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The importance of treating migraine attacks early – even in youth: A real-world argument for neuromodulation

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Early intervention represents a fundamental principle in medicine. Ailani et al. (1) assessed the efficacy of Remote Electrical Neuromodulation (REN) in a robust sample of 55,261 patients and nearly 600,000 migraine treatments, providing compelling real-world evidence on the importance of early intervention. In migraine pathophysiology, the concept that acting before the whole cascade of events leading to the full-blown attack fully develops can meaningfully alter the trajectory of an attack is well established through both experimental and clinical research (2,3-9). Similarly to pharmacological intervention, offering REN early before the full-blown attack is reasonable.

Similar to the pivotal trial where REN was offered within one hour of headache onset (10), in this study, Ailani et al. (1) demonstrate that initiating REN within one hour of migraine onset significantly enhances therapeutic outcomes, doubling the likelihood of pain freedom (28.8% vs. 14.5%) and considerably improving functional disability and associated symptom resolution compared to delayed treatment.

Importantly, this benefit was also evident in the pediatric population, where evidence generation faces unique constraints. Among the 8886 youths who performed 82,040 treatments, early REN use showed remarkable benefits, with some outcomes even exceeding those seen in adults. Considering the challenges in conducting controlled trials in pediatric populations (11), these findings are especially valuable and reflect REN's promise as a non-pharmacological option for children and adolescents with migraine. The pediatric data provide crucial evidence for a population with limited treatment options, and safety considerations are paramount.

The methodological approach employed by Ailani et al. (1) represents a paradigm particularly well-suited to timing research, despite introducing substantial methodological concerns. Traditional randomized controlled trials face regulatory constraints requiring moderate to severe baseline pain for acute treatment studies, creating an artificial barrier to investigating true early intervention effects. Real-world evidence studies, by contrast, capture naturalistic treatment behaviors that better reflect optimal clinical practice recommendations for early intervention. By leveraging patient-reported outcomes via a companion app, Ailani et al. (1) captured treatment behavior in everyday settings, enhancing the ecological validity of their findings. While such methodology introduces limitations, including potential recall bias and subjective reporting, it reflects how patients truly use REN in practice. To mitigate these limitations, Ailani et al. (1) employed strict definitions of 'evaluable treatments' (requiring both baseline and two-hour follow-up) and used statistical corrections for multiple comparisons ($p < 0.007$).

However, this real-world evidence design introduces substantial methodological concerns that warrant careful consideration. The study population represents a highly selected cohort of motivated app users willing to consistently report treatment data, potentially creating relevant selection bias toward more adherent and technologically engaged patients. The reliance on patient-reported timing introduces considerable recall bias because patients must accurately remember and report when their migraine began relative to treatment initiation – a challenging task during the acute pain state. Moreover, the absence of a randomized control group or blinding leaves the door open to contextual effects and subjective biases. This raises an enduring question in clinical research: what carries more weight, real-world outcomes in tens of thousands of patients or smaller but rigorously controlled clinical trials? This dilemma becomes particularly pertinent in pediatric research, where randomized controlled trials present several challenges (11). In this context, we must ask: Is the real-world data speaking louder than the clinical trial?

The regulatory environment presents additional complexity, as non-invasive medical devices are often subject to different approval standards than pharmaceuticals, raising valid concerns about evidence thresholds. Conversely, weak evidence of efficacy can result in limited accessibility to the device, meaning that those who could benefit from the treatment may ultimately be unable to access it. However, patient experiences and clinical realities deserve consideration alongside methodological rigor. Scientific societies must strive for higher evidence standards without dismissing patient voices or real-world use. The challenge lies in balancing scientific rigor with clinical utility, ensuring that regulatory frameworks do not inadvertently limit our understanding of optimal treatment strategies. Achieving this balance remains a key challenge in the evolving landscape of neuromodulation research.

The study by Ailani et al. (1) provides suggestive evidence that early intervention with REN may improve

acute migraine outcomes, with particularly pronounced apparent benefits in pediatric populations. However, the substantial methodological limitations, including selection bias, recall bias, and expectation bias, preclude definitive conclusions about causality. While the principle that timing matters in migraine treatment is well-established for pharmacological interventions, extending this concept to neuromodulation requires more rigorous investigation.

Despite their limitations, the observed associations represent the largest dataset available on neuromodulation timing effects and warrant consideration in clinical practice. Healthcare providers should counsel patients about the potential benefits of early treatment initiation at the same time as acknowledging the uncertainty inherent in current evidence. Future research must address the identified methodological shortcomings through randomized controlled trials with objective timing verification, standardized baseline severity measures and appropriate blinding strategies. Until such evidence emerges, early treatment recommendations for neuromodulation should be considered provisional, supported by biological plausibility and observational data, but lacking the certainty that guides pharmacological timing recommendations. Early treatment is not just a clinical recommendation; it represents a strategic imperative that deserves rigorous investigation in optimizing outcomes in migraine care.

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