes for nitrosamines and nitroso derivates. Following the objective truth remains the surest bargaining chip or guarantor of success for the benefit of an entirely universal human cause. Drug-induced carcinogenesis and Oncopharmacogenesis/Pharmacogenic of skin cancer represent a new interpretive cause. Drug-induced carcinogenesis and Oncopharmacogenesis/Pharmacogenic of skin cancer represent a new interpretive cause.

References


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