INSIGHTS-JOURNAL OF
LIFE AND SOCIAL SCIENCES

INSIGHTS-JLSS
Insights-Journal of Life and Social Sciences

EMERGING APPROACHES IN PEDIATRIC EPILEPSY MANAGEMENT: A NARRATIVE REVIEW

Narrative Review

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Conflict of Interest: None

Grant Support & Financial Support: None

Acknowledgment: The authors would like to acknowledge the contributions of researchers and clinicians whose work in the field of pediatric epilepsy has provided the foundation for this review. Special thanks to the institutions and families who continue to support advancements in epilepsy research and care.

ABSTRACT

Background: Pediatric epilepsy is a prevalent neurological disorder that significantly impacts cognitive, behavioral, and psychosocial development in children. While antiseizure medications (ASMs) remain the mainstay of treatment, approximately one-third of pediatric patients experience drug-resistant epilepsy (DRE), highlighting the need for alternative and individualized treatment strategies.

Objective: This narrative review aims to explore recent advances in pharmacological and non-pharmacological treatment approaches for pediatric epilepsy, emphasizing emerging therapies such as dietary interventions and neuromodulation techniques.

Main Discussion Points: The review synthesizes evidence on second-generation ASMs, which offer improved tolerability and tailored treatment options. Non-pharmacological strategies, including the ketogenic diet, vagus nerve stimulation, and physical activity, are discussed for their efficacy in reducing seizure frequency and enhancing quality of life. The review also highlights the integration of genetic insights into treatment planning and the trend toward multimodal, personalized care. Critical limitations in current literature—such as small sample sizes, lack of randomized controlled trials, and variability in outcome measures—are examined to contextualize the strength of evidence.

Conclusion: Emerging therapies present promising options for children with epilepsy, particularly those unresponsive to conventional medications. Clinicians should adopt individualized, evidence-informed strategies, while researchers are encouraged to conduct robust, inclusive trials to strengthen clinical guidelines and optimize patient outcomes.

Keywords: Pediatric Epilepsy, Antiseizure Medications, Ketogenic Diet, Vagus Nerve Stimulation, Drug-Resistant Epilepsy, Narrative Review.

INTRODUCTION

Epilepsy remains one of the most prevalent and disabling neurological disorders globally, affecting approximately 50 million people, with nearly half of new cases diagnosed during childhood and adolescence. In the pediatric population, epilepsy poses unique challenges due to the impact of recurrent seizures on neurodevelopment, cognition, behavior, and quality of life. Studies estimate that the incidence of epilepsy in children is around 41 to 187 per 100,000 per year, with a higher burden in low- and middle-income countries. Early-onset epilepsy is particularly concerning due to its potential to disrupt critical periods of brain maturation and social functioning, thus requiring timely and effective intervention strategies to prevent long-term deficits (1). Pharmacotherapy has long been the cornerstone of epilepsy management in children, with continuous advancements leading to the development of newer antiseizure medications (ASMs) that are better tolerated and more effective in seizure control. Over the past decade, more than 30 ASMs have become available, offering clinicians the ability to tailor treatments based on individual seizure types, comorbidities, and drug response profiles (2). However, despite these advances, about one-third of pediatric patients continue to experience drug-resistant epilepsy (DRE), defined as the failure of adequate trials of two or more appropriately chosen and used ASMs to achieve sustained seizure freedom (3). This has fueled the exploration of alternative therapeutic approaches that go beyond conventional pharmacology.

Non-pharmacological interventions have emerged as crucial adjuncts or alternatives in the management of pediatric epilepsy, particularly in cases of DRE. Among these, dietary therapies such as the ketogenic diet have demonstrated notable efficacy in reducing seizure frequency, with additional benefits on behavioral and cognitive outcomes. The ketogenic diet, a high-fat, low-carbohydrate regimen, induces ketosis, which is thought to exert anticonvulsant effects through modulation of neuronal metabolism and neurotransmitter function (4). Neuromodulation techniques, including vagus nerve stimulation (VNS) and responsive neurostimulation (RNS), offer additional avenues for seizure control, especially in children who are not surgical candidates or have multifocal epilepsy. These technologies use implanted devices to deliver targeted electrical stimulation, thereby disrupting epileptic activity and reducing seizure burden (5). Despite the progress in both pharmacological and non-pharmacological domains, the literature reveals several persistent gaps in pediatric epilepsy care. First, the heterogeneity of epilepsy syndromes in children, ranging from benign forms to catastrophic epileptic encephalopathies, complicates the generalization of treatment outcomes. Second, there is a lack of high-quality randomized controlled trials specifically in pediatric populations, limiting the ability to draw definitive conclusions about comparative efficacy and safety of newer treatments (6). Third, many non-pharmacological strategies, while promising, require further validation through long-term studies assessing not only seizure control but also impacts on development and quality of life (6,7).

This narrative review aims to synthesize recent advancements in both pharmacological and non-pharmacological treatment modalities for pediatric epilepsy. The focus will be on newly developed ASMs, including their mechanisms of action, efficacy, safety, and suitability for pediatric use (8,9). Additionally, the review will explore dietary approaches, neuromodulation techniques, and other innovative non-drug interventions that are gaining ground in clinical practice. The scope will encompass studies published in the last five years, ensuring an up-to-date and clinically relevant analysis. This review is significant because it addresses the urgent need for comprehensive, individualized, and evidence-based treatment strategies for pediatric epilepsy. By highlighting emerging therapeutic options and synthesizing current evidence, this work aims to assist clinicians, researchers, and healthcare policymakers in making informed decisions that enhance patient outcomes. Furthermore, this review underscores the importance of integrating pharmacological innovation with personalized, multimodal care approaches tailored to the unique needs of the pediatric population.

THEMATIC DISCUSSION

Advances in Pharmacological Therapies

Pharmacological intervention remains the primary approach for managing pediatric epilepsy, and recent years have witnessed significant expansion in available antiseizure medications (ASMs). The introduction of newer ASMs with improved pharmacokinetic profiles, fewer drug interactions, and enhanced tolerability has expanded therapeutic possibilities. Agents such as brivaracetam, perampanel, and cenobamate have shown promising efficacy in reducing seizure frequency and are increasingly considered for pediatric use due to favorable safety profiles (1). Additionally, comparative effectiveness studies suggest that second-generation ASMs can offer comparable, if not superior, seizure control with reduced cognitive side effects compared to older drugs (2). One notable shift in pharmacological strategy is the individualized approach to drug selection based on seizure type, genetic background, and comorbidities. This precision-medicine perspective is supported by a growing understanding of the genetic underpinnings of epileptic syndromes and their variable

drug responsiveness (3). Despite these advances, around one-third of pediatric patients continue to exhibit drug-resistant epilepsy (DRE), emphasizing the need for alternate strategies.

Dietary Interventions

Dietary therapies, especially the ketogenic diet (KD), have been pivotal in managing DRE in children. KD, characterized by high-fat and low-carbohydrate intake, induces metabolic changes that contribute to seizure reduction, although the precise mechanism remains under investigation. Clinical studies report seizure reduction in 30–60% of children on KD, with some achieving complete remission (4). Modified diets like the modified Atkins and low glycemic index treatments offer similar benefits with improved tolerability and adherence. Despite favorable outcomes, KD is associated with gastrointestinal disturbances, dyslipidemia, and potential growth retardation, requiring close monitoring. Additionally, dietary therapies necessitate a high level of caregiver commitment, specialized dietitians, and institutional support, posing logistical challenges. While evidence supports their efficacy, inconsistencies in study designs and outcome measures limit the generalizability of findings.

Neuromodulation Techniques

Neuromodulatory interventions have emerged as vital alternatives for children with DRE who are not suitable candidates for resective surgery. Vagus nerve stimulation (VNS), approved for pediatric use, reduces seizure frequency by 50% or more in up to 40% of children and improves mood and alertness (5). Responsive neurostimulation (RNS), although primarily studied in adults, is being investigated for use in older adolescents, offering the advantage of real-time detection and disruption of epileptic activity. Deep brain stimulation (DBS), targeting the anterior nucleus of the thalamus, has also been explored in pediatric cohorts, although limited by sparse data and ethical concerns. These interventions offer hope for seizure reduction with minimal cognitive impact, yet long-term outcomes, device-related complications, and cost considerations remain areas of ongoing research (6).

Physical Activity as Adjunct Therapy

Emerging evidence suggests that physical activity (PA) may serve as a non-pharmacological adjunct in pediatric epilepsy management. Though not directly anticonvulsant, PA is associated with improved cognitive outcomes, reduced anxiety, and enhanced quality of life. In a recent systematic review, PA was found to improve attention span and mood without increasing seizure risk, addressing some psychosocial deficits observed in epilepsy (7). However, more robust trials are needed to confirm these findings and delineate appropriate exercise regimens.

Integrating Genetic Insights into Treatment

Genetic discoveries have transformed the understanding of pediatric epilepsy and offer novel treatment avenues. Identification of mutations in genes like SCN1A and CDKL5 allows for tailored pharmacologic or dietary therapy and potentially gene-specific interventions. For instance, children with Dravet syndrome, often linked to SCN1A mutations, respond poorly to sodium channel blockers but benefit from stiripentol and cannabidiol-based treatments (8). Yet, translating genetic findings into mainstream therapy is limited by diagnostic accessibility, cost, and the need for targeted clinical trials.

Multimodal and Personalized Care Approaches

A clear trend across recent literature is the shift toward integrated, multimodal care strategies that combine pharmacologic, dietary, neuromodulatory, and psychosocial interventions. These strategies acknowledge the multifactorial nature of epilepsy and its impacts on the developing brain. Clinical algorithms now emphasize early identification of DRE, timely consideration of non-drug therapies, and continuous reassessment of treatment efficacy and side effects (9). However, real-world implementation of such personalized regimens faces challenges, particularly in resource-limited settings, due to the demand for multidisciplinary teams and specialized infrastructure.

Controversies and Gaps in Evidence

Despite growing therapeutic options, several controversies persist. The choice of initial ASM remains debated, particularly for generalized epilepsies, with limited head-to-head trials in children. Moreover, the comparative efficacy of KD versus newer ASMs for DRE lacks robust, randomized evidence. Neuromodulation outcomes vary widely, and most studies are observational with small sample sizes and short follow-up. Physical activity, though beneficial in theory, is underexplored in interventional designs. Another concern is the underrepresentation of diverse populations in epilepsy research, which restricts external validity and equity in care access. While pediatric epilepsy management has advanced substantially through novel drugs, dietary therapies, and neuromodulatory devices, optimal

care requires individualized, evidence-informed strategies. Integration of genetic data, lifestyle interventions, and emerging technologies holds promise for the future but demands further high-quality research to validate and refine these approaches.

CRITICAL ANALYSIS AND LIMITATIONS

While significant progress has been made in developing pharmacological and non-pharmacological treatments for pediatric epilepsy, the current body of literature is not without notable limitations. One of the most recurrent methodological weaknesses lies in the design of many studies, particularly those evaluating emerging therapies. Numerous investigations suffer from small sample sizes that limit statistical power and the ability to detect nuanced differences in treatment efficacy. For example, studies evaluating the ketogenic diet and neuromodulation approaches often include fewer than 100 participants, which may contribute to inconsistent results and limited reproducibility across larger, heterogeneous populations (10). Additionally, the absence of large-scale randomized controlled trials (RCTs) in many pediatric cohorts remains a major concern. Despite the increasing use of newer antiseizure medications, most supporting evidence stems from open-label or observational studies, which are more susceptible to various forms of bias and lack the rigor of controlled experimental frameworks (11). Beyond design limitations, methodological biases and confounding factors are pervasive throughout the literature. Selection bias is particularly prominent in studies that focus predominantly on specific epilepsy syndromes or exclude children with comorbidities, thereby limiting the applicability of findings to real-world settings. Similarly, performance bias—especially in non-blinded interventions such as dietary therapies and neuromodulation—can inflate perceived efficacy through placebo effects or observer influence. These issues are compounded by variability in outcome measurement tools. Definitions of treatment success vary widely, ranging from complete seizure freedom to partial reduction in seizure frequency, with some studies incorporating quality-of-life scores and others relying solely on clinical seizure counts. Such discrepancies make it challenging to compare studies directly or synthesize findings into generalized treatment recommendations (12).

Another significant issue is publication bias. There is a tendency for positive findings to be overrepresented in the literature, while negative or null results often go unreported. This is especially relevant in pharmacological trials sponsored by pharmaceutical companies, where favorable outcomes are more likely to be published. As a result, the true efficacy of certain therapies may be overestimated, and clinicians may be unaware of potential limitations or failures observed in unpublished studies (13). Furthermore, even when negative findings are reported, they often receive less attention or are excluded from meta-analyses, further skewing the evidence base. Generalizability also remains a pressing concern. Many studies are conducted in high-income countries with access to advanced diagnostics and multidisciplinary care teams. As a result, findings may not translate effectively to low- and middle-income settings, where diagnostic capabilities, treatment options, and follow-up resources are limited. Additionally, ethnic, cultural, and socioeconomic factors—which can influence treatment adherence, dietary practices, and even genetic predisposition to certain epilepsy syndromes—are seldom addressed in trial designs. This restricts the external validity of study conclusions and poses challenges in developing universally applicable treatment guidelines (14). In summary, while the reviewed studies contribute valuable insights into the evolving landscape of pediatric epilepsy treatment, their impact is moderated by a range of design and methodological limitations. Addressing these issues through more rigorous, inclusive, and transparent research will be essential to optimizing care and ensuring equitable access to effective therapies.

IMPLICATIONS AND FUTURE DIRECTIONS

The evolving landscape of pediatric epilepsy management, as highlighted in this review, offers several important implications for clinical practice. The increasing availability of second-generation antiseizure medications with more favorable safety profiles enables clinicians to tailor pharmacological therapy based on individual patient characteristics, seizure types, and comorbidities. This personalized approach may enhance treatment adherence and improve long-term outcomes, particularly in children with complex epilepsy syndromes (15,16). Moreover, early consideration of non-pharmacological treatments such as dietary interventions and neuromodulatory techniques should be integrated into routine care pathways for drug-resistant epilepsy (DRE), as delaying these options may compromise neurodevelopmental trajectories and quality of life (17). At the policy and guideline level, the review underscores the urgent need for updated, evidence-based clinical guidelines that incorporate both pharmacological and non-pharmacological strategies. Currently, most national and international protocols still emphasize medication-first approaches, often overlooking the benefits of multimodal interventions or newer therapeutic modalities like responsive neurostimulation. Policymakers should prioritize the development of

standardized treatment algorithms that support earlier identification of DRE, guide selection of alternative therapies, and facilitate equitable access to specialized services such as ketogenic dietary programs and neuromodulation units (18).

Despite promising advances, numerous questions remain unanswered. There is a pressing need for high-quality data on the long-term effects of newer ASMs, particularly in terms of neurocognitive development and psychosocial functioning. Additionally, while the ketogenic diet and vagus nerve stimulation have shown clinical benefits, there is limited understanding of the mechanisms that mediate these effects in children. Variability in treatment response also highlights the potential role of genetic profiling and biomarkers, which are still underutilized in current practice. Furthermore, adjunctive strategies like physical activity and behavioral therapies warrant deeper exploration to clarify their therapeutic contributions and optimal integration into treatment plans (19,20). To bridge these knowledge gaps, future research should prioritize the design of robust, multicenter randomized controlled trials with sufficient sample sizes and longer follow-up periods. Trials should include diverse patient populations and account for variables such as age, sex, socioeconomic background, and comorbid conditions to improve generalizability. Standardizing outcome measures across studies—such as seizure frequency, cognitive assessments, and quality of life indices—would greatly enhance comparability and synthesis of findings. Moreover, mixed-methods research incorporating both quantitative outcomes and qualitative patient or caregiver experiences could provide a more holistic view of treatment effectiveness and acceptability (21). Lastly, investments in translational research linking genomics, neurophysiology, and treatment response are crucial to advancing precision medicine in pediatric epilepsy. In summary, the insights from this review offer meaningful direction for clinical practice, policy refinement, and future scientific inquiry. By addressing the identified limitations and strategically guiding future research efforts, the field can move closer to ensuring effective, safe, and individualized care for every child living with epilepsy.

CONCLUSION

This narrative review highlights the growing complexity and promise of emerging treatment approaches in pediatric epilepsy, emphasizing the evolution from traditional pharmacological regimens to more individualized and integrative strategies. Key findings reveal that while newer antiseizure medications offer improved safety profiles and broader efficacy, they are not universally effective, necessitating the incorporation of non-pharmacological interventions such as ketogenic dietary therapies, neuromodulation, and supportive adjuncts like physical activity. The strength of the existing evidence, though encouraging, is tempered by methodological limitations, including small sample sizes, variability in outcome metrics, and underrepresentation of diverse populations. Nonetheless, current research provides a foundational basis for informed clinical decision-making. Clinicians are advised to adopt a patient-centered, multimodal approach to treatment, recognizing the value of early intervention and the potential benefits of combining therapies based on individual needs and responses. For researchers, there is an urgent call to design robust, inclusive, and longitudinal studies that address existing gaps, particularly in the areas of comparative effectiveness, mechanistic understanding, and long-term developmental outcomes. Expanding the evidence base through high-quality investigations will be essential to refining treatment protocols and ultimately improving quality of life for children with epilepsy.

AUTHOR CONTRIBUTION

Author	Contribution
Sahibzada Zumeran Jah	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Amina Javid Qaiser	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
Myrah Hasan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Adeel-ur-Rehman	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Tahira Jamil	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Abdul Aziz*	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Zaid Alam Siddiqui	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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