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LETTER TO THE EDITOR

Nitrosamines in antihypertensives, metformin and ranitidine as cofactors for melanoma and development of other cancers. Expert group opinion

Nitrosaminas em anti-hipertensivos, metformina e ranitidina como cofatores para melanoma e desenvolvimento de outros cancros. Artigo de opinião

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To stress the issue of sartans as a possible cause of various cancers as already reported in the case "Insights into the development of lentigo maligna and dysplastic nevi: Spotlight on the possible relation with sartans, thiazides and nitrosamines" published in vol no. 3, 2022 of this journal[1], we want to inform that there is currently no clarity on the part of regulators as to whether (1) nitrosamines (as an additional contaminant) and/or (2) the active substance of angiotensin receptor blockers are responsible for the "procarcinogenic" effect of these drugs[2].

Nevertheless, the relationship between the sartan intake and all types of neoplasms seems increasingly real, and its statistical significance has become more pronounced over the years[3].

A number of experimental data initially shed some light on the use of the sartans and the risk of melanoma as early as 2018/2019, but unfortunately did not contain definite information on whether the active substance used in their research included nitrosamines or not.

Clinical follow-up on the subject over the last decade has categorically supported the experimental data and again favors a serious risk of developing melanoma after taking the sartans. The statistics in these studies are also supportive, but still,

there is no evidence of the presence or absence of potential contamination with nitrosamines.

According to the data in the world literature, nitrosamines found so far in the sartans, and valsartan, in particular, could be up to three and according to various models for calculating the risk of cancer, the theoretical risk would be increased from 3 to 4 times[4].

Isolated publications in the world literature have focused the scientific community's attention not only on the risk of potential contamination of affected batches of the sartans with nitrosamine but also emphasize the additional "aggravation" of this risk (of melanomas, for example) due to concomitant use of thiazide diuretics[5]. By acting in a similar way (proven contamination by nitrosamines in the thiazide itself, or in combination with the sartans), or in a different pathogenetic way (i.e., photosensitization), thiazide diuretics increase the risk of developing both melanocytic and nonmelanocytic skin cancers[5].

In 2022, Pfizer surprisingly withdrew the Angiotensin-converting enzyme (ACE) inhibitor quinapril, the diuretic

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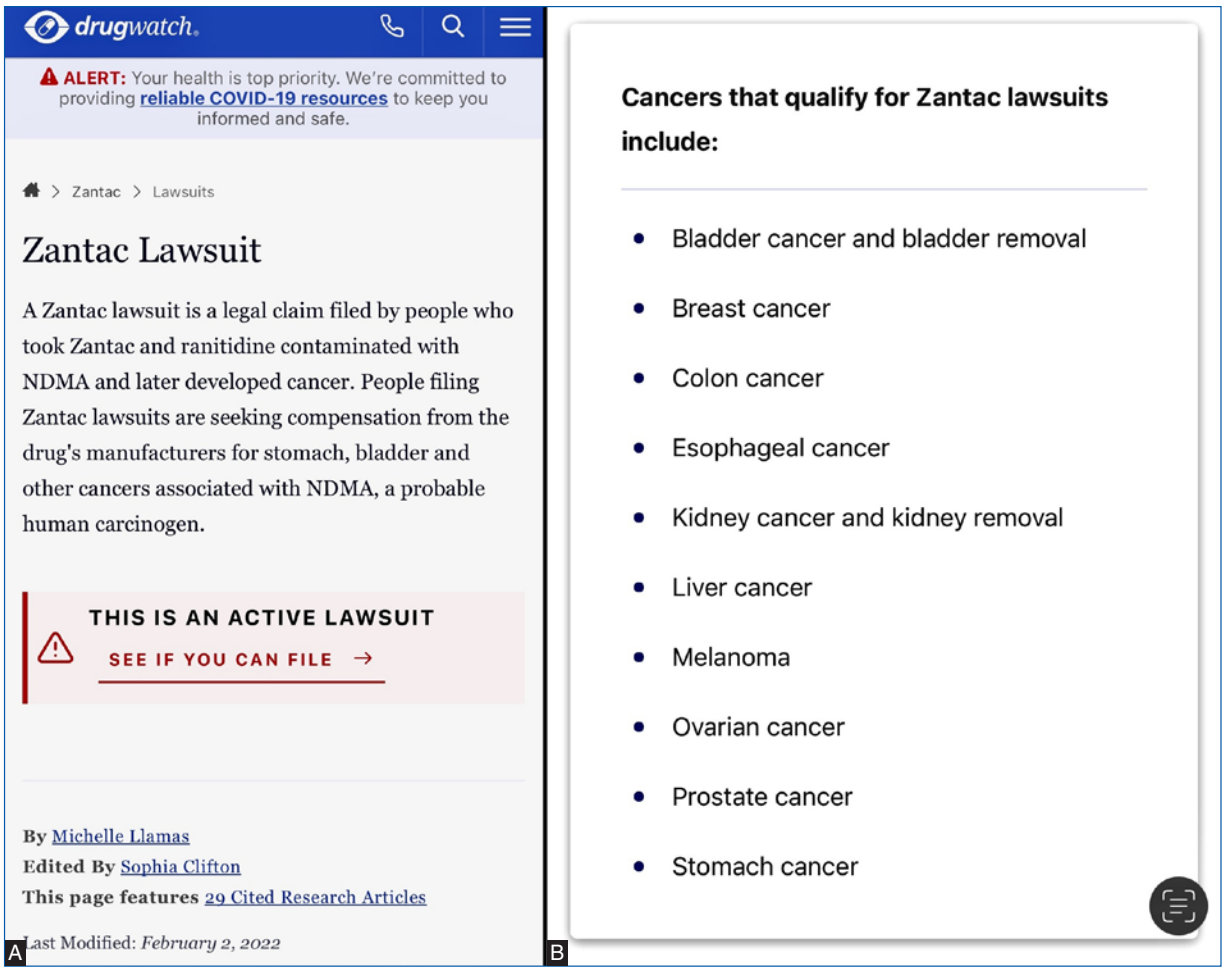

Figure 1. Drugwatch/FDA's list of compensatory claims for patients taking ranitidine/Zantac (contaminated with nitrosamines). **A**: what is a Zantac lawsuit. **B**: cancers that qualify for Zantac lawsuits.

drug hydrochlorothiazide, and the combination products containing these two ingredients due to an N-nitroso quinapril concentration well above the so-called acceptable daily intake level[6].

The contamination of metformin, ranitidine, and rifampicin with nitrosamines has been repeatedly demonstrated over the years, and several batches of these agents have been withdrawn from the market.

Polymorbid patients with diabetes who are treated with metformin could similarly be at risk for the development of melanoma or other tumors due to contamination with N-nitrosodimethylamine (NDMA)—the same ingredient found in sartans and ranitidine. Metformin is often prescribed in parallel with sartans and thus further increases the risk of developing melanoma or other skin neoplasms or preneoplastic conditions[5,6].

The nitrosamine NDMA found as a contaminant in ranitidine has been associated with an increased risk of developing melanoma since 2021, according to official DRUG WATCH/FDA data[7], although there is no evidence of even a single publication in the world scientific literature about that relationship.

By February 2022, however, melanoma was again included in the DRUG WATCH/FDA's list of compensatory claims for patients taking ranitidine/Zantac (contaminated with NDMA), but only a few months later it was removed from the bulletin without any explanation (Fig. 1a, 1b)[8]. It is curious that, despite the growing number of melanomas in the world literature after taking potentially NDMA-contaminated sartans, DRUG WATCH/FDA does not include them in the compensation claims of those affected. On the contrary, they were excluded from this group for Zantac on May 5, 2022 (whereas they were initially included on February 2, 2022), despite the growing number of scientific publications favoring the pathogenetic link between NDMA and the development and progression of melanoma.

After an in-depth analysis of the published data (DRUG WATCH), it could be reasonably assumed that, in the face of the FDA/European Medicines Agency, the regulatory authorities should have unpublished data sheets for self-reported side effects that prove or are at least highly indicative for the presence of a link between ranitidine intake and the development of melanoma.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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