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COGNITIVE AND BEHAVIORAL EFFECTS OF LONG-TERM ANTIEPILEPTIC DRUG USE IN ADOLESCENTS WITH GENERALIZED EPILEPSY

Narrative Review

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ABSTRACT

Background: Adolescents with generalized epilepsy often require long-term antiepileptic drug (AED) therapy during a critical phase of cognitive and emotional development. While AEDs are essential for seizure control, increasing evidence suggests they may adversely affect cognition and behavior, raising concerns about their broader impact on quality of life and neurodevelopment.

Objective: This narrative review aims to explore and synthesize current evidence on the cognitive and behavioral consequences of prolonged AED use in adolescents with generalized epilepsy, highlighting differences among commonly prescribed medications and identifying areas in need of further investigation.

Main Discussion Points: The review discusses cognitive impairments associated with older AEDs such as valproate and carbamazepine, which are more pronounced compared to newer agents like levetiracetam and oxcarbazepine. Behavioral issues, including emotional instability and attention deficits, are also prevalent. Themes such as treatment duration, monotherapy versus polytherapy, variability in neuropsychological assessments, and methodological gaps in the literature are critically analyzed. Emerging therapies and the need for routine cognitive monitoring are highlighted.

Conclusion: The existing literature supports a cautious, individualized approach to AED therapy in adolescents, with attention to neurocognitive outcomes alongside seizure control. Further pediatric-focused, long-term research is essential to guide safer clinical practices and informed policy development.

Keywords: Generalized Epilepsy, Antiepileptic Drugs, Adolescents, Cognitive Impairment, Behavioral Effects, Narrative Review.

INTRODUCTION

Adolescence is a critical developmental period characterized by rapid neurobiological maturation and cognitive growth, making any disruption during this phase potentially long-lasting and profound. Among the medical conditions impacting this age group, epilepsy remains a significant global neurological disorder, with generalized epilepsy accounting for a considerable proportion of pediatric and adolescent cases. Globally, epilepsy affects nearly 50 million people, with approximately 10.5 million being children and adolescents, many of whom are diagnosed with generalized seizure types that require long-term pharmacological management (1). In high-income countries, the prevalence of active epilepsy in adolescents is estimated at 3 to 6 per 1,000 individuals, with even higher rates reported in low-resource settings due to limited access to healthcare and early diagnosis (2). In Pakistan, neurological conditions such as ischemic stroke have also been documented with comorbid atrial fibrillation (3) [client 9 Shaikh BA, Gurbakhshan]. The increasing incidence of pediatric epilepsy and the widespread use of antiepileptic drugs (AEDs) underscore the importance of understanding the broader consequences of prolonged pharmacological treatment beyond seizure control.

The cornerstone of epilepsy management is the administration of AEDs, aimed primarily at achieving seizure freedom with minimal side effects. However, accumulating evidence suggests that AEDs may negatively influence neurocognitive development and behavior, particularly in younger populations. Cognitive domains such as attention, memory, processing speed, and executive functioning are frequently reported as areas of concern, and these effects can manifest independently of the underlying seizure pathology. Behavioral disturbances, including irritability, aggression, emotional lability, and attentional deficits, are also commonly observed, further complicating the psychosocial development of adolescents with epilepsy. Moreover, while some AEDs, especially newer-generation drugs, are believed to have a more favorable cognitive profile, others—such as valproic acid and carbamazepine—have shown mixed effects depending on dosage, duration, and individual susceptibility (4).

Despite significant advances in epilepsy research, major gaps persist in understanding the nuanced and long-term cognitive and behavioral effects of AED therapy in adolescents. Most studies to date have focused either on adult populations or short-term outcomes, with limited high-quality, age-specific data available on adolescents undergoing chronic AED treatment. Additionally, methodological inconsistencies across studies—ranging from varied neuropsychological assessment tools to differences in seizure types and comorbidities—have made it difficult to generalize findings or establish clear causative links. Importantly, while seizure control remains the primary goal, clinicians must also consider the developmental trajectory of the adolescent brain and the potential for AEDs to interfere with learning, socialization, and emotional regulation during this formative stage (5).

The objective of this narrative review is to systematically examine the current body of literature surrounding the cognitive and behavioral effects of long-term AED use in adolescents diagnosed with generalized epilepsy. Specifically, this review seeks to synthesize available findings on how different AEDs influence various domains of cognitive function and behavioral outcomes, while also addressing the role of monotherapy versus polytherapy, treatment duration, and individual variability in drug response.

In scope, this review will consider peer-reviewed studies published between 2020 and 2025, including observational studies, longitudinal analyses, and clinical trials that specifically involve adolescents with generalized epilepsy. Studies that focus solely on focal epilepsy or adult populations will be excluded unless they provide comparative insights relevant to the adolescent generalized epilepsy cohort. Emphasis will be placed on commonly prescribed AEDs such as valproate, carbamazepine, levetiracetam, oxcarbazepine, and lamotrigine, given their widespread use and documented cognitive profiles.

The rationale for this review lies in its potential to fill existing knowledge gaps and provide a more comprehensive understanding of the neurobehavioral risks associated with prolonged AED use during adolescence. As educational attainment, psychological well-being, and social integration are heavily dependent on intact cognitive and behavioral functioning, the findings of this review may guide clinicians in optimizing treatment plans that minimize harm while maintaining seizure control. Furthermore, this synthesis aims to aid in developing informed guidelines for long-term epilepsy management in pediatric populations and identifying areas for future research, particularly in light of emerging AEDs and evolving therapeutic strategies.

By providing a cohesive evaluation of existing evidence, this narrative review aspires to contribute meaningfully to clinical practice and policy development, ensuring that treatment decisions are both seizure-focused and developmentally informed. Ultimately, the goal is

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to empower healthcare providers, caregivers, and patients with knowledge that balances seizure control with quality of life considerations for adolescents navigating the dual challenges of epilepsy and neurodevelopment.

THEMATIC DISCUSSION

Comparative Cognitive Effects of Common AEDs

Among the most widely prescribed antiepileptic drugs (AEDs) in adolescents—valproic acid, carbamazepine, levetiracetam, and oxcarbazepine—clear differences exist in their cognitive and behavioral side-effect profiles. A case-control study demonstrated that adolescents with epilepsy treated with these AEDs exhibited significantly lower IQ scores and executive functioning compared to healthy controls. Valproic acid and carbamazepine had a more pronounced negative impact on cognitive abilities, while levetiracetam and oxcarbazepine were associated with relatively milder cognitive effects. However, levetiracetam and valproic acid had more adverse behavioral outcomes, particularly in terms of aggression and emotional regulation (6). These findings reinforce the importance of tailoring drug choice not only based on seizure control but also on neuropsychological safety.

Behavioral and Speech Disturbances Associated with AED Therapy

Behavioral disturbances are increasingly recognized in adolescents on AED monotherapy. A longitudinal analysis found changes in both cognitive and speech functions in children with idiopathic generalized epilepsy on AEDs, even when no prior cognitive impairments were present. Alterations in higher mental functions and expressive speech were documented, with adverse drug reactions reported in over 30% of the cohort. These included emotional instability, attention problems, and speech delays, all of which can impede academic performance and social development (7). These effects necessitate early neuropsychological evaluation and continuous monitoring, particularly in children at risk of developmental vulnerability.

Effect of AED Duration and Polytherapy on Cognitive Integrity

Long-term exposure to AEDs has been consistently linked to worsening cognitive and behavioral outcomes. In a retrospective review involving over 400 pediatric and adult patients, valproic acid and carbamazepine were associated with more frequent side effects over time compared to newer drugs such as levetiracetam and topiramate. Moreover, polytherapy increased the likelihood of adverse effects, especially when older-generation AEDs were combined (8). This is compounded by evidence that the longer the duration of therapy, the higher the risk of cognitive decline—suggesting the need for periodic reevaluation of drug necessity and dosage adjustments.

Emotional and Psychopathological Outcomes Post-Treatment Initiation

Early initiation of AEDs after epilepsy diagnosis may impact mood and psychological well-being more significantly than cognition. A six-month naturalistic follow-up of newly diagnosed adolescents found notable increases in anxiety, depression, and behavioral problems—despite only minimal changes in IQ scores. This implies that AEDs may exert stronger influence on emotional regulation than on core cognitive abilities in the short term, particularly in the initial adaptation phase of therapy (9). These findings support the integration of psychosocial interventions alongside pharmacological treatment early in the course of disease management.

Emerging Concerns: AEDs and Bone Metabolism

Beyond neurocognitive domains, AEDs may also impair bone health, which is especially concerning in adolescents undergoing rapid skeletal development. A recent study on long-term AED users showed that 34.2% had decreased bone mineral density, including osteopenia and osteoporosis. The risk increased with therapy duration, especially in those treated with valproate or carbamazepine. This raises concerns about under-recognized long-term physical side effects of AEDs that may indirectly influence behavior and well-being via chronic pain or mobility limitations (10). Routine screening for bone health in adolescents on prolonged AED therapy should thus be considered.

AED-Induced Lipid Metabolism and Behavioral Implications

Recent studies have linked older-generation AEDs to dysregulated lipid profiles, which could have indirect consequences on cognitive and emotional health. In pediatric cohorts, valproate and carbamazepine were associated with elevated LDL and triglyceride levels, alongside a reduction in HDL cholesterol. These metabolic changes may contribute to systemic inflammation or cerebrovascular

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alterations, potentially exacerbating cognitive or behavioral side effects (11). Levetiracetam, by contrast, demonstrated a more neutral metabolic profile, adding further rationale for its use in cognitively vulnerable populations.

Novel Agents and Their Neurobehavioral Safety

Emerging AED candidates such as substituted pyrazoles have shown promise in preclinical models with minimal cognitive or behavioral disruption. One compound demonstrated potent anticonvulsant activity in animal models without impairing behavior or causing central nervous system toxicity. Its antioxidant and anti-inflammatory effects may contribute to a neuroprotective profile, indicating a new direction for AED development focused on efficacy without neurocognitive compromise (12). However, clinical data are lacking, and further research is needed to determine long-term safety in human populations.

Cognitive Monitoring: A Critical Yet Underutilized Strategy

Despite well-documented risks, routine cognitive monitoring is rarely standardized in clinical epilepsy care. Expert reviews emphasize the importance of integrating neuropsychological testing before and during AED therapy, particularly in school-age children. Structured assessment can help identify early declines and allow for timely intervention or treatment modification (13). Future guidelines should incorporate cognitive monitoring as a core element of epilepsy management, akin to seizure tracking.

Table 1: Summary of Common AEDs and Their Cognitive/Behavioral Effects

Antiepileptic Drug	Cognitive Effects	Behavioral Effects
Valproate	Lower IQ, memory deficits	Emotional lability, irritability
Carbamazepine	Attention and processing impairments	Sedation, mood changes
Levetiracetam	Minimal cognitive decline, some reports of executive dysfunction	Aggression, mood swings
Oxcarbazepine	Generally mild cognitive impact	Mild irritability
Topiramate	Language and verbal memory impairment	Fatigue, behavioral dulling
Lamotrigine	Mild, occasionally improves attention	Activation symptoms in rare cases

Table 2: Key Research Gaps and Recommendations for Future Research

Research Gap	Recommendation
Limited RCTs in adolescents	Design multicenter RCTs specific to pediatric populations
Short follow-up durations	Conduct longitudinal studies spanning 2+ years
Lack of standardized cognitive assessments	Implement consistent neuropsychological test batteries
Minimal data on polytherapy impact	Evaluate cognitive outcomes in polytherapy settings
Underreporting of behavioral outcomes	Use validated behavioral rating scales routinely
Sparse data on long-term reversibility	Study post-withdrawal cognitive recovery

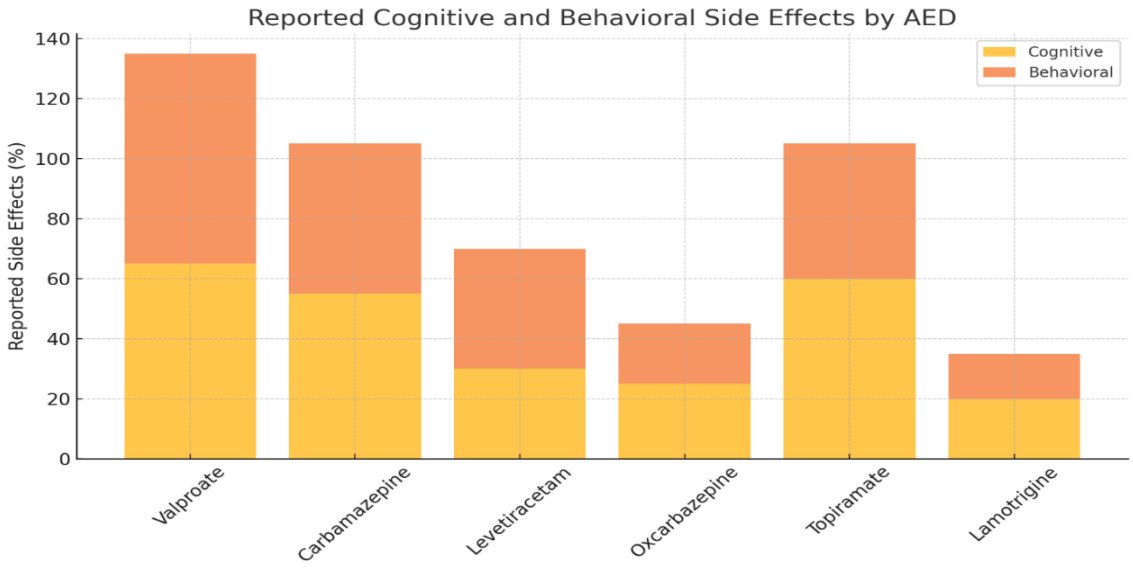

Figure 1 Reported Cognitive and Behavioral Side Effects by AED

CRITICAL ANALYSIS AND LIMITATIONS:

The current literature on the cognitive and behavioral effects of long-term antiepileptic drug (AED) use in adolescents with generalized epilepsy reveals valuable insights, but it is not without significant limitations. One of the most recurrent methodological shortcomings across studies is the reliance on small sample sizes. Many investigations are conducted with fewer than 100 participants, which restricts statistical power and limits the ability to generalize findings to the broader adolescent epilepsy population (14). Small samples also reduce the feasibility of conducting subgroup analyses, such as comparing cognitive outcomes based on seizure type, drug type, or gender.

Another limitation is the lack of large-scale, randomized controlled trials (RCTs). Most existing evidence is derived from observational or retrospective cohort studies, which are inherently vulnerable to various biases and confounding variables. The absence of randomization in many studies allows for unmeasured variables—such as socioeconomic status, baseline cognitive ability, and epilepsy severity—to skew the observed effects of AEDs (15). Furthermore, short follow-up durations, often spanning only six months to one year, fail to capture the long-term trajectory of cognitive development in adolescents, a critical period during which brain maturation and academic achievement intersect.

Methodological bias further complicates the interpretation of results. Selection bias is prevalent in studies that exclude adolescents with comorbid psychiatric or neurological conditions, thereby focusing predominantly on milder cases of epilepsy. This leads to underrepresentation of patients with more complex or drug-resistant forms, who may be more susceptible to adverse neurocognitive outcomes (16). Performance bias also emerges in studies lacking blinding procedures, where knowledge of treatment status may influence cognitive assessments or behavioral ratings by both patients and researchers.

Another under-addressed issue is publication bias. Studies that find significant negative cognitive or behavioral effects of AEDs are more likely to be published than those reporting neutral or inconclusive outcomes. This skew in the literature creates a distorted perception of the extent and consistency of AED-induced cognitive impairment (17). Moreover, the underreporting of side effects—particularly in newer AEDs where safety profiles are still being established—may lead to premature conclusions about their tolerability.

There is also considerable variability in measurement outcomes across studies. Cognitive functioning is assessed using a wide range of tools, from comprehensive neuropsychological batteries to brief screening tests. This heterogeneity hinders direct comparisons and makes meta-analysis challenging. Additionally, some studies emphasize global IQ changes, while others examine specific domains like

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attention, memory, or executive function, further fragmenting the evidence base (18). Behavioral assessments often rely on parent-reported questionnaires, which may be influenced by subjective perception rather than objective measurement.

Generalizability remains a major concern. Much of the research has been conducted in controlled academic settings or tertiary epilepsy centers, which do not reflect the broader, more diverse patient population seen in community clinics. Moreover, most studies focus on monotherapy and do not account for the growing number of adolescents managed with polytherapy or newer-generation AEDs. Cultural and linguistic differences in cognitive assessments are another factor limiting cross-population applicability, particularly when standardized tools are not appropriately adapted (19).

Finally, emerging AEDs and adjunctive treatments such as cognitive-behavioral therapy (CBT) or neuroprotective agents have shown promise in isolated studies but lack replication in large, controlled trials. While early data suggest these interventions may mitigate some of the adverse cognitive effects associated with AED use, their role remains speculative due to insufficient evidence (20).

IMPLICATIONS AND FUTURE DIRECTIONS:

The findings of this review hold significant implications for clinical practice in the management of adolescents with generalized epilepsy. Given the consistent evidence that long-term antiepileptic drug (AED) use can lead to adverse cognitive and behavioral effects, clinicians must prioritize individualized treatment strategies. Drugs such as levetiracetam and oxcarbazepine, which are associated with relatively milder cognitive side effects, may be more appropriate first-line options, particularly for patients at risk of academic or emotional difficulties (21). Moreover, routine cognitive and behavioral assessments should be integrated into standard care protocols, enabling early identification of emerging side effects and allowing timely intervention, such as dose adjustment or medication switching.

From a policy standpoint, the growing body of evidence highlighting neuropsychological risks demands the inclusion of cognitive monitoring guidelines in national and international epilepsy treatment protocols. At present, most epilepsy management guidelines emphasize seizure control without sufficiently addressing long-term cognitive and psychosocial outcomes in pediatric populations. Policymakers should consider formal recommendations for periodic neuropsychological evaluations, ideally every 6–12 months, especially in those receiving high-risk AEDs or polytherapy regimens (22). Incorporating these evaluations into school-based health programs may also provide a more comprehensive framework for support.

This review also underscores several critical research gaps. The long-term comparative effects of newer AEDs remain insufficiently explored, especially beyond 12 months of therapy. Additionally, while some studies have begun to evaluate the differential effects of AEDs based on sex, socioeconomic status, and pre-existing cognitive baselines, these variables are not consistently reported or controlled across studies. The absence of pediatric-focused randomized controlled trials (RCTs) further limits the ability to make evidence-based decisions about the safest and most effective AED regimens in adolescents (23). There is also limited research on the reversibility of cognitive and behavioral impairments after cessation or switching of AEDs, which could significantly influence treatment planning.

To address these gaps, future research should adopt multicenter longitudinal RCTs with larger and more diverse adolescent populations. These studies should include rigorous neuropsychological batteries sensitive to developmental changes and should assess both objective cognitive outcomes and real-world functioning, such as academic performance and social integration. Importantly, future research should also investigate the potential neuroprotective effects of adjunctive therapies, such as cognitive rehabilitation, dietary interventions, and exercise programs, which may help mitigate the adverse effects of chronic AED use (24). Studies exploring the molecular and genetic underpinnings of AED-related cognitive vulnerability may also offer personalized medicine strategies for minimizing risks.

Lastly, novel drug development should prioritize both seizure control and neurocognitive safety. Promising agents such as substituted pyrazoles have demonstrated anticonvulsant activity without behavioral toxicity in preclinical models, suggesting that dual efficacy–safety profiles are attainable (25). Future pharmacological innovations should be guided by translational studies that incorporate cognitive outcomes as primary endpoints, not secondary or exploratory ones.

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CONCLUSION:

This review highlights that long-term use of antiepileptic drugs in adolescents with generalized epilepsy can significantly affect cognitive performance and behavioral development, with varying degrees of impact depending on the type, dosage, and duration of the medication. Older-generation AEDs such as valproate and carbamazepine tend to be associated with more pronounced adverse effects, while newer agents like levetiracetam and oxcarbazepine appear comparatively safer but are not without risks. Emotional disturbances, speech impairments, and academic challenges are among the most frequently reported concerns, particularly in patients exposed to polytherapy or extended treatment durations. While current evidence provides a compelling basis for cautious AED selection and proactive cognitive monitoring, the literature remains limited by methodological inconsistencies, small sample sizes, and a scarcity of pediatric-focused randomized controlled trials. Therefore, clinicians are encouraged to adopt individualized treatment plans, integrating neuropsychological assessments into routine care and balancing seizure control with quality-of-life considerations. Researchers should prioritize well-designed, long-term studies that evaluate both the neurocognitive safety and therapeutic efficacy of AEDs in adolescent populations, with the ultimate goal of guiding safer, more effective epilepsy management strategies.

AUTHOR CONTRIBUTION

Author	Contribution
Hafsa Hameed Thakur*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Haris Bin Umer	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Bilal Anwar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Shazma Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Amna Noor	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Shanza Akbar	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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