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Letter to the Editor

Comment on "Levetiracetam in childhood epilepsy: Expanding the evidence base"

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Introduction

We read with genuine interest the article by Toksöz and Teber recently published in the Turkish Journal of Pediatric Disease, which presents long-term efficacy and safety data on levetiracetam (LEV) monotherapy in 101 children managed at a tertiary pediatric neurology centre (1). The reported seizure-response rate of 72.3%, with complete seizure freedom in 38.0% of patients, positions this study squarely within the broader real-world evidence base and confirms LEV's standing as a first-line antiseizure medication (ASM) in childhood epilepsy. Particularly clinically useful is the identification of age over four years and low pre-treatment seizure frequency as independent predictors of a favourable response—two stratification criteria that translate directly into day-to-day prescribing decisions. Yet, precisely because this paper contributes to a growing corpus of retrospective evidence on LEV, it also highlights several dimensions that deserve more rigorous prospective investigation.

To begin with, situating the results of Toksöz and Teber within the comparative effectiveness literature raises questions that a single-arm retrospective design cannot resolve. A systematic review and meta-analysis of four randomised controlled trials including 381 children demonstrated that LEV monotherapy was associated with a significantly lower frequency of at least one seizure and a 76% reduction in dermatological adverse events relative to carbamazepine (CBZ), while seizure-freedom rates did not differ significantly between the two agents (2). This context matters: an overall response rate of 72.3% is meaningful, but without a comparator arm—whether historical or concurrent—it remains difficult to determine whether this figure reflects a drug effect, a patient-selection effect, or an institutional effect. A large Turkish tertiary centre cohort of 281 children treated with LEV monotherapy across a decade found seizure reduction rates that, while broadly consistent with the current paper, varied substantially by epilepsy aetiology—ranging from idiopathic to symptomatic and cryptogenic forms (3). Heterogeneity in patient mix is therefore a critical variable, and its underreporting limits how far the findings of Toksöz and Teber can be generalised to other settings, Table I summarises the efficacy and adverse-event profiles across the major cohorts and meta-analyses cited in this commentary, placing the index study in comparative perspective.

A closely related limitation concerns the absence of structured epilepsy syndrome classification in the cohort. The International League Against Epilepsy (ILAE) 2017 framework—distinguishing focal, generalised, combined generalised-and-focal, and unknown epilepsies—is not a bureaucratic formality; it carries direct and differential therapeutic implications (4). LEV holds regulatory approval as adjunctive therapy for focal-onset seizures and juvenile myoclonic epilepsy, but its behaviour across syndrome subtypes diverges in ways that aggregate response rates flatten into invisibility. A head-to-head systematic review and meta-analysis comparing LEV versus oxcarbazepine in children found that focal epilepsy subgroups drove most of the seizure-free advantage observed with LEV, while outcomes in other syndromic categories were considerably narrower (5). The clinical decision that a practitioner makes when initiating LEV in a child with Rolandic epilepsy—a syndrome with a favourable natural history regardless of treatment—should not be conflated with the decision made for a child with drug-resistant generalised epilepsy. Disaggregating outcomes by ILAE-classified syndrome type is not merely a methodological nicety; it is the minimum granularity needed to transform observational data into actionable prescribing evidence. Future work from this group should prioritise syndrome classification at enrolment.

The adverse-event profile documented by Toksöz and Teber —45.5% of patients affected, with drowsiness, irritability, and fatigue predominating—is numerically consistent with prior series (6). The published literature, however, draws attention to a dimension of LEV toxicity that chart-based retrospective ascertainment systematically underestimates: the neuropsychiatric spectrum. Behavioural dysregulation under LEV, encompassing irritability, emotional lability, hyperactivity, and, in a minority of cases, frank psychotic symptoms, has been documented in up to 37.6% of pediatric patients in series that used structured ascertainment methods (7). A systematic

Table I: Comparison of levetiracetam efficacy and adverse-event profiles across selected pediatric epilepsy cohorts and meta-analyses cited in this commentary.

Study / Country	N	Design	Mean age	Efficacy (%)	Seizure freedom (%)	Adverse events (%)
Martins et al. (2) Brazil	381 (4 RCTs)	SR & meta-analysis	7.3–9.3 yr	LEV = CBZ (seizure freedom)	~85% vs ~75% (ns)	Derm. AE: LEV < CBZ*
Liu et al. (5) China	Pooled RCTs	SR & meta-analysis	Children	LEV > OXC (focal subgroup)†	NR	No significant difference
Halma et al. (8) Netherlands	727 (13 studies)	Systematic review	1 mo – 18 yr	Not primary outcome	Not reported	Behav. AE: RR 2.18 vs placebo‡
Toksöz and Teber (1) Türkiye	101	Retrospective cohort	NR (>4 yr: predictor)	72.3	38.0	45.5
Yıldırım et al. (3) Türkiye	281	Retrospective cohort	Mean 9 yr	~74%	~40%	~18%
Hadzagic Catibusic et al. (6) Bosnia-Herzegovina	NR (15-yr cohort)	Prospective cohort	>1 month	NR	NR	Comparable to (1)
Ganjikunta et al. (7) India	Case series	Retrospective	Mixed	—	—	Psychiatric AE: up to 37.6%
Verrotti et al. (10) Italy	Review	Narrative review	Children	Summary of cohort data	Variable	PK: faster clearance <4 yr

:** *Dermatological adverse events: RR 0.24 (95% CI 0.09–0.64; p<0.010) in favour of LEV,* **†:** *LEV showed superior seizure-free rates vs. OXC in the focal epilepsy subgroup; no significant difference in generalised epilepsy subgroups,* **‡:** *Behavioural adverse events vs. placebo across 13 studies (n=727); hostility, nervousness, and aggression predominated.* ***N: *sample size,* ***NR :*** *not reported,* ***OXC:*** *oxcarbazepine,* ***CBZ:*** *carbamazepine,* ***LEV:*** *levetiracetam,* ***RCT:*** *randomised controlled trial,* ***SR****: systematic review,* ***AE:*** *adverse event,* ***Derm.:*** *dermatological,* ***Behav.:*** *behavioural,* ***PK:*** *pharmacokinetic,* ***ns:*** *not significant,* ***mo:*** *months,* ***yr:*** *years.*

review specifically examining behavioural side effects in children on LEV confirmed a statistically significant relative risk of 2.18 for total behavioural adverse events compared to placebo—hostility, nervousness, and aggression being the most frequently reported domains (8). These reactions are not trivial. A child whose seizures are controlled but who becomes aggressive, oppositional, or emotionally dysregulated has not simply 'tolerated' the drug; the family's quality of life has been exchanged for seizure freedom, which is a different clinical outcome entirely. Neurodevelopmental comorbidities magnify this risk: children with pre-existing cognitive or psychiatric vulnerabilities are disproportionately susceptible to LEV-related behavioural deterioration, a factor impossible to fully control for in retrospective designs (9). Integrating standardised tools—the Child Behavior Checklist (CBCL) or the Strengths and Difficulties Questionnaire (SDQ)—at baseline and at each scheduled visit would allow future studies to detect these effects early and systematically, before they become reasons for treatment discontinuation rather than data points in the record.

A dimension not discussed by Toksöz and Teber, yet central to understanding long-term LEV performance in children, is the concept of treatment retention as an integrated measure of efficacy and tolerability. In a real-world European pediatric cohort, the one-year LEV continuation rate was estimated at 72%, with insufficient efficacy—rather than adverse events—accounting for the majority of discontinuations. This architecture of drug attrition carries a practical message: achieving initial seizure control is necessary but not sufficient; sustaining it without accumulated tolerability burden is the harder clinical problem. Age-specific pharmacokinetic variability compounds this challenge. LEV clearance in young children is substantially faster than in adults, resulting in lower plasma concentrations at standard weight-based doses and potentially explaining some of the apparent efficacy ceiling observed in younger age groups —a finding that aligns with the age-related predictor identified by Toksöz and Teber (10). Prospective designs incorporating therapeutic drug monitoring would allow disentanglement of pharmacokinetic from pharmacodynamic sources of treatment failure, a distinction with direct therapeutic implications for dose adjustment strategies in the under-four age group.

A final perspective, critical from a global pediatric neurology standpoint, concerns the generalisability of these findings beyond well-resourced tertiary settings. A systematic review and meta-analysis estimated the prevalence of childhood epilepsy in sub-Saharan Africa at 7.8 per 1000 population, with treatment gaps exceeding 80% in several regions (11). The recent inclusion of LEV on the WHO Essential Medicines List was a meaningful step, yet access remains constrained in low-and middle-income countries (LMICs) by drug cost, cold-chain logistics, and the scarcity of trained pediatric neurologists (12). A scoping review of epilepsy care outcomes in LMICs underscored that real-world effectiveness data generated in Turkish or European tertiary centres cannot be uncritically transposed to contexts where EEG is unavailable, neuroimaging is sporadic, and the interval between seizure onset and specialist consultation may span years (13). The cohort of Toksöz and Teber does not report on diagnostic delays, socioeconomic stratification, or access-related variables—all of which shape LEV outcomes in resource-limited settings in ways that standard efficacy metrics do not capture. Collaborative networks linking high-income and LMIC centres could help establish globally representative benchmarks and identify which elements of current management protocols are feasibly exportable, Figure 1 proposes a syndrome-stratified, neurobehaviourally monitored prospective framework that could serve as a blueprint for such collaborative efforts.

In summary, the study by Toksöz and Teber makes a genuine and valuable contribution: it provides real-world evidence of LEV's efficacy in a sizeable pediatric cohort, documents the adverse-event landscape with clinical honesty, and offers two stratification criteria with immediate utility at the point of prescribing. The path to a more complete understanding of LEV in childhood epilepsy runs through syndrome-specific

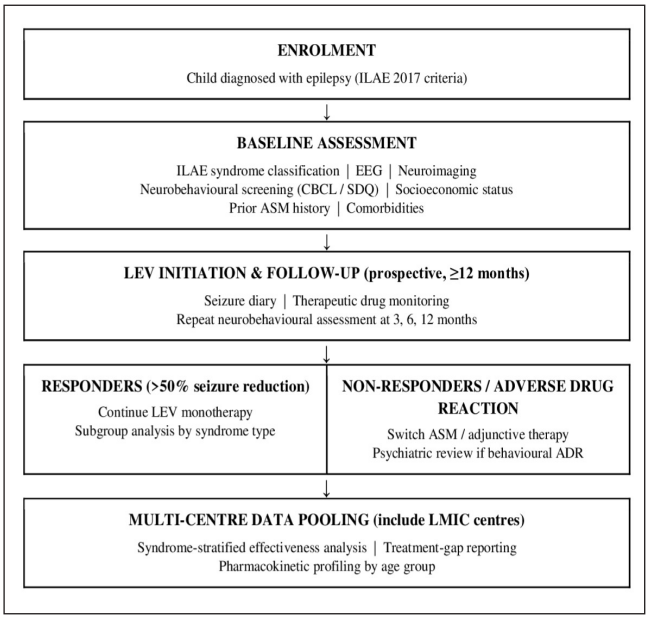

Figure 1: Proposed framework for a syndrome-stratified, neurobehaviourally monitored prospective evaluation of levetiracetam in pediatric epilepsy. **ILAE:** International League Against Epilepsy, **EEG:** electroencephalogram, **ASM:** antiseizure medication, **LEV:** levetiracetam, **ADR:** adverse drug reaction, **CBCL:** Child Behavior Checklist, **SDQ:** Strengths and Difficulties Questionnaire, **LMIC:** low- and middle-income country

prospective designs, standardised neurobehavioural monitoring incorporated from enrolment, retention and therapeutic drug monitoring analyses, and deliberate cross-centre collaboration that places these findings within a global epidemiological frame. Levetiracetam has more than justified its first-line status; the question of for whom, at what dose, and at what neuropsychiatric cost remains, in meaningful ways, open.

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