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Letter to the Editor

Efficacy and Tolerability of Valproate Versus Topiramate in Migraine Prevention, A Randomized Controlled Multi-Center Trial

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DEAR EDITOR,

We commend the authors for their work in the published article "Efficacy and tolerability of valproate versus topiramate in migraine prevention, a randomized controlled multi-center trial," which provides valuable insights into the comparative efficacy of two well-established antiepileptic drugs, valproate and topiramate, for the treatment of migraine [1]. While this study makes a significant contribution to the field, certain aspects warrant further discussion to enhance the robustness of the findings. In this study, the authors have described a well-structured randomization process by using a blocked randomization sequence obtained through computer-generated random numbers; however, since the authors have used a fixed block size of four, this can introduce predictability, potentially introducing selection bias. To mitigate this risk, more robust randomization methods, such as stratified randomization or an Interactive Response Technology (IRT) system, could have been considered, which provide better allocation concealment and adaptability, ensuring a more rigorous and unbiased trial design, in accordance with a multicenter RCT by Wang et al. which was a large multicenter study conducted in different centers across 11 countries, using IRT system provided a centralized randomization which helped maintained consistency across different regions and hence contributed to its strength [2]. Although the study is single-blinded to the investigators, however, since patients are not blinded, experiencing different adverse effects specific to valproate and topiramate may lead to unexpected recognition of their assigned treatment, which could compromise blinding. Since double-blinding is a fundamental component of high-quality RCTs [3], using a double-blind design, where patients and clinicians are unaware of treatment allocation, is crucial for minimizing such bias [4-7]. Even though migraine is associated with numerous comorbidities, the study did not include patients with pre-existing comorbid conditions. A systematic review described a bidirectional relationship between psychiatric comorbidities and migraine, with major depression and anxiety disorders being the most frequent psychiatric comorbidities associated with migraine and their potential common underlying mechanisms [8]. Another study identified migraine with aura as a significant risk factor for ischemic stroke and also discussed the bidirectional relationship between migraine and epilepsy. Therefore, future studies should consider including patients with comorbidities and implement tailored treatment approaches to enhance the applicability of their findings to real-world clinical settings [9]. There are a number of factors that impact migraine treatment that were not addressed. The MENA region is heterogeneous in terms of genetics, race, and ethnicity, highlighting the necessity to make generalizations with caution. Gormley et al.'s meta-analysis of 375,000 individuals identified 38 susceptibility loci for migraine. This means they found 38 specific locations on human chromosomes where genetic variations are associated with an increased risk of migraine [10]. Another review highlights the influence of race and ethnicity on pharmacokinetics. This has a direct impact on migraine medications [11]. Moreover, the study does not assess the influence of age, migraine subtype, or hormones on the treatment outcomes. A study explored

the effectiveness and tolerability of topiramate in patients with chronic migraine over a six-month period and indicated a significant reduction in migraine frequency and intensity, notably in women with menstruation-related migraines, suggesting hormonal influences may affect treatment response [12]. Therefore, we suggest a subgroup analysis for more robust results [13].The migraine study's reliance solely on comparing topiramate and valproate, without a placebo control, might raise concerns given the well-established susceptibility of migraine to the placebo effect. Research has demonstrated that subjective symptoms in migraine are particularly responsive to placebo interventions, with patients reporting significant improvements even when receiving inert treatments. Consequently, without a placebo group to account for these psychological influences, the observed reductions in VAS and HIT-6 scores in both the topiramate and valproate groups might be reflected. This limitation highlights the necessity for future studies to incorporate a placebo control arm to accurately assess the absolute treatment effects [14]. According to a meta-analysis, migraine prevention trials have seen an increase in placebo response during the previous three decades. When planning clinical trials and performing meta-analyses, this tendency should be taken into account [15]. Although the study has assessed the efficacy of the two drugs through symptom reduction. assessment of neuroimaging and migraine-specific biomarkers like calcitonin gene-related peptide (CGRP) and C-reactive protein (CRP) would provide a more comprehensive evaluation of efficacy and provide deeper mechanistic insights [16-18]. Finally, the present study evaluating only the short-time findings of the interventions warrants the need for extended follow-up periods to help assess relapse rates and late-onset side effects, which would strengthen the study's clinical relevance [19]. Addressing the aforementioned points would further strengthen the results of this study. Nevertheless, we commend the authors for their efforts in conducting this well-structured study of the comparative efficacy and tolerability of valproate and topiramate in migraine prevention. Its credibility is increased by its well-organized approach, which provide remarkable findings that can shape future treatment choices.

CRediT authorship contribution statement

Hafsa Shuja: Writing –original draft, Writing- review & editing, Conceptualization

Umer Wamiq: Writing –original draft, methodology, data curation

Hamida Memon: Investigation, Writing –original draft

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During the preparation of this work the authors used Chatgpt in order to enhance readability and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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