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DRUG DEVELOPMENT IN THE PEDIATRIC POPULATION FOR EPILEPSY

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ABSTRACT

Epilepsy in the pediatric population presents unique challenges in terms of diagnosis,management, and treatment,requiring careful consideration of pharmacokinetics,safety, and developmental factors. Although advances in antiepileptic drugs (AEDs) have significantly improved the management of epilepsy in children,treatment options remain limited,and many existing medications are not specificallyapproved for pediatric use. This review examines current drugdevelopment strategiesfor pediatric epilepsy, with a focus on recent advances in the discovery and clinicaltestingof novel AEDs. It highlights the importance of age-appropriate formulations,dosing regimens, and the consideration of coexisting conditions such asneurodevelopmental disorders. The review also addresses the keychallenges faced in pediatric clinical trials, including ethical considerations, recruitment, and the need for biomarkers to guide therapy. Special attention is given to recentinnovations in personalized medicine, includingthe potential of genetic testingand precision therapies for optimizing treatment outcomes in pediatric epilepsy.Finally,we discuss the unmet needs in pediatric epilepsy drug development, emphasizing theneed for safer, moreeffective treatments with fewer side effects to improve quality oflife and long-term prognosis for affected children.

KEYWORDS: *Pediatric epilepsy, drug development, antiepileptic drugs, clinical trial, Pharmacokinetics,personalized medicine, novel therapies.*

INRODUCTION

- Epilepsy is a prevalent neurological disorder that affects a significant number of children worldwide, with an estimated incidence of 1 in 100 children. This condition presents unique challenges in diagnosis and management due to the variability in seizure types, underlying etiologies, and the developmental stage of pediatric patients. The treatment landscape for pediatric epilepsy primarily relies on antiepileptic drugs (AEDs), which are critical for controlling seizures and minimizing their impact on a child's development and quality of life.
- However, the pharmacological management of epilepsy in children is complex. Pediatric patients differ from adults not only in terms of their physiological responses to medications but also in their developmental and cognitive needsMany AEDs were initially developed and tested in adults, leadingto gaps in understanding their safety and efficacy in children.
- Furthermore, the pharmacokinetics and pharmacodynamics of drugs can vary significantly during different stages of childhood, necessitating careful consideration when determining dosages and treatment plans.
- This review explores the current state of drug development for pediatric epilepsy, examining recent advances in treatment options, the challenges associated with research in this population, and potential future directions that could enhance therapeutic outcomes. Understanding these dynamics is crucial foroptimizing the care of children with epilepsy and ensuring that they receive safe and effective treatments tailored to their unique needs.
- Epilepsy is a common disorder in children and adults that causes significant morbidity and affects manyaspects of a patient's lives. Two-thirds of patients with epilepsy are controlled with established antiseizure medications, leaving a significant number of patients searching for other options. The purpose of this review is to provide an overview of recent advancements in the management of treatment-resistant epilepsy in pediatric patients.
- Recent publications have shown the efficacy of new pharmaceutical options such as fenfluramine and cannabidiol, some of which have been tested specifically in patients with childhood-onset epilepsy syndromes such as Dravet's syndrome and Lennox–Gastaut's syndrome. Furthermore, recent approval by the U.S. Food and Drug Administration of stiripentol has made available a previously difficult-to- obtain option for patients with Dravet's syndrome. Finally, implanted responsive neurostimulation devices for direct cortical stimulation and deep brain stimulation have shown efficacy in adult patients and may represent a thrilling new horizon for pediatric patients.
- The goal is to enhance the quality of life for children living with epilepsy and their families through better therapeutic options and a deeper understanding of their unique needs.
- Historically, the majority of antiepileptic drugs (AEDs) have been developed and tested primarily in adult populations, leading to a significant gap in knowledge regarding their use in children. This disparity is critical, as children differ markedly from adults in terms of physiology, metabolism, and developmental stages.
Factors such as growth rates, organ maturity, and the

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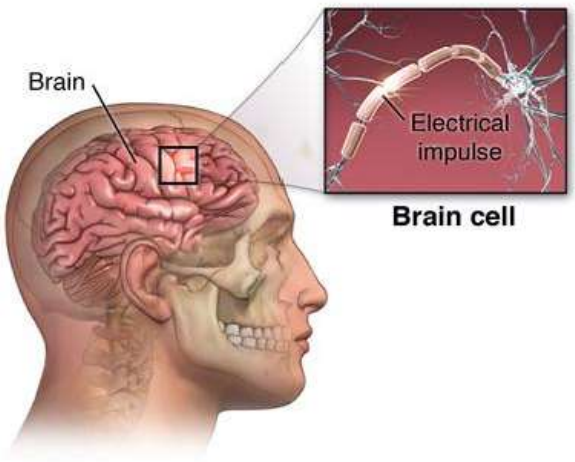
maturation of the central nervous system can influence both the pharmacokinetics and pharmacodynamics of medications. Consequently, medications that are safe and effective in adults may not yield the same results in children,raising concerns about efficacy, side effects, and long-term implications of treatment.

- Treatment of pediatric epilepsy requires a careful evaluation of the safety and tolerability profile of antiepileptic drugs (AEDs) to avoid or minimize as much as possible adverse events (AEs) on various organs, hematological parameters, and growth, pubertal, motor, cognitive and behavioral development.
- Physiological changes occurring during development age (different body composition, immature metabolic patterns, reduced renal activity), can significantly affect the pharmacokinetic profile of manyAEDs .
- Young children show increased capacity of metabolizing AEDs, and thus require larger dosages per kg.
- Neonates tend to show reduced clearance and capacity of metabolizing AEDs, and thus require lower dosages per kg.
- With 65 million people aff ected worldwide, epilepsy is the most common, chronic, serious neurological disease.1 People with epilepsy suff er from discrimination, misunderstanding, social stigma,2 and the stress of living with a chronic unpredictable disease that can lead to loss of autonomy for activities of daily living.

DEFINITION

- An epileptic seizure is defined by the International League against Epilepsy (ILAE) as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in thebrain. Epilepsy is characterised conceptually as an “enduring predisposition of the brain to generate epileptic seizures, with neurobiologic, cognitive, psychological, and social consequences”.7Key featuresof epilepsy in children5 and adults6 were discussed in two previous Seminars. Here, we focus on new advance.
- Attention deficit/hyperactivity disorder (ADHD) is a common brain disorder with onset in early childhood, due to structural and functional abnormalities in wide spread, but specific areas of the brain[1]. ADHD is a frequent comorbidity experienced by children with epi lepsy, has a negative impact on their quality of life, and represents a significant risk factor for academic underachievement.
- Epilepsy is a common disorder in children that often requires antiepileptic drug (AED) treatment for many years [1]. However, most AEDs have inadequate paediatric use information [2]. Indeed, AEDs are evaluated primarily in adult patients [3], and only a few randomised controlled trials (RCTs) have been performed in paediatric population [1]. Furthermore, despite reviews and guidelines establishing the importance of comprehensive drug development programs in children [2,4], most pivotal paediatric trials have been completed in Phase IV as a postapproval replication of adult data. Formulations, target doses, and expected effect size— which determines trial design and sample size—have been largely extrapolated from data collected in adult studies. Overall, the typical practice has been to extend the useof AEDs approved for adult epilepsy to children [5].
- Among the treatment tools for individuals with epilepsy, which include medication, diet, surgery, neuromodulation, and psychological interventions, the latter most specifi cally aim to improve health- related quality of life (HRQOL).
- Given the significant impact that psychosocial factors and epilepsy treatments can have on the HRQOLof indi viduals with epilepsy and their families, there is great clini cal interest in the role of psychologicalevaluation and treatments to improve HRQOL
- The increasing number of new treatments promises a better quality of life for individuals with epilepsy. However, the ever-growing list of options also makes it much more difficult to select the optimal treatment or combination of treatments. Because the medical litera ture may not provide information regarding the use of a therapy in a particular clinical situation, clinicians must at times rely on their medical judgment: it is in this &dquo;gray area&dquo; where expert opinion can be most helpful.



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CAUSES OF EPILEPSY IN THE PEDIATRIC POPULATION

1. **Genetic Factors**
   - Genetic predispositions play a significant role in many cases of pediatric epilepsy.
   - **Inherited Epilepsy Syndromes:** Conditions such as Dravet syndrome, Lennox-Gastaut syndrome, and juvenile myoclonic epilepsy are often linked to specific genetic mutations. These syndromes typically present with distinct seizure types and developmental outcomes.
   - **Chromosomal Abnormalities:** Genetic conditions like Down syndrome and Turner syndrome can also predispose children to seizures.

2. **Structural Brain Abnormalities**
   - Structural anomalies in the brain are common causes of epilepsy in children.
   - **Tumors and Lesions:** Brain tumors, whether benign or malignant, can provoke seizures. Other lesions, such as vascular malformations or traumatic injuries, may also lead to epileptic activity.
   - **Cerebral Hemispheric Syndromes:** Conditions like hemimegalencephaly, where one hemisphere of the brain is abnormally large, can result in frequent seizures.

3. **Metabolic Disorders**
   - Metabolic disturbances can lead to epilepsy through various mechanisms.
   - **Inborn Errors of Metabolism:** Disorders such as phenylketonuria (PKU) and mitochondrial diseases can disrupt normal brain function and increase seizure susceptibility.
   - **Electrolyte Imbalances:** Abnormal levels of sodium, calcium, or glucose can lead to seizures. For example, hypocalcemia or hyponatremia can trigger epileptic activity.

4 **Infectious Diseases.**

Certain infections can significantly increase the risk of developing epilepsy in children.

- **Central Nervous System Infections:** Conditions such as meningitis, encephalitis, and neurocysticercosis can cause inflammation and neuronal damage, leading to seizures.
- **Post-Infectious Epilepsy:** Some children may develop epilepsy following a febrile illness, where theseizuresare linked to the body's immune response.

5. **Perinatal and Neonatal Factors**

Events during pregnancy, childbirth, or early infancy can contribute to the onset of epilepsy.

- **Birth Trauma:** Oxygen deprivation (asphyxia) during delivery can lead to conditions like hypoxic-ischemic encephalopathy (HIE), which is associated with a higher risk of seizures.
- **Prematurity:** Premature infants are at increased risk for seizures due to immature brain development and potential complications like intraventricular hemorrhage.
- **Maternal Conditions:** Infections during pregnancy (e.g., rubella, syphilis) or maternal substance abuse can adversely affect fetal brain development, increasing seizure risk.

6. **Environmental Factors**

Environmental influences can also contribute to the development of epilepsy.

- **Head Injuries:** Traumatic brain injuries in children, whether from accidents or abuse, can lead to post-traumatic epilepsy.
- **Toxins:** Exposure to neurotoxic substances (e.g., lead) can impair neurological function and increase seizure risk.

7.Psychosocial Factors

While not direct causes, psychosocial stressors can exacerbate seizure disorders.

- **Stress and Anxiety:** High levels of stress and anxiety can trigger seizures in susceptible individuals, particularly in those with existing epilepsy.

SIGN AND SYMPTOMS

1. Loss of consciousness
2. Weakness.
3. Anxiety.
4. Muscle contraction and jerking
5. Confused speech
6. Staring.

LITRATURE REVIEW

1. **Anna rosati, et.al, drug development for rare padiatric epilepsy ,2023,** The commonly held opinion that new and newer AEDs have a better safety profile than old ones does not appear to be supported by evidence .
2. **Catherine j. Chu-shore md, et.al,antiepileptic drug development in childen, 2022,** Newer-generation AEDs have been developed with the intention of improving the ease of use, decreasing drug interactions, decreasing adverse side effects , and identifying drugs with unique mechanisms of action.
3. R**oger J. Porter, ET,AL, clinical drug development in epilepsy, 2022,** Childhood epilepsies area heterogeneous group of conditions that differ in diagnostic criteria and management and have dramatically different outcomes.
4. **Linda J. Stephen , et.al, new drug in padiatric epilepsy ,2021,**The availability of new AEDs has widened the choices for clinicians treating patients with epilepsy.
5. Hee hwang, clinical development of drug for epilepsy ,2020, We review the mechanisms of action, pharmacokinetic adverse reactions, efficacy, and tolerability of eight new AEDs (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin, and zonisamide), focusing on currently available

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treatment guidelines and expert opinions regarding pediatric epilepsy.

6. **Roger J. Porter, et,al, development of new treatment aproaches of epilepsy ,2019,**This article wascommissioned with the intent of comparing the clinical development process for antiepileptic drugs in the United States and Europe. Obviously, the process of drug development is very complex, and can only be lightly touched upon in this article. For example, areas not covered in this article include issues related to children, the elderly, parenteral formulations, and orphan drugs. This is an article about fundamentals.
7. **Nicola Marchi, et,al, Efficacy of Anti-Inflammatory Therapyina Model of Acute Seizuresandina Population of Pediatric Drug Resistant Epileptics,2019**, Drug-resistant seizures pose a formidablchallenge for drug development. Recently, the Consensus Proposal by the adhoc Task Force of the International Leagueagainst Epilepsy Commissionon Therapeutic Strategies pointed out that drug resistance is''a dynamic process rather thana fixed state''and in spite of the available therapeutic interventions for seizure disorders.
8. **Gyri Veiby ,et,al, Early Child Development and Exposure to Antiepileptic Drugs Prenatally and Through Breastfeeding A Prospective .Cohort Study on Children of Women With Epilepsy,2018,** The primary aim of this stud was to examine whether prenatal exposure to anti epileptic drugs has an effecton develop mental ready during the first 6 months. The secondary aim was to explore adverse effects of antiepileptic drug exposure through breastfeeding. Children of mothers using antiepileptic drugs were compared with a large reference group of children with outparental epilepsy. Children off athers and untreated others with epilepsy serve das internal control groups, accounting for genetic and socioeconomiceffects of parental epilepsy.

AIM: DRUG DEVELOPENT IN THE PADIATRIC POULATION FOR EPILEPSY .

OBJECTIVE

1. **Safety and Tolerability**: Ensure that medications are safe for children, with minimal side effects, and assess how they interact with growing bodies.
2. **Efficacy**: Demonstrate that the drug effectively controls seizures in the pediatric population, consideringthe specific types of epilepsy common in children.
3. **Age-Specific Formulations**: Develop age-appropriate formulations (e.g., liquid, chewable) that facilitateadministration and improve adherence.
4. **Pharmacokinetics**: Understand how the drug is metabolized in children, as their metabolism can differsignificantly from adults.
5. **Long-Term Effects**: Assess the long-term safety and efficacy of the treatment, considering the potential impact on cognitive and physical development.
6. **Dosing Guidelines**: Establish clear dosing guidelines that take into account weight and age to avoid overdosing or underdosing.
7. **Psychosocial Considerations**: Address the psychosocial aspects of epilepsy management in children,including impacts on education and social interactions.
8. **Access and Affordability**: Ensure that the developed medications are accessible and affordable for families, addressing potential socioeconomic barriers.
9. **Regulatory Compliance**: Adhere to regulatory requirements for pediatric drug development, includingspecific guidelines from agencies like the FDA or EMA.
10. **Inclusion of Diverse Populations**: Ensure that clinical trials include diverse pediatric populations to understand variations in response among different ethnic and demographic groups.

TYPES OF PEDIATRIC EPILEPSY

- Pediatric epilepsy refers to seunderlying cause, or the specific syndrome they belong to. Below are some common types of pediatric epilepizures in children caused by abnormal electrical activity in the brain. There are several types of epilepsy in children, and they can be classified based on the type of seizures they involve, the sy:

1. Focal (Partial) Epilepsy

- **Focal Seizures**: These seizures begin in one area of the brain and may or may not spread. The child may experience a range of symptoms depending on the affected brain region.
- **Focal Onset Aware Seizures** (previously called simple partial seizures): The child remains aware duringthe seizure.
- **Focal Onset Impaired Awareness Seizures** (previously called complex partial seizures): The child mayhave altered awareness and may appear confused or unresponsive.
- **Common Syndromes**
- **Focal Seizures with Secondary Generalization**: Focal seizures that spread to become generalized, affecting the entire brain.
- **Temporal Lobe Epilepsy**: Often associated with complex focal seizures and sometimes memory or emotional disturbances.

2. Generalized Epilepsy

- **Generalized Seizures**: These seizures involve both sides of the brain from the start. They can cause lossof consciousness and can manifest in several different forms.
- **Tonic- Clonic Seizures** (formerly called Grand Mal): Characterized by a loss of consciousness and violent muscle contractions.
- **Absence Seizures** (formerly Petit Mal): Brief episodes of staring or "spacing out" without

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convulsions,usually lasting a few seconds.

- **Myoclonic Seizures**: Sudden, brief jerks or twitches of the body or limbs.
- **Atonic Seizures**: Sudden loss of muscle tone leading to falls or "drop attacks."
- **Tonic Seizures**: Muscle stiffening and loss of consciousness.
- **Clonic Seizures**: Repetitive jerking movements.

3. Epileptic Syndromes in Children

Some pediatric epilepsy syndromes are associated with specific patterns of seizures, developmental delay, other features. These include:

- **West Syndrome (Infantile Spasms)**: Typically starts in infancy (usually between 3 and 12 months). It is characterized by sudden jerking movements (spasms), often associated with developmental regression and abnormal EEG findings.
- **Dravet Syndrome**: A severe, early-onset form of epilepsy often triggered by fever. It can lead to developmental delays and other neurological impairments.
- **Lennox-Gastaut Syndrome**: A severe form of epilepsy that usually begins in early childhood and is characterized by multiple types of seizures, including tonic, atonic, and myoclonic seizures. It often involves intellectual disability and developmental delays.
- **Landau-Kleffner Syndrome**: A rare syndrome where children lose their ability to speak and develop seizures, often between ages 3 and 7.
- **Rolandic Epilepsy (Benign Epilepsy of Childhood with Centrotemporal Spikes)**: Typically starts between ages 3 and 13, and involves seizures originating in the area around the Rolandic cortex, usually affecting the face and mouth. It tends to improve or resolve by late childhood or early adolescence.
- **Benign Childhood Epilepsy with Centrotemporal Spikes**: A type of epilepsy with seizures that originate in the temporal lobes of the brain, often characterized by simple focal seizures that may involvespeech or facial muscles.

4. Reflex Epileps

- **Reflex Seizures**: These seizures are triggered by specific stimuli or activities, such as flashing lights, reading, or hyperventilation. Some common examples include:
  a. **Photosensitive Epilepsy**: Seizures triggered by flashing lights or certain visual patterns.
  b. **Reading Epilepsy**: Seizures triggered by reading or other specific tasks.

5. Unknown or Unclassified Epilepsy

- In some cases, the type or cause of epilepsy may not be immediately clear. These cases may eventually fall into a recognized category as more information becomes available.

6. Epilepsy Related to Underlying Conditions

- **Genetic Epilepsy**: Some types of epilepsy in children are linked to genetic mutations or inheritedconditions.
- **Metabolic Epilepsies**: Seizures related to metabolic disorders such as mitochondrial disease or phenylketonuria (PKU).
- **Structural Epilepsies**: These are caused by physical abnormalities in the brain (e.g., brain malformations, tumors , or injury).
- **Infectious Epilepsies**: Seizures caused by infections affecting the brain, such as meningitis orencephalitis.
- **Post-traumatic Epilepsy**: Seizures that occur after a head injury or trauma.

DIAGNOSIS AND TREATMENT

The classification of pediatric epilepsy is important for determining the best treatment approach. It usually involves:

- **EEG (Electroencephalogram)**: To record electrical activity in the brain and identify seizure patterns.
- **MRI or CT scans**: To detect structural abnormalities in the brain.
- **Genetic testing**: If a genetic cause is suspected.

TREATMENT OF ANTIEPILEPTIC AGENT

Barbiturate	Phenobarbitone
Hyndatoin	Phenytoin Phosphenytoin
Succinamide	Ethosuximide
Benzodiazepine	ClonazepamDiazepam Lorazepam Clobazam
Newer Drugs	Topiramate Zonisamide Levetiracetam
Deoxybarbiturate	Primidone
Imminostilbene	CarbamazepineOxcaebazepine
Aliphatic Carboxylic Acid	Valproate Sodium(Valproic Acid) Divalpreox
Phenyltriazine	Lamotrigine
Cyclic Gaba Anologous	GabapectinPregabalin

Innovations in Drug Development.

- Innovation in drug development for pediatric epilepsy involves various strategies to enhance treatmentoutcomes safety, and accessibility.

1. **Targeted Therapies**: Developing medications that specifically target the underlying mechanisms of different types of epilepsy, such as genetic mutations, which can lead to more effective treatments.
2. **Personalized Medicine**: Utilizing pharmacogenomics to tailor treatments based on individual geneticprofiles, optimizing efficacy and minimizing side effects.
3. **Novel Drug Delivery Systems**: Creating advanced delivery methods, such as transdermal patches, inhalation therapies, or nanotechnology-based formulations, to improve absorption and compliance inchildren.

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4. **Long-Acting Formulations**: Innovating long-acting formulations that reduce the frequency of dosing, thereby improving adherence and convenience for families.
5. **Digital Health Solutions**: Integrating mobile apps and wearable devices to monitor seizure activity and medication adherence, providing real-time data for both families and healthcare providers.
6. **Combination Therapies**: Exploring combinations of existing medications or novel compounds to enhance efficacy and reduce side effects through synergistic effects.
7. **Regenerative Medicine**: Investigating the potential of stem cell therapies or gene editing (e.g., CRISPR) to address the root causes of certain epilepsies.
8. **Artificial Intelligence (AI) and Machine Learning**: Utilizing AI to analyze vast datasets for identifying new drug candidates, predicting patient responses, and personalizing treatment plans.
9. **Collaborative Research Initiatives**: Fostering partnerships between pharmaceutical companies, academic institutions, and patient advocacy groups to drive innovation and share insights on pediatric epilepsy.
10. **Enhanced Clinical Trials**: Adopting adaptive trial designs that allow for modifications based on interim results, increasing the efficiency of the development process and ensuring a more rapid response to emerging data.

Future Directions in Pediatric Epilepsy Treatment

1. Genetic and Biomarker Research

- **Genomic Studies**: Continued exploration of genetic causes of epilepsy will facilitate the development of targeted therapies for specific genetic mutations.
- **Biomarkers**: Identifying biomarkers for seizure types and treatment responses can help tailor therapiesand monitor effectiveness.

2. Advanced Drug Delivery Systems:

- **Novel Formulations**: Developing innovative delivery systems, such as nanotechnology or microspheres, to enhance drug solubility and bioavailability.
- **Non-Invasive Methods**: Exploring non-invasive delivery methods, such as transdermal or intranasal routes, for rapid seizure control.

3. Personalized Medicine

- **Pharmacogenomics**: Using genetic profiling to customize treatment plans based on individual responsesto medications, minimizing trial and error.
- **Patient-Centric Approaches**: Involving families in treatment decisions to better align therapies with lifestyle and preferences.

4. Digital Health Technologies

- **Wearable Devices**: Utilizing wearables to monitor seizure activity and physiological responses, providing real-time data to caregivers and clinicians.
- **Mobile Health Apps**: Creating applications for tracking medication adherence, seizures, and side effects to enhance communication with healthcare providers.

5. Combination and Adjunctive Therapies

- **Polytherapy Approaches**: Exploring combinations of existing drugs or adding non-pharmacological treatments (like dietary therapies) to optimize seizure control.
- **Investigational Agents**: Conducting research on novel compounds that can act as adjunct therapies alongside traditional antiepileptic drugs.

6. Neurostimulation Techniques

- **Responsive Neurostimulation (RNS)**: Investigating the use of devices that detect abnormal brainactivity and deliver targeted stimulation to prevent seizures.

CONCLUSION

1. **Need for Tailored Approaches**: Pediatric epilepsy requires drug development that considers the distinct physiological and developmental characteristics of children. This includes creating age-appropriate formulations and dosage guidelines.
2. **Emphasis on Safety and Tolerability**: Given the potential for long-term effects on growth and development, ensuring the safety and tolerability of antiepileptic medications is paramount. This involves rigorous testing and monitoring throughout the drug development process.
3. **Advancements in Technology**: Innovations in drug delivery systems, such as non-invasive methods and digital health technologies, are transforming how treatments are administered and monitored, improving adherence and outcomes.
4. **Personalized Medicine**: The integration of genetic and biomarker research is paving the way for personalized treatment approaches, enabling healthcare providers to tailor therapies to individual patients based on their unique genetic makeup.
5. **Holistic Management**: Effective treatment of pediatric epilepsy goes beyond medication. It requires a comprehensive approach that includes psychological support, educational resources, and involvement of families in decision-making.
6. **Collaborative Efforts**: Ongoing collaboration among researchers, healthcare providers, pharmaceutical companies, and advocacy groups is essential for driving innovation and ensuring that new treatments meet the specific needs of children with epilepsy.
7. **Focus on Quality of Life**: Future drug development must prioritize not only seizure control but also the overall quality of life for pediatric patients, addressing the educational, social, and emotional aspects of living with epilepsy.

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