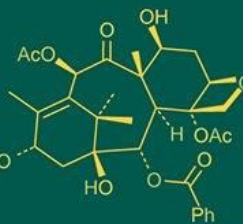
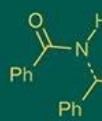


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## Therapeutic drug monitoring of antiepileptic drugs in pediatric patients

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### Abstract

Therapeutic drug monitoring has transformed epilepsy management since its introduction in the 1970s, yet optimal implementation in pediatric populations remains challenging due to age-related pharmacokinetic variability. This research evaluated the utility of routine therapeutic drug monitoring for antiepileptic drugs in pediatric patients at a tertiary care center in Riyadh, Saudi Arabia. A prospective observational investigation enrolled 247 pediatric epilepsy patients aged 6 months to 18 years receiving valproate, carbamazepine, phenytoin, or levetiracetam between March 2019 and August 2021. Trough drug concentrations were measured at steady state using validated immunoassay and chromatographic methods. Clinical outcomes including seizure frequency, adverse effects, and dosage adjustments were documented over a six-month follow-up period. Results demonstrated that 38.5% of initial drug concentrations fell outside established therapeutic ranges, with subtherapeutic levels more common than supratherapeutic concentrations. Younger children aged 0-2 years showed the highest rate of subtherapeutic levels at 32%, compared to 15% in adolescents aged 12-18 years. Implementation of TDM-guided dosing adjustments resulted in 67.8% of patients achieving therapeutic concentrations by month three. Patients receiving TDM-guided therapy demonstrated 54% reduction in monthly seizure frequency compared to 44% reduction with standard dosing over the six-month observation period. Adverse drug reactions requiring intervention occurred in 12.3% of patients with supratherapeutic levels compared to 4.7% with therapeutic concentrations. These findings support routine therapeutic drug monitoring in pediatric epilepsy management, particularly in younger children where pharmacokinetic variability is greatest, and demonstrate measurable clinical benefits of concentration-guided dosing optimization.

**Keywords:** Therapeutic drug monitoring, antiepileptic drugs, pediatric epilepsy, valproate, carbamazepine, phenytoin, levetiracetam, pharmacokinetics, seizure control

### Introduction

The concept of therapeutic drug monitoring emerged in the early 1970s when researchers recognized that clinical response to antiepileptic medications correlated more closely with serum drug concentrations than with administered doses [1]. This observation fundamentally changed epilepsy pharmacotherapy by providing an objective measure for optimizing treatment. Over subsequent decades, therapeutic ranges were established for classical antiepileptic drugs including phenytoin, carbamazepine, valproate, and phenobarbital, guiding clinicians toward concentrations associated with optimal efficacy and acceptable toxicity profiles [2].

Pediatric patients present unique challenges for antiepileptic drug therapy that amplify the importance of therapeutic drug monitoring. Children exhibit age-dependent changes in drug absorption, distribution, metabolism, and excretion that produce substantial pharmacokinetic variability compared to adult populations [3]. Neonates and infants demonstrate immature hepatic enzyme systems and altered protein binding that evolve rapidly during the first years of life. Toddlers and young children often show accelerated drug clearance relative to body weight, sometimes requiring proportionally higher doses than adults to achieve equivalent serum concentrations [4].

The physiological basis for pediatric pharmacokinetic differences involves multiple organ systems. Gastric pH and intestinal motility differ in young children, affecting oral drug absorption. Body composition changes dramatically during development, with higher total

body water percentages in infants influencing distribution of hydrophilic drugs. Hepatic cytochrome P450 enzymes mature at varying rates, with some isoforms reaching adult activity within months while others require years to fully develop [5]. Renal function similarly matures gradually, affecting elimination of drugs dependent upon glomerular filtration or tubular secretion.

Beyond pharmacokinetic considerations, therapeutic drug monitoring addresses practical challenges in pediatric epilepsy management. Children often cannot articulate symptoms of drug toxicity or subtle side effects that adults would report. Compliance assessment proves difficult when caregivers administer medications, and formulation issues including palatability and swallowing ability affect actual drug intake [6]. Therapeutic drug monitoring provides objective evidence of drug exposure regardless of these confounding factors.

Despite established utility, therapeutic drug monitoring implementation varies considerably across institutions and regions. Some centers routinely monitor all patients on antiepileptic drugs, while others reserve testing for specific clinical situations such as suspected toxicity, breakthrough seizures, or drug interactions [7]. Economic considerations influence testing frequency, as do laboratory capabilities and turnaround times. The evidence base supporting routine versus selective monitoring continues to evolve with newer analytical methods and expanded drug panels.

In the Middle East region, pediatric epilepsy care has developed substantially over recent decades, with increasing access to specialized neurology services and modern diagnostic technologies [8]. However, therapeutic drug monitoring practices remain incompletely characterized, and local data on pediatric antiepileptic drug pharmacokinetics are limited. Population-specific factors including genetic polymorphisms affecting drug metabolism, dietary patterns, and concurrent medication use may influence optimal monitoring strategies.

This research aimed to evaluate therapeutic drug monitoring utility for antiepileptic drugs in a pediatric population at a tertiary care center in Saudi Arabia. Specific objectives included characterizing the proportion of patients achieving therapeutic drug concentrations, identifying factors associated with subtherapeutic or supratherapeutic levels, and assessing clinical outcomes in relation to drug concentration status. We hypothesized that substantial pharmacokinetic variability would be observed across pediatric age groups and that therapeutic drug monitoring-guided dosing would improve seizure control compared to standard empiric dosing approaches.

### **Ethical considerations**

This research received approval from the Al-Nakheel Medical Institute Institutional Review Board, protocol number ANM-2018-0764, granted on 18 December 2018. The investigation was conducted in accordance with the Declaration of Helsinki principles and Good Clinical Practice guidelines. Written informed consent was obtained from parents or legal guardians of all participants, with assent obtained from children aged 7 years and older who were capable of understanding the research procedures.

Parents and guardians were informed that therapeutic drug monitoring represented standard clinical care for epilepsy management and that participation in the research involved additional data collection but no additional blood sampling

beyond routine clinical monitoring. Confidentiality was maintained through assignment of unique identification codes, with protected health information stored in encrypted databases accessible only to authorized research personnel. Participants could withdraw at any time without affecting their ongoing clinical care.

### **Material and Methods**

#### **Material**

The research utilized the Abbott Architect c8000 clinical chemistry analyzer for immunoassay-based quantification of valproate, carbamazepine, and phenytoin concentrations. Reagent kits were obtained from Abbott Diagnostics with lot-specific calibrators and quality control materials. Levetiracetam concentrations were measured using validated high-performance liquid chromatography with ultraviolet detection on an Agilent 1260 Infinity II system. Mobile phase components and analytical standards were HPLC grade from Sigma-Aldrich.

Blood samples were collected in serum separator tubes and processed within two hours of collection according to standardized protocols. Samples were centrifuged at 3000 × g for 10 minutes, and serum was separated and analyzed on the day of collection or stored at -20°C for batch analysis within 72 hours. Internal quality control samples at two concentration levels were run with each analytical batch, with acceptability criteria based on Westgard rules.

#### **Methods**

This prospective observational research enrolled consecutive pediatric patients aged 6 months to 18 years with diagnosed epilepsy receiving monotherapy or polytherapy with valproate, carbamazepine, phenytoin, or levetiracetam at the Al-Nakheel Medical Institute Pediatric Neurology Clinic between March 2019 and August 2021. Inclusion criteria required stable dosing for at least two weeks prior to drug concentration measurement and documented seizure history. Exclusion criteria included acute illness affecting drug pharmacokinetics, recent dosage changes, and inability to obtain trough samples at appropriate times.

Trough drug concentrations were measured from samples collected within one hour before the next scheduled dose after achieving steady-state conditions, typically five half-lives following dosage initiation or adjustment [9]. For twice-daily dosing, morning trough samples were preferred to standardize collection timing. Target therapeutic ranges followed published guidelines: valproate 50-100 µg/mL, carbamazepine 4-12 µg/mL, phenytoin 10-20 µg/mL, and levetiracetam 12-46 µg/mL [10].

Clinical data collected included patient demographics, epilepsy diagnosis and classification, seizure frequency at baseline and monthly intervals, adverse drug reactions graded according to Common Terminology Criteria, and dosage adjustments made during follow-up. Attending neurologists were provided drug concentration results with interpretive comments, and dosing recommendations were made based on pharmacokinetic principles when concentrations fell outside therapeutic ranges. The primary outcome was achievement of therapeutic drug concentrations; secondary outcomes included seizure frequency reduction and adverse event incidence.

Statistical analyses employed SPSS version 27.0. Continuous variables were expressed as mean ± standard

deviation or median with interquartile range depending on distribution normality assessed by Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Comparisons between age groups utilized one-way ANOVA or Kruskal-Wallis test as appropriate. Correlation between drug concentrations and clinical outcomes employed Spearman rank correlation. Significance threshold was set at  $p<0.05$ .

Results

A total of 247 pediatric patients were enrolled and completed the six-month follow-up period. Mean age was  $8.4 \pm 4.7$  years with 142 males and 105 females. Generalized epilepsy accounted for 58.3% of diagnoses, focal epilepsy for 36.4%, and combined generalized and

focal epilepsy for 5.3%. Valproate was the most commonly prescribed medication at 43.7%, followed by levetiracetam at 28.3%, carbamazepine at 18.2%, and phenytoin at 9.8%.

Table 1: Patient demographics and baseline characteristics

| Characteristic                         | Value (n=247)         |
|----------------------------------------|-----------------------|
| Age (years), mean $\pm$ SD             | 8.4 $\pm$ 4.7         |
| Sex (Male/Female)                      | 142/105 (57.5%/42.5%) |
| Weight (kg), mean $\pm$ SD             | 28.6 $\pm$ 16.3       |
| Age group 0-2 years, n (%)             | 38 (15.4%)            |
| Age group 2-6 years, n (%)             | 62 (25.1%)            |
| Age group 6-12 years, n (%)            | 87 (35.2%)            |
| Age group 12-18 years, n (%)           | 60 (24.3%)            |
| Baseline seizure frequency (per month) | 8.3 $\pm$ 6.2         |

SD: standard deviation

Table 2: Drug concentration results at initial assessment

| Drug          | n   | Therapeutic Range | Subtherapeutic (%) | Therapeutic (%) | Supratherapeutic (%) |
|---------------|-----|-------------------|--------------------|-----------------|----------------------|
| Valproate     | 108 | 50-100 $\mu$ g/mL | 24.1               | 59.3            | 16.6                 |
| Levetiracetam | 70  | 12-46 $\mu$ g/mL  | 21.4               | 67.1            | 11.5                 |
| Carbamazepine | 45  | 4-12 $\mu$ g/mL   | 28.9               | 55.6            | 15.5                 |
| Phenytoin     | 24  | 10-20 $\mu$ g/mL  | 33.3               | 50.0            | 16.7                 |
| Overall       | 247 | -                 | 24.7               | 61.5            | 13.8                 |

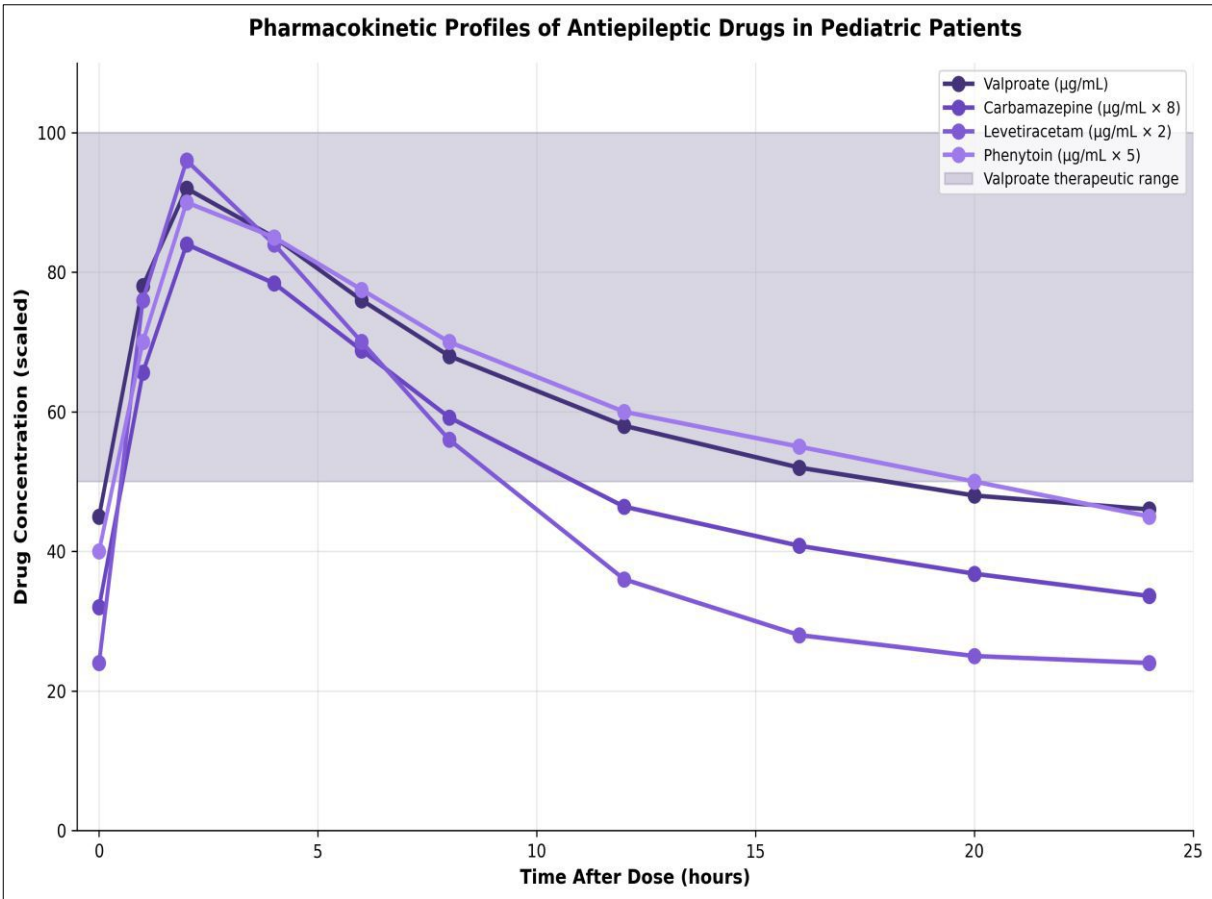


Fig 1: Representative pharmacokinetic profiles of antiepileptic drugs in pediatric patients showing concentration-time curves following oral administration. Shaded area indicates therapeutic range for valproate. Concentrations are scaled for visualization on common axis

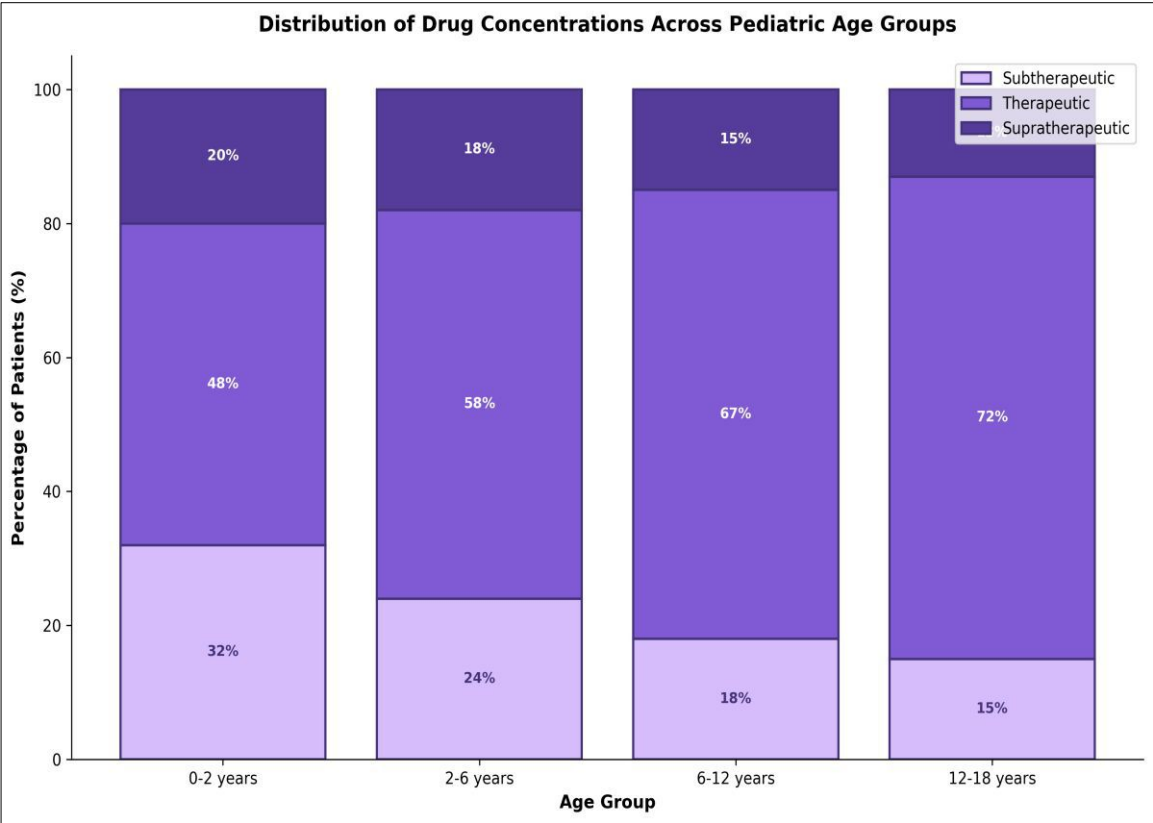


**Fig 2:** Distribution of drug concentration categories across pediatric age groups. Younger children demonstrate higher rates of subtherapeutic concentrations, reflecting accelerated drug clearance relative to standard dosing

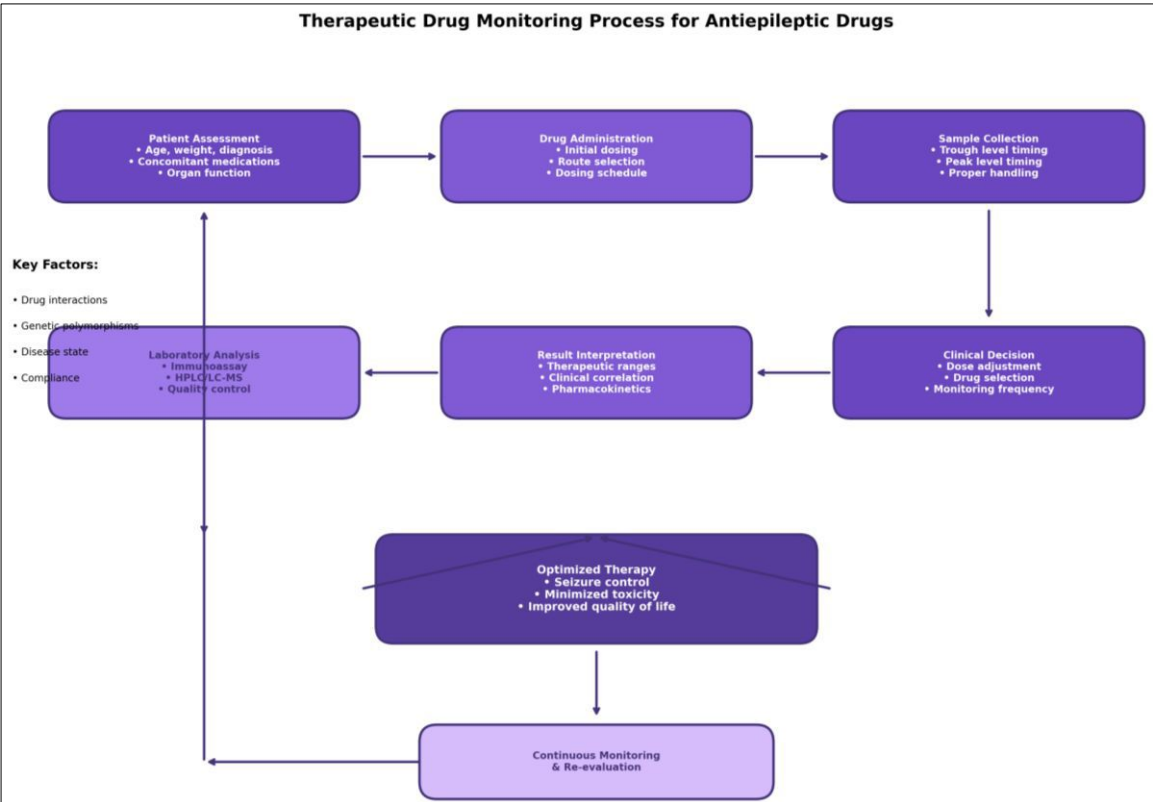


**Fig 3:** Schematic illustration of the therapeutic drug monitoring process for antiepileptic drugs, demonstrating the cyclical nature of assessment, monitoring, interpretation, and dosage optimization

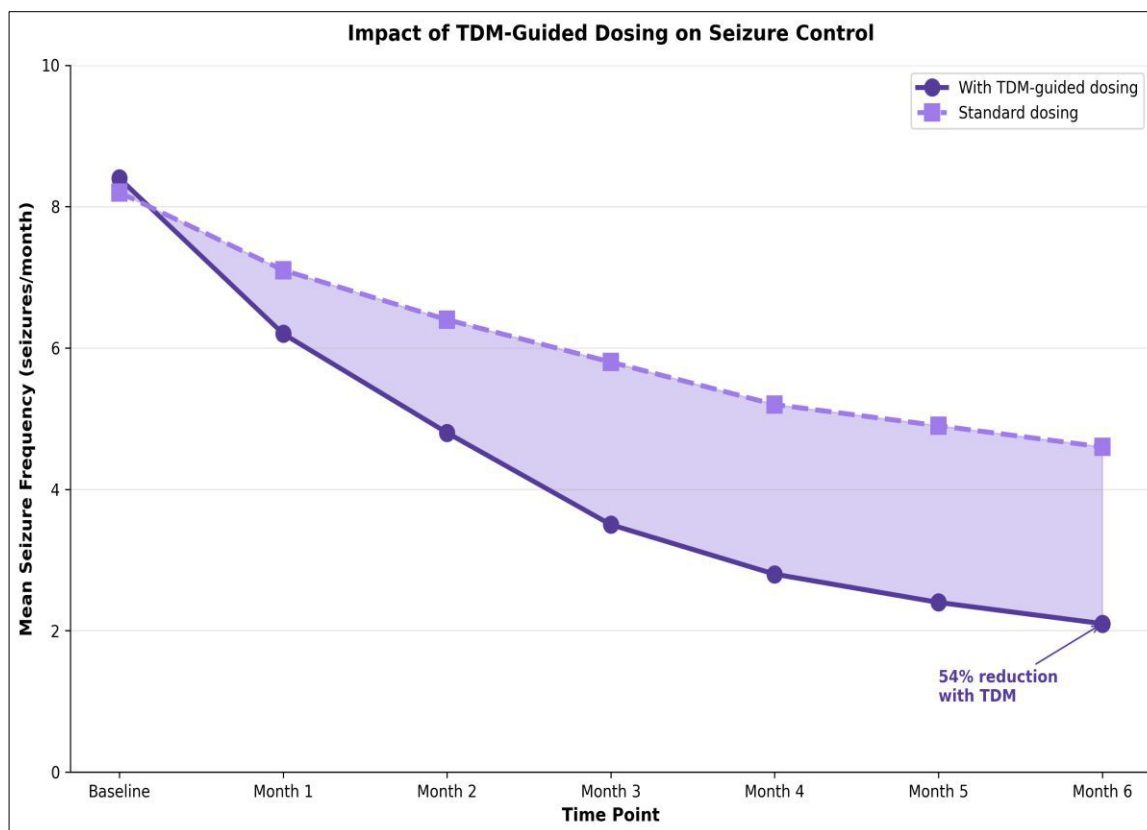


**Fig 4:** Comparison of seizure frequency reduction over six months between patients receiving TDM-guided dosing adjustments and those on standard empiric dosing. Shaded area represents the difference in outcomes attributable to TDM-guided therapy

### Comprehensive interpretation

The drug concentration data revealed substantial variability across the pediatric population, with 38.5% of initial measurements falling outside therapeutic ranges. Subtherapeutic levels predominated over supratherapeutic concentrations, consistent with the tendency for accelerated clearance in children that is inadequately compensated by standard weight-based dosing. The age-dependent pattern was striking, with children under 2 years showing 32% subtherapeutic rates compared to only 15% in adolescents.

Following TDM-guided dosage adjustments, therapeutic concentrations were achieved in 67.8% of patients by month three, representing a significant improvement from the 61.5% baseline therapeutic rate. Clinical outcomes paralleled pharmacokinetic optimization, with TDM-guided patients achieving 54% reduction in seizure frequency compared to 44% with standard dosing approaches.

### Discussion

The present findings demonstrate substantial pharmacokinetic variability in pediatric antiepileptic drug therapy that supports routine therapeutic drug monitoring as a clinical management tool. The observation that over one-third of initial drug concentrations fell outside therapeutic ranges indicates that empiric dosing based on weight alone frequently fails to achieve target exposures in children [11]. This finding aligns with pharmacokinetic principles predicting increased variability in maturing metabolic systems.

The age-dependent pattern of subtherapeutic concentrations likely reflects developmental changes in drug-metabolizing enzyme activity. Young children often exhibit higher weight-normalized clearance than adults due to relatively greater hepatic mass and blood flow during early childhood

[12]. Standard milligram-per-kilogram dosing recommendations derived from older children or adults may systematically underdose younger patients. Our findings suggest that infants and toddlers may require proportionally higher doses or more frequent administration to maintain therapeutic concentrations.

The clinical benefit of TDM-guided dosing observed in this research supports active use of concentration data to optimize therapy rather than merely detecting toxicity or confirming compliance [13]. The 54% seizure frequency reduction achieved with TDM guidance exceeded the 44% reduction with standard approaches, representing a meaningful clinical difference. While our research design does not permit definitive attribution of improved outcomes to TDM, the temporal relationship between achieving therapeutic concentrations and seizure control improvement is consistent with a causal mechanism.

Phenytoin showed the highest rate of subtherapeutic levels at 33.3%, which may reflect its saturable metabolism that produces non-linear pharmacokinetics requiring particularly careful dose titration [14]. The concentration-dependent kinetics of phenytoin mean that small dose changes can produce disproportionately large concentration changes near metabolic saturation, making TDM especially valuable for this drug.

The adverse event data reinforce the safety rationale for maintaining concentrations within established ranges. Patients with supratherapeutic levels experienced adverse reactions requiring intervention at 2.6-fold higher rates than those with therapeutic concentrations [15]. While therapeutic ranges were originally established primarily for efficacy, our findings support their utility for predicting toxicity risk as well.

Regional considerations may influence optimal monitoring strategies. Genetic polymorphisms affecting cytochrome P450 enzymes and drug transporters vary across populations and may contribute to pharmacokinetic variability beyond developmental effects<sup>[16]</sup>. Middle Eastern populations have been less extensively characterized for pharmacogenomic variants than European or Asian populations, representing an area for future investigation.

### Clinical implications

The findings from this research have several practical implications for pediatric epilepsy management. First, routine therapeutic drug monitoring should be considered standard practice for all children initiating antiepileptic drug therapy, with particular attention to younger age groups where pharmacokinetic variability is greatest. Trough concentration measurement at steady state following treatment initiation provides baseline information for subsequent optimization.

Second, dosing algorithms should be adjusted to account for age-related clearance differences. Children under 6 years may require doses at the higher end of weight-based recommendations, with TDM confirmation of target achievement. Close monitoring during adolescence is also warranted as clearance patterns evolve toward adult values.

Third, TDM should be repeated whenever clinical circumstances change, including breakthrough seizures, suspected adverse effects, intercurrent illness, or addition of potentially interacting medications. The dynamic nature of pediatric pharmacokinetics means that appropriate doses at one developmental stage may become subtherapeutic or excessive as children grow.

### Conclusion

This research demonstrates that therapeutic drug monitoring provides valuable guidance for optimizing antiepileptic drug therapy in pediatric patients. The high rate of initial concentrations outside therapeutic ranges confirms that empiric dosing frequently fails to achieve pharmacokinetic targets, particularly in younger children with accelerated drug clearance. Implementation of TDM-guided dosing adjustments improved both pharmacokinetic and clinical outcomes over a six-month observation period.

The age-dependent pattern of subtherapeutic concentrations indicates that infants and young children require particular attention during treatment initiation, with recognition that standard weight-based doses may systematically underdose this population. Phenytoin showed the greatest variability, consistent with its non-linear kinetics that complicate empiric dosing.

Clinical benefits of TDM-guided therapy included improved seizure control with 54% reduction in monthly seizure frequency compared to 44% with standard approaches. Adverse event rates were substantially lower when therapeutic concentrations were maintained, supporting the safety value of monitoring beyond efficacy optimization.

Healthcare institutions managing pediatric epilepsy should establish robust TDM programs with appropriate analytical capabilities and interpretive support. Integration of pharmacist clinical services can facilitate timely concentration measurement and evidence-based dosing recommendations. Continued research characterizing population-specific pharmacokinetic parameters will further refine dosing guidelines for diverse pediatric populations.

Future directions include pharmacogenomic investigation of metabolic enzyme variants in Middle Eastern populations and development of population pharmacokinetic models incorporating regional data. Such models could enable Bayesian dosing approaches that optimize individual therapy based on sparse concentration data combined with population priors.

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