Letter to the Editor

Cephalalgia
An International Journal of Headache

International Headache Society

Complementary, but not equivalent: Clarifying the role of RWE and RCT in migraine research

Cephalalgia
2025, Vol. 45(10) 1–2

DOI: 10.1177/03331024251381333
journals.sagepub.com/home/cep

Sage

Keywords
migraine treatment, neuromodulation, randomized controlled trial, real-world evidence

Date received: 6 September 2025; accepted: 7 September 2025

We thank Lax et al. (1) for their thoughtful response, which adds valuable perspectives to this important discussion on evidence generation in migraine research. Their defense of real-world studies emphasizes the complementary nature of different research methodologies, and we agree that this should not be framed as an "either-or" debate. The study by Ailani et al. (2) represents a landmark contribution to neuromodulation research, providing the largest dataset on timing effects in this therapeutic domain. Such comprehensive real-world data offer critical insights into treatment patterns, patient behavior and clinical effectiveness that are difficult to capture in traditional controlled settings. The study findings on early intervention align with established biological principles and offer practical suggestions that clinicians can reasonably incorporate into decision-making. However, several points merit further consideration to advance our collective understanding of optimal evidence hierarchies.

While the scale and clinical relevance of this real-world data are undeniable, the fundamental challenge remains in distinguishing causation from association. Patients who treat early may differ systematically from those who delay treatment in ways that independently influence outcomes, such as migraine severity perception, attack phenotype, treatment adherence, intake of other acute medications or healthcare engagement. Without randomization, these confounders cannot be disentangled from true timing effects. Although prospectively filled electronic diaries minimize recall bias, real-world studies often face additional limitations, including incomplete confounder adjustment, missing data, and non-adherent reporting to standardized outcome measures (3).

Biological plausibility for early intervention, while well established (4), cannot substitute for empirical demonstration in neuromodulation contexts. Pharmacological timing effects achieved their evidence base through placebo-controlled trials that explicitly controlled for expectation and selection biases (5,6).

Lax et al. (1) correctly highlight where real-world studies excel: demonstrating effectiveness in diverse populations, identifying safety signals and characterizing treatment patterns. For truly establishing causal timing effects, particularly when recommendations may influence vulnerable pediatric populations, controlled trials remain essential for their ability to minimize confounding variables and apply rigorous methodological standards.

The US Food and Drug Authority's real-world evidence (RWE) framework explicitly recognizes this hierarchy, emphasizing the value of RWE for questions that are difficult to address through traditional randomized control trials (RCTs) and for post-marketing surveillance, while maintaining controlled trials as the gold standard for causal inference (7). Similarly, International Headache Society guidelines state that RWE "is not a substitute for evidence from RCTs, rather it is complementary" (3).

Importantly, these discussions extend beyond academic debate. Coverage determinations often hinge on perceived evidence strength. Overemphasizing the limitations of RWE without acknowledging its clinical utility may inadvertently jeopardize patient access to effective therapies such as remote electrical neuromodulation (i.e. REN). While RCTs remain the gold standard for causal inference, RWE provides critical complementary insights that inform both clinical practice and health policy. A balanced interpretation is essential to ensure reimbursement frameworks evolve in step with scientific progress and patient needs. Rather than viewing these as competing paradigms, leveraging robust real-world data to inform the design of targeted controlled studies can be useful. Innovative trial designs could compare optimal timing with current standard practice without requiring deliberately delayed treatment, which is an especially important consideration for pediatric populations where treatment options remain limited (8).

The field benefits most when we maintain clarity about the comparative strengths of different evidence types while

recognizing their complementary roles in advancing patient care. Real-world studies, such as that by Ailani et al.,[2] provide invaluable insights that should guide clinical practice as we work toward more definitive causal evidence where feasible and ethically appropriate.

Declaration of conflicting interests

Mario F.P. Peres has received honoraria as a consultant and speaker from Ache, Allergan-AbbVie, Eli-Lilly, Eurofarma, Libbs, Lundbeck, Novartis, Pfizer, Sanofi and Teva. He is President of the International Headache Society.

Hsiangkuo Yuan, in the past 24 months, has received funding from AHS Early-Stage Investigator Research Award; institutional support for serving as an investigator from Teva, AbbVie, Ipsen, Pfizer, Parema, Shiratronics, Johnson & Johnson and Lundbeck; consultant/advisory fees from Salvia, AbbVie, Pfizer and Cerenovus; and royalties from Cambridge University Press and MedLink Neurology.

Cristina Tassorelli has received personal fees for participating in advisory boards or for lecturing at sponsored symposia for AbbVie, Dompé, Eli Lilly, Ipsen, Lundbeck, Medscape, Pfizer and Teva. She is principal investigator or collaborator in clinical trials sponsored by AbbVie, Eli Lilly, Ipsen, Lundbeck, Pfizer and Teva. She has received research grants from the European Commission, the Italian Ministry of Health, the Italian Ministry of University, the Migraine Research Foundation and the Italian Multiple Sclerosis Foundation.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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