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INVITED COMMENTARY

Indigenous Clinical Evidence on Newer Anti-seizure Medications: The Need of the Hour

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Epilepsy is one of the common neurological conditions globally. Nearly 80% of 50 million persons with epilepsy (PWE) reside in low- and middle-income countries, with prevalence of lifetime epilepsy in Asian countries nearing 6.7 per 1000 [1, 2]. The prevalence of childhood epilepsy in India is around 0.8% with infantile epilepsies like infantile epileptic spasms syndrome accounting for 1.2% of epilepsy in children [3, 4]. Anti-seizure medications (ASMs) constitute the cornerstone of epilepsy management, complemented by surgical and dietary interventions in drug-resistant cases [5]. Until the early 1990s, treatment options were limited to six "first-generation" ASMs. The subsequent introduction of second- and third-generation ASMs, with improved tolerability and fewer systemic adverse effects, has transformed contemporary epilepsy care, enhancing treatment adherence and quality of life. There has been significant adoption of newer ASMs in clinical practice globally over the last two decades. However, this has been primarily based on evidence and trials from high-resource settings. Therefore, studies on newer ASMs in resource-limited settings are needed to address concerns of pharmacogenomic variations, socioeconomic factors, and cost- effectiveness.

Levetiracetam is a widely-used newer ASM globally. It is also an important alternative drug for benzodiazepine-resistant status epilepticus [6]. Oral levetiracetam has recently been included in the World Health Organization (WHO) Model List of Essential Medicines (EML) and Essential Medicines for Children (EMLc) for treatment of focal and generalized seizures, while parenteral levetiracetam has been included in a complementary list for benzodiazepine-resistant status epilepticus [7]. This is likely to increase its use in clinical practice by promoting access through government pharmaceutical formularies.

Despite its better safety profile, levetiracetam has been associated with behavioral adverse effects. It may trigger new-onset behavioral symptoms or exacerbate pre-existing issues. Concerns regarding levetiracetam-associated behavioral adverse effects—ranging from irritability and hyperactivity to aggression and mood dysregulation—have persisted, with reported prevalence varying widely across studies [8]. However, longitudinal data on this aspect for Indian children with epilepsy is sparse. Against this backdrop, the recent prospective cohort study assumes clinical and epidemiological relevance [9].

The methodological strength of this study lies in its simplicity and clinical clarity [9]. The prospective cohort design including 60 typically developing, drug-naïve children aged 4–12 years with epilepsy, with serial behavioral assessments at baseline, day 14, and six weeks, allowed emerging behavioral changes to be temporally linked to treatment initiation in a way that closely reflects routine clinical practice [9]. The use of two complementary, validated behavioral tools—the Child Behavior Checklist (CBCL) and the Strengths and Difficulties Questionnaire (SDQ)—administered in a standardized manner by a trained investigator under specialist supervision, further strengthens the internal validity and limits the observer-related bias. High follow-up completion, clear exclusion criteria, and systematic analysis of dose–behavior relationships together make the methodology robust and the results credible.

The results demonstrate an early, quantifiable behavioral abnormality following the initiation of levetiracetam with a dose–effect relationship. With no behavioral concerns at baseline, behavioral abnormalities were detected in 3.3% of children on day 14, increasing to 11.7% for any subdomain abnormality and to 6.7% for abnormal total scores at six weeks of levetiracetam initiation. These figures are notably lower than the 20–30% rates reported in retrospective

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and mixed-population studies but closely mirror rates from prospective cohorts using standardized instruments, where early behavioral adverse effects have ranged from 3 to 12% [8]. Despite these measurable effects, drug discontinuation was required in only one child [9]. Together, these findings support the interpretation that levetiracetam commonly produces early, mild, and dose-related behavioral changes, which are often subclinical and rarely mandate treatment withdrawal when identified and managed promptly.

However, the absence of a control group in this study suggests that behavioral changes cannot be attributed to levetiracetam with absolute certainty and may, in part, reflect the effects of epilepsy itself or the underlying etiology of epilepsy. Further, nearly half of the cohort received levetiracetam as a part of polytherapy, and the potential behavioral contribution of concomitant ASMs was not explicitly adjusted for, leaving room for residual confounding. Also, measures of seizure control and early disease trajectory were not integrated into the analysis. Higher doses may simply be a marker of more severe or poorly-controlled epilepsy, a factor which might be linked to behavioral dysfunction. Additionally, a short six-week follow-up captures only early behavioral effects and misses problems emerging later in the course of therapy. These limitations have also been acknowledged by the authors in the article [9].

From a practical standpoint, these findings support cautious, informed use rather than avoidance of levetiracetam. Initiation at the lowest effective dose, gradual titration, and early, structured behavioral surveillance are needed. Although not discussed in this recent study, clinicians should be aware of management strategies for levetiracetam-induced behavioral adverse effects. These include pyridoxine supplementation, dose adjustment, switching to other ASMs, and the addition of psychotropic drugs in severe cases [10]. Further, levetiracetam should be avoided in children with pre-existing problem behaviors.

Overall, this study reinforces that levetiracetam-associated behavioral adverse effects are real but predominantly early, mild, and dose-related, underscoring the importance of thoughtful dosing and proactive monitoring rather than therapeutic hesitation.

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