Comment on: Exploring the association between weight loss-inducing medications and multiple sclerosis: insights from the FDA adverse event reporting system database

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Shirani *et al.* used the US adverse events reporting database to perform a disproportionality analysis and raised repurposing hypotheses regarding the beneficial effect of antidiabetic drugs with weight loss-inducing effects in multiple sclerosis (MS).[1] The results generated considerable interest in the scientific community with echoes in health-related news.[2]

Although drug repurposing using adverse event reporting databases represents an emerging research area in pharmacovigilance, we would like to express concern about both results interpretation and methodological aspects.[3] The authors specifically aimed at detecting inverse associations, defined by an upper limit of the 95% confidence interval for reporting odds ratio (ROR) < 1, and suggested a potential for repurposing GLP-1 receptor agonists, SGLT2 inhibitors and metformin in MS, the *adverse event* of interest. However, the interpretation of a statistically significant negative ROR as inverse causality (i.e. a potential protective effect) is highly controversial for a number of reasons, including the fact that cases collected in these databases are mostly voluntarily reported when a drug is suspected to cause an adverse event (not a beneficial effect) and inherent limitations such as unanticipated reporting biases, lack of certainty on causality, unknown population exposure, and interdependence of disproportionality measures. Therefore, inverse disproportionality signals should rather be described as a *lower-than-expected* reporting of MS with weight-loss-inducing drugs, especially as the pathophysiological basis linking obesity to MS remains elusive.[4] Moreover, this Brief Report did not fully disclose a number of key methodological issues (e.g. duplicate removal, selection of the comparator) and, importantly, there was neither attempt for diagnosis confirmation nor for controlling biases and confounders (competition bias, channeling bias, co-prescription bias, and confounding by indication), no use of positive/negative controls, lack of sensitivity/robustness analyses (e.g. removing cases where at least one co-reported drug used for MS or having MS as indication was recorded).[5]

Innovative methods are needed beyond the mere interpretation of inverse disproportionality signals. For example, the development of methods for matching adverse event profiles and metabolomic or genetic signatures appears promising, since they incorporate a biological rationale.[3,6] Moreover, complementing pharmacovigilance data with other sources such as in vitro/in silico testing of drug candidates may allow to prioritize and exclude some biased signals.[7] Exploring drug-induced disorders could represent an additional "bedside to bench" hypothesis-generating approach, especially for neurological diseases with unclear multifactorial etiology such as MS:

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the identification of drugs plausibly associated with MS sharing targets potentially associated with the development or worsening of the disease may open new avenues for translational studies to investigate relevant disease mechanisms.[8,9]

In summary, we believe it is still too early to consider antidiabetics as real candidates for MS on the sole basis of an inverse association in disproportionality analysis. Before pursuing further complementary methodologies and prospective studies (as advocated by the authors), a better understanding of the underlying biological basis between obesity and MS, as well as the actual pleiotropic effects of antidiabetics in neuropsychiatric disorders, is warranted.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Charles Khouri: Conceptualization; Writing – original draft.

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Competing interests
The authors declare that there is no conflict of interest.

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References

1. Shirani A, Cross AH and Stuve O. Exploring the association between weight loss-inducing medications and multiple sclerosis: insights from the FDA adverse event reporting system database. *Ther Adv Neurol Disord* 2024;17:17562864241241383.

2. *Altmetric. Altmetric database in JSON format. Unpublished raw data,* https://sage.altmetric.com/details/161543995 (2024)

3. Morris R, Ali R and Cheng F. Drug repurposing using FDA Adverse Event Reporting System (FAERS) database. *Curr Drug Targets* 2024; 25(7): 454–464.

4. Cutroneo PM, Sartori D, Tuccori M, et al. Conducting and interpreting disproportionality analyses derived from spontaneous reporting systems. *Front Drug Saf Regul* 2024; 3: 1323057.

5. Fusaroli M, Salvo F, Begaud B, et al. The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): development and statement. *Drug Saf* 2024; 47(6): 585–599.

6. Zaza P, Matthieu R, Jean-Luc C, et al. Drug repurposing in Raynaud's phenomenon through adverse event signature matching in the World Health Organization pharmacovigilance database. *Br J Clin Pharma* 2020; 86: 2217–2222.

7. Chrétien B, Jourdan J, Davis A, et al. Disproportionality analysis in VigiBase as a drug repositioning method for the discovery of potentially useful drugs in Alzheimer's disease. *Br J Clin Pharma* 2021; 87: 2830–2837.

8. Antonazzo IC, Raschi E, Forcesi E, et al. Multiple sclerosis as an adverse drug reaction: clues from the FDA Adverse Event Reporting System. *Expert Opin Drug Saf* 2018; 17: 869–874.

9. Gaimari A, Fusaroli M, Raschi E, et al. Amyotrophic lateral sclerosis as an adverse drug reaction: a disproportionality analysis of the Food and Drug Administration Adverse Event Reporting System. *Drug Saf* 2022; 45: 663–673.