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Response to Xing et al.: post-marketing safety concerns with Lecanemab: a pharmacovigilance study based on the FDA adverse event reporting system database

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Abstract

A recent paper published a lecanemab analysis with data from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. While the authors mention the limitations of FAERS, such as "voluntary (underreporting), the inability to establish causality, reporting bias, data quality issues, and the absence of a denominator, which precludes calculating incidence rates", they proceed with generalizations, clinical conclusions, and even treatment recommendations based on the crude disproportionality analysis. Consideration of post-marketing safety reports, including those found in the FAERS database, is an essential component of pharmacovigilance. However, FDA guidance [2, 3] highlights that: (1) "Rates of occurrence cannot be established with reports," (2) "Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes," and (3) "Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug." The FAERS database includes reports from many sources, including reports by companies, as well as from health care professionals and consumers. The reports in the FDA database have significant limitations, including submission of incomplete, inaccurate, untimely, duplicate, relatedness to drug uncertainty, and/or unverified information. Therefore, broader generalizations, clinical conclusions, and treatment recommendations should not be made based solely on FAERS databases analyses.

Keywords Lecanemab, FAERS, Limitations, Unsupported conclusions

Response

We would like to comment on the Xing, et al., publication on FAERS analysis of lecanemab, entitled '*Post-marketing safety concerns with lecanemab: a pharmacovigilance study based on the FDA Adverse Event Reporting System database*' [1]. While the authors mention the limitations of FAERS, such as "voluntary (underreporting), the inability to establish causality, reporting bias, data quality issues, and the absence of a denominator, which precludes calculating incidence rates", they proceed with generalizations, clinical conclusions, and even treatment recommendations based on the crude disproportionality analysis.

Consideration of post-marketing safety reports, including those found in the FAERS database, is an essential component of pharmacovigilance. However, FDA guidance [2, 3] highlights that:

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- "Rates of occurrence cannot be established with reports".
- "Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes".
- "Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug".

The FAERS database includes reports from many sources, including reports by companies, such as Eisai, and from health care professionals and consumers. The reports in the FDA database have significant limitations, including submission of incomplete, inaccurate, untimely, duplicate, and/or unverified information. One post-marketing requirement for lecanemab is for Eisai to submit adverse event reports to the FDA regardless of whether anyone considers the event to be related to lecanemab. Therefore, it is incorrect to assume that all the events in the FAERS database are considered as potential adverse drug reactions. In addition, despite the FDA's efforts, there are frequently duplicate reports in FAERS because of the same event being reported by more than one party, and these are not straightforward to detect.

We note that the analysis is from the time period Jan 1, 2023 to June 31, 2024. Lecanemab received accelerated approval on Jan 6, 2023, and full approval with Center for Medicare Services (CMS) reimbursement under Coverage with Evidence Determination (CED) on July 6, 2023, with gradual treatment uptake in the United States after this time point. Many of the reports in FAERS are from clinical trials and the open label extensions, for which updated safety data was published [4]. The events reported in FAERS to date are consistent with the safety profile in the United States prescribing information and labels in the other countries in which lecanemab has been approved (Japan, China, Korea, United Arab Emirates, Hong Kong, Israel, United Kingdom, Mexico and Macau, as of Jan 1, 2025). Post-marketing safety studies, including registries, are ongoing in United States, Korea, Japan, and are being initiated in the United Kingdom and European Union (pending European Commission Decision after the positive CHMP opinion received Nov 14, 2024 [5]), which will provide higher quality real world data on the safety profile of lecanemab and will not be subject to the significant limitations of reports submitted to FAERS.

As noted above, we are concerned about the generalizations, clinical conclusions, and even treatment recommendations the authors have published based on their analysis. For example, the authors state in the first sentence of the Discussion section that '*our findings reveal notable safety concerns, and we identified four key findings.*' This statement is both a generalization and overstates the results beyond what the data warrants. In addition, Xing et al. state in the first sentence of the Conclusions section: '*Our analysis identified new and unexpected lecanemab-related AEs not previously reported in regulatory trials, such as tremor, migraine, pancreatic carcinoma and brain fog, highlighting the need for prescribers to be vigilant about these AEs.*' These are examples of *clinical interpretation and generalization* based off data that is inadequate to make these conclusions. Attributing these as "lecanemab-related AEs", directly contradicts to the FDA's guidance that causality cannot be established on the basis of FAERS reports. For example, the authors highlight "pancreatic carcinoma" when all the reports in FAERS as of the date accessed by the authors of pancreatic carcinoma reflect clinical trial adverse events without any suspected relationship to lecanemab; events on placebo are not reported to FAERS database. Another example can also be found in the Conclusion section, where the authors state: '*Certain patient subgroups, particularly for polypharmacy for Alzheimer's disease, aspirin, acid-suppressing medications, statins, antidepressants or benzodiazepines, may be more vulnerable to serious AEs. This underscores the importance of careful monitoring and risk assessment in these vulnerable populations to enhance patient safety and help with the clinical decision-making process. These results have significant implications for clinicians, patients, and policy-makers regarding lecanemab.*' FAERS analyses have significant limitations and so it is just not scientifically supported to state that the analyses presented in this paper have 'significant implications.' Although not explicitly stating the word 'recommendation,' this summary statement is clearly making the *recommendation* to consider the findings of this FAERS database analysis when prescribing lecanemab to any individuals who are on multiple therapies, which is not a claim supported by this analysis. As with all FAERS analyses, the data needs to be presented with the significant limitations and recommendations need to be based on the totality of data available, including well-controlled clinical trial data and all components of pharmacovigilance.

Articles analyzing adverse event entries for a medication with data from the FAERS database have become commonplace, with over 300 papers published in just the past year. Given the ubiquitous nature of this type of FAERS database analysis article in the literature and the clear limitations of the FAERS data, it is important to consider the implications of these above-mentioned shortcomings to clinical practice in general. First, these limitations may lead to inflation of risk attributable to a medication based on the FAERS pharmacovigilance. This perceived enhanced risk could then lead the scientific community to be hesitant to treat an individual that may benefit from therapy because of non-validated safety

concerns from a FAERS database analysis. In addition, due to the lack of clear causality of an adverse event in the FAERS database, the danger exists that a clinician could miss the actual cause of an adverse event, allowing an individual to move forward potentially without medication and proper mitigation of the side effect. The most rigorous information on the benefits and risks of treatment, including the boxed warning for amyloid related imaging abnormalities, are in the prescribing information for lecanemab.

Given these clear issues, we urge the scientific community in general, journal editors, and peer reviewers to proceed with caution when evaluating FAERS database publications, especially when more informative sources of safety data are available (such clinical trials, registries, post-marketing studies, electronic health records and claims databases). Careful review is necessary to place the output of these analyses in proper context for benefit-risk discussions with clinicians and patients.

Abbreviations

CED	Coverage with Evidence Determination
CHMP	The Committee for Medicinal Products for Human Use
CMS	Center for Medicare Services
FAERS	FDA Adverse Event Reporting System
FDA	United States Food and Drug Administration

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