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Transformative Approaches to Epilepsy Treatment: A Review of Recent Developments

Chandra Prakash Joshi[1], Shikha Agarwal[2], Lalit Singh Chauhan[1], Shivali Singla[3], Ashish Baldi[4], Joohee Pradhan[1*]

[1]Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan-313001, India. [2]Department of Chemistry, Mohanlal Sukhadia University, Udaipur, Rajasthan-313001, India. [3]Department of Anaesthesiology & Critical Care Medicine, University of New Mexico School of Medicine, Albuquerque, NM 87106, USA. [4]Department of Pharmaceutical Sciences, Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab, India.

**Corresponding author: Joohee Pradhan.*

Abstract

Epilepsy remains a prevalent and challenging neurological disorder, with a significant subset of patients facing drug-resistant epilepsy and adverse effects from existing treatments. This review examines recent advancements in next-generation therapies, presenting promising directions in pharmacological and non-pharmacological approaches aimed at enhancing seizure control and improving patient quality of life. Advances in pharmacotherapy include novel antiepileptic drugs that target specific ion channels and neurotransmitter pathways, offering mechanisms distinct from traditional treatments. Additionally, neuromodulation techniques-such as vagus nerve stimulation, responsive neurostimulation, and transcranial magnetic stimulation-have shown potential in patients unresponsive to medication. Emerging gene and cell-based therapies offer targeted treatments for genetically rooted epilepsies, paving the way for personalized medicine. Moreover, biomarker identification and precision medicine are rapidly advancing, allowing clinicians to tailor treatments to individual patients more effectively. Artificial intelligence (AI) applications, including seizure prediction algorithms and wearable devices, add a new dimension to patient management, offering continuous monitoring and early intervention. Innovations in drug delivery systems, like nanoparticle formulations and transdermal patches, aim to improve bioavailability and reduce systemic side effects. Despite these promising developments, challenges remain, including accessibility, cost, and the need for further research and clinical validation. This review provides an in-depth analysis of these cutting-edge approaches, underscoring the potential impact on epilepsy care and the necessity for ongoing innovation to meet patient needs.

Keywords: Epilepsy; Drug-resistant epilepsy; Next-generation therapies; Antiepileptic drugs (AEDs); Seizure management

Introduction

Epilepsy is a group of disorders characterized by recurrent epileptic seizures. Epileptic seizures are hypersynchronous or/and excessive abnormal activities of neurons present in cerebral cortex part of brain (Engel, 1995). Epilepsy is a long-term brain disorder marked by a lasting tendency to produce seizures that occur without an immediate trigger, such as an injury to the central nervous system. It also involves neurological, cognitive, psychological, and social effects caused by repeated seizures (Beghi, 2020). Epilepsy is considered to be a global burden. Over 50 million people were estimated to be suffering from epilepsy by a study report in year 2000. More than 125,000 deaths were reported each year all over the world due to epilepsy (Singh & Sander, 2020). The prevalence of epilepsy was found to be increasing with increase in age and it peaks during 5 to 9 years of age and in patients over 80-years of age (Beghi *et al.*, 2019). Burden of epilepsy was also found to be higher in countries with lower-income economies. There are more premature deaths in lower-income countries due to epilepsy (Bell *et al.*, 2014). The remarkable difference may be explained by stigma and socioeconomic factors. Traumatic brain injuries, brain infections and treatment gaps are also more common in poor countries (Beghi & Hesdorffer, 2014). Drug therapies and surgical treatment are two methods practiced for management and treatment of epilepsy. For mesial temporal lobe epilepsy, surgical treatment should be given priority right from initial stages. However, for nonlesional extemporal lobe epilepsies, other treatment options, such as drug therapies should be given priority (Kawai, 2015). There are a number of antiepileptic drugs available with different mechanisms, tolerability and efficacies. Monotherapy is often prescribed, and is considered as a gold standard option (Santulli *et al.*, 2016).

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However, efficacies of available drugs are limited and with several undesired effects. They do not have potential to cure the disease, but to only provide symptomatic relief from seizures. These drugs can only suppress the incidents of seizures without curing the cause. Furthermore, most of the available drugs have adverse effects, deleterious interactions and withdrawal symptoms, limited their uses for only short period of time. Even some antiepileptic drugs have been reported to actually potentiate certain types of seizures (Santulli *et al.*, 2016). Despite of introduction of new antiepileptic drugs, almost every 3 out of 10 patients develop drug-resistant epilepsy (DRE). DRE comprises of psychosocial dysfunction, cognitive decline, neurobiochemical changes and intractable seizures. DRE is an ongoing challenge for both clinicians and researchers, due to the heterogenic nature of patient group (Dalic & Cook, 2016). Hence, there is an urgent need for next-generation antiepileptic drugs that can effectively manage DRE while minimizing adverse effects and addressing the underlying causes of the condition.

Advances in Pharmacological Treatments

Traditional antiepileptic drugs are more focused in management of seizures rather than addressing the cause of disorder. Though it is effective treatment for many, however, almost one-third of patients experience DRE (Engel, 2016), necessitating the development of novel pharmacological therapies. The new therapies are focused on novel mechanism of actions, improved safety profiles and enhanced efficacies for patient who are unresponsive to conventional treatment approaches (Hu *et al.*, 2023).

Ion Channel Modulators: A Targeted Approach

Ion channels are involved in pathology of many disorders. Both acquired and genetic epileptogenesis involves ligand-gated and voltage gated channels. Sodium channel inhibition is basic mechanism of many classic antiepileptic drugs including lamotrigine, phenytoin and carbamazepine. Voltage-gated potassium channels are comparatively novel targets for development of antiepileptic drugs (Armijo *et al.*, 2005). Ion channel modulators works by blocking sodium and calcium ion channels, more recently, by opening potassium channels (Camerino *et al.*, 2007). Potassium ion channels are involved in regulation of and neuronal excitability and resting potential. Genetic abnormalities in these channels have been shown to disrupt firing of neurotransmitters resulting into epileptic episodes, thereby, making these an important target for treatment of epilepsy (R. Khan *et al.*, 2024). Cenobamate, an ion channel modulator, was recently approved for commercial sale in the US and Europe. Its mechanisms include binding to a non-benzodiazepine binding site and enhancing inactivated state of voltage-gated Na^+ channels, while also blocking the persistent sodium current. Additionally, it acts as a positive allosteric modulator of $GABA_A$ receptors, contributing to its antiseizure activity by increasing inhibitory neurotransmission and reducing neuronal excitability (Barbieri *et al.*, 2023). A novel Potassium channel opener azetukalner (XEN1101) showed good efficacy and safety profile in a phase 2b randomized clinical trial (French *et al.*, 2023), for the management of focal seizures, tonic-clonic seizures, and depression problems.

Neurotransmitter Pathway Modulation: Expanding Therapeutic Targets

Recent pharmacological advances have expanded the therapeutic targets to include more refined mechanisms. An example of this is Stiripentol, a positive allosteric modulator of $GABA_A$ receptors (J. L. Fisher, 2009). Stiripentol is found to be beneficial in status epilepticus due to modulatory effects on δ-containing $GABA_A$ receptors (Nickels & Wirrell, 2017). Stiripentol has been shown to enhance inhibitory GABAergic neurotransmission by increasing the activity of neuronal and recombinant GABA\(_A\) receptors, with its positive modulation being most effective at receptors containing an α3 subunit, which is highly expressed in the immature brain, explaining its greater efficacy in childhood-onset epilepsies such as Dravet syndrome (J. L. Fisher, 2011). Similarly, perampanel, a non-competitive AMPA-type glutamate receptor antagonist, with high selectivity, orally active and high potency was developed by Eisai Research Laboratories as a potent drug for treatment of initial stages of epilepsy (Satlin *et al.*, 2013). A randomized trial shown perampanel to be a well-tolerated and potent drug for those suffering from primary generalized tonic-clonic seizures that are resistant (French *et al.*, 2015).

Genetics play an important role in prevalence of epilepsy (Speed *et al.*, 2014). Epilepsy in 30 to 40% of all children and early adults belongs to idiopathic generalized epilepsies (IGE). The predominant cause of IGE is mutations in genes that are responsible for coding of ion channels and associated subunits

(Steinlein, 2004). Early linkage studies and mutational analysis have revealed a number of mutations that are associated with occurrence of IGE. The mutational genes are involved in both ion and non-ion channels (Chen *et al.*, 2017). Wang et al. (2017) summarized and grouped 977 genes associated with epilepsy into 4 groups, i.e., 84 genes that are directly and only responsible for causing epilepsy, 73 genes are associated with neurodevelopmental disorders, 536 genes that are related to systemic abnormalities and 284 genes with potential to cause epilepsy. retigabine, a potassium channel opener was the first approved neuronal potassium channel opener for epilepsy treatment. It is highly relevant to certain genetic epilepsies, especially those involving mutations in KCNQ2/3 genes (Striano & Minassian, 2020). Another antiepileptic drug Ganaloxone is oriented for treatment of rare genetic epilepsies and status epilepticus (Lattanzi *et al.*, 2021). Gene therapies are also been introduced and successfully used for transferring and expressing the genes into brain tissues using vectors such as Herpes simplex virus vector and adeno-associated virus vector (Sørensen & Kokaia, 2013).

Improved Safety and Tolerability of Antiepileptic Drugs

Development of newer antiepileptic drugs is more focused on improving safety, tolerability and to address the limitations associated with older treatments such as cognitive impairment, sedation and systemic toxicity (Eddy *et al.*, 2012; Kowski *et al.*, 2016). Many next-generation AEDs are designed with higher specificity for molecular targets, minimizing off-target effects and enhancing patient adherence. For instance, locasamide developed for treatment of partial-onset seizures has demonstrate good tolerability and efficacy in controlled trials (Halász *et al.*, 2009). It modifies the protein-2 collapsing response mediator and specifically encourages sodium channel inactivation (Doty *et al.*, 2007). Another compound, cannabidiol, approved for rare genetic epilepsies, exhibits a unique safety profile with mild-to-moderate adverse events like fatigue and diarrhoea, making it an attractive option for paediatric and adult patients alike (Samanta, 2019). Novel drug delivery systems, such as nanotechnology-based formulations are also been evaluated for enhancing tolerability and reducing dose frequencies of drugs targeting central nervous systems (Keservani & Sharma, 2019).

Innovative Non-pharmacological Therapies

Almost 1 in every 3 patients with epilepsy undergoing drug treatment experiences seizures. Epilepsy can remain refractory even after taking one or more antiepileptic drugs. The circumstances frequently call for non-pharmacological treatments that can be utilized either in addition to or instead of antiepileptic medications (Jackson *et al.*, 2015). These interventions may include epilepsy surgery, transcranial magnetic stimulation, vagal nerve stimulator, deep brain simulator and ketogenic diet (Parakh & Katewa, 2014). Wolf & Okujava (1999) conducted a study to understand the possibility of non-pharmacological interventions in management of epilepsy. Their study suggested patients with generalized tonic-clonic seizures were mostly benefitted from additional therapies. Fig. 1 represents some innovative non-pharmacological methods used for treatment and management of epilepsy.

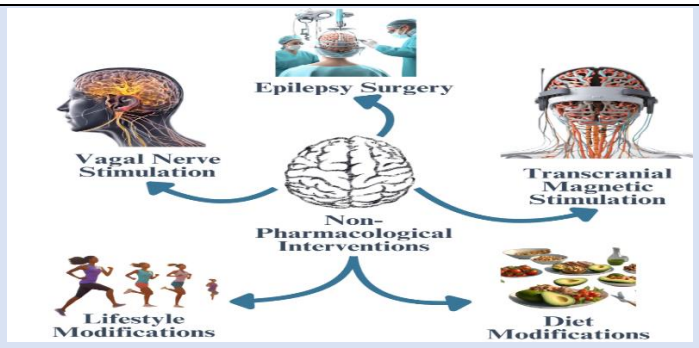

Figure 1: Non-pharmacological Therapies for Epilepsy Treatment

Epilepsy surgery

Neurosurgery is a potential yet underutilized option for curing drug-refractory epilepsy. careful multidisciplinary presurgical evaluation can further increase the chances of success and of better outcomes. Neuroimaging techniques can also assist in diagnosis and guiding surgical procedures (Vakharia *et al.*, 2018). A meta-analysis revealed better outcomes in surgery than drug treatments in paediatric patients. Further, the study suggested highest seizure freedom

for hemispheric surgery, though, it declined overtime, that is, from 64.8% to 39.7% from 1st year to 10th year respectively (Widjaja *et al.*, 2020). Bjellvi et al. (2019) also observed similar trend showing a favorable correlation between seizure freedom and shorter length.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) was initially meant for studying corticospinal motor conduction, however, later the potential of TMS in evaluating distinct excitory and inhibitory functions of cerebral cortex was discovered. It became a promising technique for evaluation of effects of antiepileptic drugs in patients. Later, repetitive TMS (rTMS) was proposed for treatment of epilepsy (Tassinari *et al.*, 2003). TMS is safe, inexpensive and simple to perform technique for investigation and treatment of epilepsy (Tassinari *et al.*, 2003). A randomized, double-blind controlled trial showed significant reduction in events of seizures after rTMS without any serious adverse effects (Fregni *et al.*, 2006). Mild adverse effects such as headache were only reported in 17.1% of patients undergoing rTMS treatment (Bae *et al.*, 2007).

Vagal Nerve Stimulation

Vagal Nerve Stimulation (VNS) is a surgical intervention for patients with pharmacoresistant epilepsy and for those who cannot receive a resective surgery. VNS works by repetitive stimulation of vagus nerve resulting into widespread activation or deactivation of brain circuits that are responsible for conducting seizure signals (Guberman, 2004). The technique was first introduced in year 1988, and since then more than 50,000 VNS were successfully implanted in patient by year 2012 (Krahl & Clark, 2012). A randomized control trial for use of VNS in paediatric patients showed decrease in the number of seizures by 50% in more than 26% along with improvements in seizure severity (Klinkenberg *et al.*, 2012). A randomized active controlled trial conducted by Handforth et al. (1998) revealed 28% and 15% reduction in patients receiving high and low stimulations respectively. For patients with refractory partial-onset seizures, VNS has been shown to be a safe and effective alternative treatment.

Ketogenic Diet and Other Diet Treatments

Ketogenic diet (KD) was first introduced in 1921, and is been recommended worldwide in last few decades. KD is a adequate-protein, low-carbohydrate and high-fat diet, that is an effective nonpharmacological intervention for treatment of intractable childhood epilepsy (Sampaio, 2016). A randomized controlled trial conducted by Neal et al. (2008) included 145 children grouped into 2 categories, one which received ketogenic diet and other as control group. 38% children receiving ketogenic diet and 7% children of same group showed decrease in seizure frequency by 50% and 90% respectively. Fewer side effects such as hunger, fatigue, emesis and constipation were also reported in the study. Another randomized controlled trial for using KD in patients between 1 and 18 years of age also revealed similar results; 56% reduction in KD group than controlled group in 4 months (Lambrechts *et al.*, 2017). Another popular diet used for managing epilepsy is Modified Atkins Diet (MAD). The diet consists of low carbohydrate and high fat intake. Ketogenic ratio of MAD is between 1:1 to 2:1 (Rezaei *et al.*, 2019). A randomized clinical trial for effect of MAD in adults show reduction in number of seizures by 25% after completing the intervention (Kverneland *et al.*, 2018). Another prospective study conducted by Kossoff et al. (2008) showed reduction >50% seizures in 47% adult patients, though the study also revealed a high discontinuation rate. Medium Chain Triglyceride (MCT) diet with ketogenic ratio of 3:1 has also shown 50% to 100% reduction in number of seizures in paediatric patients (Sills *et al.*, 1986).

Lifestyle Modifications and Epilepsy

Lifestyle modifications can significantly influence the effectiveness of drug treatments for epilepsy. sleep wake cycle can play an important role in generation of epilepsy. Patients diagnosed with epilepsy are commonly advised to maintain a proper sleep hygiene (Stirling *et al.*, 2023). Stirling *et al.*, (2023) in their research concluded that, patients with epilepsy should pay more attention to when they go to bed and wake up than how long they sleep. Stress is another risk factor associated with onset of epilepsy. Temkin & Davis (1984) monitored 12 adults with epilepsy to analyse effects of stress and frequency of seizures. They confirmed higher association between high stress levels and increase in seizure frequencies. Alcoholism is another risk factor that can worsen epilepsy. the prevalence of epilepsy was found to be at least 3 times more in alcoholics than non-alcoholic population (Chan, 1985). A meta-analysis conducted by Samokhvalov et al. (2010) revealed a dose dependent relationship between amount of alcohol consumption and frequency of seizures. However,

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another study suggest small amount of alcohol to be unharmful in potentiating epilepsy symptoms, though, alcohol withdrawal was found to be important in lowering seizure thresholds (Gordon & Devinsky, 2001). Furthermore, avoiding external stimuli such as complex music, complex readings, tactile stimuli, auditory stimuli, vestibular stimuli, visual stimuli, hot water, fixation-off and light flashes are particularly important in prevention of reflex epilepsies (Okudan & Ozkara, 2018).

Gene and Cell Based Therapies

Gene and cell-based therapies are advanced comparatively advanced treatment approaches with high potential to improve condition of patients with epilepsy. Presently, gene therapy involves delivery of neuro-modulatory peptide encoding genes via adeno-associated virus. Cell therapy for epilepsy is the process of transplanting cells such as MSC-derived exosomes, neural stem cells, bone marrow mononuclear cells and mesenchymal stem cells (Shaimardanova *et al.*, 2022).

Gene Therapies

Gene therapies can be an effective alternative to surgical and drug therapies for treatment of refractory epilepsy. Causes of majority of epilepsy remain unknown and have genetic origins to some extent (Thomas & Berkovic, 2014). With recent advances in sequencing techniques, few gene mutations responsible for monogenetic epilepsies have been identified. Most of these mutations are accountable for alterations in ion channels, synaptic receptors or transporter proteins (Striano & Minassian, 2020). With innovations in technologies, it is now possible to understand genetic mechanisms of epilepsy. In gene therapy approach, genetic materials such as DNA and RNA are incorporated into patient's body to enhance expressions of genes and therapeutic responses (L. Zhang & Wang, 2021).

Vector Selection and Design

Viral vectors and non-viral vectors can be used for delivery of genetic materials in patients. Choice of vectors and route for delivery is important for the success of therapy. Most effective method for introducing foreign genetic materials into host is via viral vectors (Simonato, 2014). Some valid viral vectors that have shown potential for same includes adenovirus, adeno-associated viral vector, lentivirus-associated viral vector and herpes simplex viral vector. Amongst these adeno-associated viral vectors and lentivirus are considered as most promising due to their high delivery capacity, low pathogenicity and ability to target specific cells and tissues (Bettegazzi *et al.*, 2024). Lipids and polymer-based vectors are included in category of non-viral vectors. Transfection in nondividing cells, low immunogenicity and high loading capacity provide some advantages to lipid-based gene delivery systems (Riban *et al.*, 2009). Nanoparticles have been extensively explored for delivery of epilepsy treatments directly to the brain (Musumeci *et al.*, 2019). Nanoparticles, particularly formulated using natural polymers possess advantages such as significant uptake, high drug-binding capacity, abundant surface functional groups and low cytotoxicity (Elzoghby *et al.*, 2016). Most common polymer used for nanoparticle formulation for gene delivery is polyethyleneimine for its ability to bind with genetic material and form homogenous and stable bond (Lungwitz *et al.*, 2005).

Cell-based Therapies

To restore the tissue's potential and functionality, cell therapy involves replacing damaged or dead cells with brand-new, identical cells. It is a potent method for restoring functioning of damaged nervous tissues causing symptoms of epilepsy (Mehdizadeh *et al.*, 2019). Transplantation of foetal cells is considered to be a potential way for treatment of epilepsy. Cell transplantation have been considered for treatment of neurodegenerative disorders associated with degeneration of basal ganglia, such as Hunting's disease and Parkinson's disease (Björklund & Lindvall, 2000; Harrower & Barker, 2004). In theories, stem cell transplantation can have disease modifying effects that can restore malfunctioning of epileptic tissues by modulating secretion of neurotransmitters, reorganizing synapses, repairing degeneration or by replacing the damaged cells with newer cells (B.-L. Chang & Chang, 2022).

Sources and Types of Stem Cells

A number of types of stem cells have been tested as treatment method for epilepsy. Grafts made from embryonic stem cells are a promising therapeutic approach for treating mesial temporal lobe epilepsy by restoring dentate gyrus granule inhibition. introduction of cell lines that can release anticonvulsant molecules of GABA in brain were already established in past studies to be an effective method for treatment of epilepsies (Maisano *et al.*, 2009). Neural stem cells are another component that have potential to generate oligodendrocytes, astrocytes and neurons in brain (Al-Mayyahi *et al.*,

2018). Transplantation of neural cells in epileptic rats showed suppression of pilocarpine-induced status epilepticus (Chu *et al.*, 2004). Mesenchymal stem cells can provide neuroprotection, for treatment of epilepsies. Neuroprotection and neurogenesis effects by mesenchymal stem cells is due to growth factors such as PDGF, NT3, VEGF, GDNF, NGF and BDNF (Mead *et al.*, 2014). Mesenchymal stem cells transplantation into rats have demonstrated showed promising results in managing temporal lobe epilepsy (Salem *et al.*, 2018).

Precision Medicine and Biomarker Development

Precision medicine improves the quality of treatment by customizing treatment process by taking care of unique health status of individual patient (Kosorok & Laber, 2019). The growing wealth of genetic data in epilepsy offers a solid foundation for positioning the condition as a model for advancing precision medicine. This includes creating sophisticated *in-vitro* and *in-vivo* systems to analyze biological effects of genetic mutations, applying these models in drug screening, and fostering collaborative research networks to streamline discoveries and innovations (Consortium, 2015). A biomarker for epilepsy is a measurable characteristic of the disease that allows identification of localization, progression, severity, development and presence of epilepsy (Pitkänen & Immonen, 2014).

Types of Biomarkers in Epilepsy

There are various types of biomarkers that are associated with and relevant in epilepsy. These include genetic biomarkers, microRNAs, structural biomarkers, functional biomarkers, microvascular injury biomarkers and biomarkers for neuroinflammation (Pitkänen *et al.*, 2016).

Genetic Biomarkers

Genetic biomarkers are found to be useful in prognosis of disease, understanding and predicting response of medication and to evaluate side effects of antiepileptic drugs (Weber *et al.*, 2014). More than 900 genes are yet identified that are linked to the development and progress of epilepsy (Oliver *et al.*, 2023). Table 1 describes some genes and associated function of that gene in context of epilepsy.

Table 1: Genes and associated function of that gene in context of epilepsy.

Gene	Associated Function	Role in Epilepsy	Reference
GABRB1, GABRB2, GABRB3, GABRG2	GABAergic neurotransmission	Variants in GABA receptor subunit genes linked to impaired inhibitory neurotransmission, increasing susceptibility to seizures.	(Maillard *et al.*, 2022; Srivastava *et al.*, 2014; Xi *et al.*, 2011)
GAD1	GABA synthesis	Associated with reduced GABA production, influencing inhibitory signaling in epilepsy.	(Neuray *et al.*, 2020)
ALDH5A1	GABA degradation	Implicated in GABA metabolism abnormalities, contributing to seizure susceptibility.	(Lorenz *et al.*, 2006)
HTR1B, SLC6A4	Serotonergic transmission	Polymorphisms associated with increased susceptibility to temporal lobe epilepsy (TLE).	(Córdoba *et al.*, 2012; Leal *et al.*, 2013)
SCN1A	Regulation of neuronal excitability	Linked to voltage-gated sodium channel mutations, affecting neuronal firing and seizure thresholds.	(Escayg & Goldin, 2010)
PDYN	Neurotransmitter regulation	Implicated in modulating excitatory pathways, contributing to epilepsy development.	(Stögmann *et al.*, 2002)
MTHFR	Folate metabolism	Variants associated with altered neuronal excitability and seizure risk.	(Prasad *et al.*, 2011)
ASIC1α	Acid-sensing ion channel activity	Altered channel function linked to heightened seizure susceptibility.	(Lv, He, Fu, Zhang, *et al.*, 2011)
CD40, IL1β, IL1α, IL1 receptor antagonist	Pro-inflammatory mediators	Polymorphisms associated with increased inflammation, which affects neuronal plasticity and excitability, contributing to epilepsy.	(Abdel Rasol *et al.*, 2014; B. Zhang *et al.*, 2014)
ALDH2, NFE2L2, PRNP	Protection against oxidative stress	Variants linked to reduced defense against oxidative stress, increasing vulnerability to seizures.	(Liu *et al.*, 2015; Walz *et al.*, 2002; H. Yang *et al.*, 2014)
KCNJ10	ATP-sensitive potassium channel (macroglia)	SNPs associated with seizure susceptibility and TLE, particularly in combination with AQP4 polymorphisms affecting water conductance.	(Reichold *et al.*, 2010)

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CALHM1	Cytosolic calcium regulation	SNPs alter protein functions affecting calcium levels and amyloid β concentrations, linked to TLE susceptibility.	(Lv, He, Fu, Shao, *et al.*, 2011)
PCDH7, NRG1, BDNF	Cell-cell interactions and neuronal plasticity	Polymorphisms linked to excitability and neuronal interaction, contributing to epilepsy development.	(ILAECCE, 2014; McNamara & Scharfman, 2010; Zhu *et al.*, 2016)
C3	Innate immune response and inflammation	Genetic variants associated with changes in neuronal plasticity and excitability, contributing to seizure susceptibility.	(Vezzani, 2008)

MicroRNAs (miRNAs)

There are approximately 1600 miRNAs in humans that regulate almost half of all the protein regulating genes. Human brain have some unique miRNA that control glial function, neuronal migration, ion channel levels and dendritic morphology (Jimenez-Mateos & Henshall, 2013). Any alterations in specific miRNAs have been shown to cause neurodegenerative disorders (Hébert & De Strooper, 2009). Over the past 10 years, more than 100 miRNAs have yet discovered that are associated with epilepsy, indicating a major part in the disease's pathogenesis. These miRNAs are involved in key processes such as inflammation, synaptic plasticity, neuronal excitability, and apoptosis, which are crucial in the development and progression of epilepsy (Cava *et al.*, 2018).

Structural Biomarkers

Epilepsy such as chronic temporal lobe epilepsy is often characterized by some structural changes such as axonal reorganization, gliosis, segmental neuronal loss or characteristic patterns of damage (Pitkänen *et al.*, 2016). Nehlig (2011) studied hippocampal MRI and other structural biomarkers such as P magnetic resonance spectroscopy, H spectroscopy, diffusion tensor imaging and tractography in rat models. Diffusion-weighted imaging allowed early detection of abnormal water movement to detect epilepsy in early stages.

Functional and Electrophysiological Biomarkers

Electrophysiological biomarkers, such as pathological high-frequency oscillations (HFOs) in the 80–600 Hz range, are promising tools for identifying epileptogenic zones and predicting epilepsy development. HFOs, observed through invasive EEG, are linked to seizure severity and drug response, with surgical removal improving outcomes. Non-invasive techniques like scalp EEG and magnetoencephalography are being explored for broader applicability. Challenges include managing high-resolution data, distinguishing HFOs from noise, and validating methods for clinical use. Future research aims to refine HFO classification, improve detection accuracy, and establish their role as predictive biomarkers in epilepsy (Pitkänen *et al.*, 2016).

Advances in Biomarker Development

Biomarker research in epilepsy has seen significant advances with the integration of cutting-edge omics technologies. With introduction of next-generation sequencing (NGS), genomics and epigenomics have uncovered some novel genetic markers associated with rare epilepsy syndromes. A large number of genes have been discovered with the introduction of NGS, such as SCN8A, SCN2A, KCNT1, GRIN2A, HCN1, DNM1, GABRB3 and ALG13 (Møller *et al.*, 2015). Table 2 represent some of the epilepsy genes that were identified using NGS.

Table 2: Epilepsy genes identified using Next Generation Sequencing (Møller et al., 2015).

Gene	Phenotype
SYNGAP1	Epileptic encephalopathy, autism, ID
STX1B	Fever-associated epilepsy symptoms
SLC35A2	EOEE
SCN8A, RYR3, GABBR2, FASN	Epileptic encephalopathy
GRIN2B, DNM1	Infantile spasms, ID
GRIN2A	Epilepsy–aphasia syndromes
GNAO1	Ohtahara syndrome, infantile spasms
GABRB3	Lennox-Gastaut syndrome, Infantile spasms
GABRA1	Infantile spasms, Dravet syndrome
DEPDC5	Familial focal epilepsy
CHD2	MAE

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ALG13	Infantile spasms, Lennox–Gastaut syndrome

Proteomics and metabolomics are also contributing in identification of distinct molecular profiles in epilepsy patients. Sadeghi et al. (2021) identified novel potential targets for treatment of epilepsy by conducting proteomic profiling of rat hippocampus. in similar study, Browning et al. (2024) identified some new targets for blast-associated post-traumatic epilepsy by utilizing computational techniques and proteomics. Implementation of metabolomics allowed researchers to identify a small biomolecule, taurine, as a biomarker of epilepsy in paediatric patients (Akiyama *et al.*, 2024). In order to promote further researches in precision medicine using proteomics, metabolomics and lipidomics, The International League Against Epilepsy/American Epilepsy Society (ILAE/AES) Joint Translational Task Force created a common data element for standardization and improve quality of experiments associated with epilepsy (Bindila *et al.*, 2022). Novel techniques such as liquid biopsy is also showing, and a non-invasive approach to biomarker collection (Soda *et al.*, 2019). Liquid biopsies are almost non-invasive and allows assessment across multiple time points. It can allow collection, detection and assessment of biomarkers including non-coding RNAs, transfer RNAs, cell-free DNA and miRNAs, enabling more accessible and accurate epilepsy diagnosis and management (Whitlock *et al.*, 2022).

Role of Artificial Intelligence in Epilepsy Management

Artificial Intelligence (AI) has revolutionized healthcare sector. It has increased the ability of healthcare data and is allowing rapid progress of analytic techniques (Jiang *et al.*, 2017). Some important components of AI providing great services in healthcare industry includes Machine Learning (neural networks and deep learning), Natural Language Processing, Rule-based Expert Systems and physical robots (Davenport & Kalakota, 2019). In epilepsy, AI has shown great promise in management of disease. It can allow early prediction of epilepsy in population at risk, it can detect and monitor events of seizures, it can also differentiate between seizures and mimics, it can improve neuroanatomic lateralization and localization, and it allows proper tracking of disease and predict the response to antiepileptic drugs (Kerr & McFarlane, 2023). Fig. 2 represents some areas where AI is getting actively involved for better treatment and management of epilepsy.

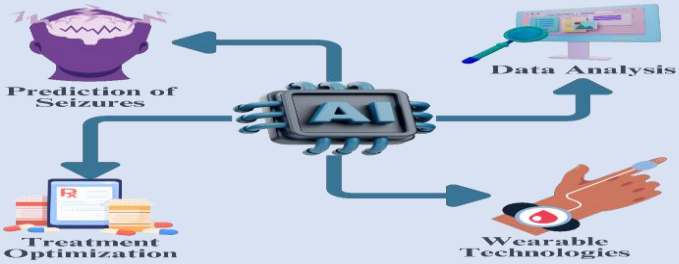

Figure 2: Role of AI in management of Epilepsy

Prediction of Epileptic Seizures

With advances in AI and signal processing technologies, by generating powerful algorithms, and by combining classifiers and features, it is possible to predict epileptic seizures (Bou Assi *et al.*, 2017). With ML, it is possible to predict a coming seizure event by using Electroencephalography (EEG) signals. EEG signals helps in differentiating between normal and abnormal functioning of brain (Rasheed *et al.*, 2021). Usman et al. (2017) proposed a model that eliminates need for pre-processing of EEG signals and feature extraction to detect beginning of preictal state that marks the onset of seizure. Average detection time was found to be 23.6 minutes. T. A. Khan et al. (2019) also utilized IoT concept and developed a hardware model and used modified cuckoo search to predict seizure events. The proposed model was found to be cost-effective and more accurate. In another approach, an automated detection technique was developed using AI, that processes correlated of seizures to classify seizures and non-seizures. This approach offers several advantages to clinicians such as no requirement of special training , cost effective and faster interpretations (Fergus *et al.*, 2015).

Optimization of Treatment Regimen

AI can transform treatment of epilepsy via data-driven approaches. ML models can analyse diverse data, including clinical history, genetic profiles, imaging,

and electroencephalogram (EEG) patterns, to predict patient-specific responses to antiepileptic drugs (AEDs) and recommend optimal therapeutic options (Keikhosrokiani *et al.*, 2024). This reduces the chances of errors due to trial and error during drug selection, hence, improv outcomes and minimize side effects (Gunasekera *et al.*, 2023). Wearable devices powered by AI allows real time monitoring of antiepileptic drugs. It allows dynamic adjustment of doses in treatment plans (Halimeh *et al.*, 2022).

Analysing of Large Datasets for Better Patient Management

Last 2-3 decades have observed digitalization of medical information. All paper-works, including prescription and medical order slips have gone paperless over last few decades (De Lusignan *et al.*, 2014). Advanced computer systems and AI have allowed analysis of these piles of healthcare data to provide useful information of healthcare benefits (Shaikh & Ali, 2019). Epilepsy is a chronic condition that is spread worldwide, and therefore, a large amount of data including laboratory results, prescriptions and medical records is available in form of digital data from all over the world. This data has potential in providing support in future researches for developing treatment and management strategies against epilepsy (Chung *et al.*, 2022). Fürbass et al. (2021) used AI for analysing epilepsy data to understand temporal activation patters of interictal discharges. They identified 5 different patterns that were further related with sleep and seizures.

Wearable Devices and Seizure Detection Technologies

Wearable devices is an emerging field of personal gadgets, with potential to fuel AI methods to widen the range of their applications. Wearable devices have already been used for carrying out various tasks utilizing supervised, unsupervised, semi-supervised and reinforcement learning (Nahavandi *et al.*, 2022). ML algorithms, deep neural networks in particular have been employed in wearable data and seizure videos to interpret the disease state (Han *et al.*, 2024). The most distressing feature of seizure is unpredictability. Prediction of seizure can allow patient and caregivers to take necessary actions in order to avoid consequences. Wearable devices used non-EEG modalities, such as assessments of biomarkers for prediction of seizures. Wearable technology is now limited to the prediction of general tonic-clonic seizures, however, with advancement in technologies and integration with AI, applications of wearable devices for prediction of seizures will widen (Beniczky *et al.*, 2021). Integration of AI in wearable devices for detection and monitoring seizures have been demonstrated in many studies. Yu et al. (2023) demonstrated integration of deep learning technology in wearable devices for detection of broad range of seizures. In another study, Larsen *et al.*, (2024) developed an automated seizure detection wearable that senses movement using integration with artificial neural networks for tonic seizures.

Novel Drug Delivery Systems for Epilepsy Management

Traditional dosage system offers numerous drawbacks such as fast release of medicines, fluctuations in plasma level, first pass metabolism, lower stability, low availability and requirement of high doses. Novel Drug Delivery Systems (NDDS) is a new approach in developing novel carrier of active compounds to eliminate or address these drawbacks offered by traditional drug delivery systems (Kumar *et al.*, 2021). Introduction to various NDDS including nanoparticles, transdermal systems and controlled release formulations have significantly enhanced the epilepsy therapeutics.

Nanoparticles-Based Drug Delivery System

Nanoparticles are nano-sized reservoir for drugs, with receptor-specific binding agents such as antibodies attached to it to facilitate target drug delivery. Nanoparticles can act as carriers and depot vehicles that can act as packaging for transporting antiepileptic drugs to the targets (R. S. Fisher & Ho, 2002). Lipid-based nanosystems have demonstrated encouraging outcomes in increasing efficacy and in enhancing stability of antiepileptic drugs such as cryptolepine and phenytoin (Ghane *et al.*, 2024; Mante *et al.*, 2021). Nose-to-brain delivery of lipid-based nanosystems has also shown great efficacy in some studies, however, it demands more *in-vivo* studies to support the clinical trials (Costa *et al.*, 2019). Another kind of NDDS that has demonstrated remarkable efficacy for drug target delivery is metallic nanoparticles. In a study, bismuth ferrite nanoparticles were evaluated for delivery of antiepileptic drug, ethosuximide. Characterization studies revealed promising results, along with a 5 hour lasting sustained release was obtained in *in-vitro* analysis (Guldorum *et al.*, 2024). In another experiment, silver nanoparticles were developed and loaded with *Malva sylvestris* flower extract as reducing

and antiseizure agent. Surface of nanoparticles were covered with reduced graphene oxide. The green decorated graphene oxide silver nanoparticles shown good antioxidant along with antiepileptic activity in mouse model (Y. Yang *et al.*, 2024). Green synthesis has received good attention in healthcare industry in last few decades. Boruah et al. (2021) developed a green method for developing gold nanoparticles for delivery of antiepileptic plant extract from *Moringa oleifera* plant. *In-vitro* tests on animal models suggested less cytotoxicity of novel formulation in comparison with conventional antiepileptic drugs and regeneration of neuronal cells were also observed. The developed nanoparticles also showed good photo-catalytic efficiency. In context to some innovative nanoparticle drug delivery methods, Huang et al. (2009) developed a nanosystem for magnetically-controlled release of antiepileptic drugs. They used magnetite oxide as magnetic core shell at Silicon-dioxide nanoparticles and attached onto electrically active flexible PET substrate. The developed system was evaluated for delivery of ethosuximide in rat model to demonstrate advantages of nanosystems for delivery of antiepileptic drugs.

Transdermal Drug Delivery Systems (TDDS)

Transdermal Drug Delivery System (TDDS) is a NDDS for delivery of drugs through skin at a predetermined and controlled rate. It provide advantages such as enhanced bioavailability, fewer side effects, prolonged therapeutic effects and better patient compliance (Rastogi & Yadav, 2012). TDDS is often utilized for drugs that has lower stability at gastric pH and supposed to high first-pass metabolism. It also act as an alternative to hypodermic injections in terms of former been less painful and generate less medical wastes (Prausnitz & Langer, 2008). There are some limitations of TDDS in delivering antiepileptic drugs, such as potency and solubility, however, continual research to overcome these drawbacks can make TDDS and attractive option for antiepileptic drugs (R. S. Fisher & Ho, 2002). Numerous studies have been carried out. for improvising and for evaluating the effectiveness of TDDS for delivery of antiepileptic drugs. Yadav & Dubey (2021) prepared transdermal patch by using varying polymer ratio for delivery of ethosuximide, and evaluated its physicochemical parameters. Polyethylene glycol and methanol were found to be good skin penetration enhancing agents for TDDS. In another study, in order to overcome the drawbacks such as lower bioavailability and need of frequent dosing of midazolam, Shefrin et al. (2019) developed neosomal transdermal patches. The prepared formulation was found to have better entrapment and release parameters, and suggested lower dosage frequency, hence, better patient compliance. In a novel approach, microneedles were introduced to transdermal patches to study its influence in release of tiagabine HCl and Carbamazepine drugs. A significant enhancement in flux, that is, 6.74-fold increase was noticed after introduction of microneedles in transdermal patches (Nguyen *et al.*, 2016). El-Enin & AL-Shanbari, (2018) developed nanostructured cubosomal-gel for delivery of clonazepam via transdermal route. The developed patch with cubosomal gel showed increase in permeation of clonazepam along with improved retention time and skin deposition.

Extended-Release Formulations

Extended-release formulations (ERs) provide a constant plasma drug concentration and reduces the need of frequent dosing, thus, having benefits over conventional dosage forms. It minimise adverse effects associated with antiepileptic drugs, provide flexibility in dosing and the flat plasma concentration results in better management of epilepsy patients (Bialer, 2007). Powell et al. (2016) reviewed and compared efficacy and adverse effects of immediate release (IR) and ER carbamazepine in patients with epilepsy. They observed fewer side effects in ER group than IR group, suggesting worth of ER antiepileptic formulations. In contradiction, study based on administration of ER pregabalin and IR pregabalin in patients with epilepsy does not show significant difference in efficacy and tolerability between both the formulations (Morano *et al.*, 2019). A few of the approved medications as extended formulations for indication in epilepsy includes Topiramate. Phenytoin sodium, Oxcarbazepine, Levetiracetam, Lamotrigine, Gabapentin, Divalproex, Carbamazepine (Wheless & Phelps, 2018).

Challenges and Limitations

Despite the promising potential of next-generation therapies for epilepsy, several limitations hinder their widespread implementation. These include regulatory, ethical, and cost-related challenges, which present significant obstacles to translating experimental treatments into clinical practice.

Regulatory Challenges

Wileman & Mishra (2010) identified 7 key regulatory challenges responsible for lag in any new drug

formulation development. These challenges include harmonisation, document authentication, pricing approval, good manufacturing processes, critical process parameters, lowest commercially determinable dose and western approval. Modernisation of pharmaceutics have shown creativity in novel antiepileptic formulation, that includes cell therapies, gene therapies, regenerative medicines, targeted medicines and digital health. Former regulatory guidelines cannot accommodate these formulations. However, regulatory associations, such as FDA has implemented various initiatives to adopt some modern guidelines in their regulatory programs. The aim is to ensure balance between innovation and safety of patients (Cuffari, 2024).

Ethical Challenges

One of the easiest ways to demonstrate the efficacy of a new antiepileptic drug is by comparing its efficacy with already approved and available drug in a randomized controlled trial. However, ethical concerns arise for use of a novel drug candidate as monotherapy in patients with an active epilepsy condition (Perucca, 2008). To address this, new antiepileptic drug is only given to patient as an adjunctive drug with an already established drug. The data obtained is often biased and scrutinization of the data is challenging (Perucca, 2018). It is also considered unethical to expose a patient to experimental drugs when surgery can likely cure the patient. It became more challenging in countries where advancements have made surgeries more feasible (Friedman & French, 2012).

Cost-related Challenges

One of the biggest hurdles in developing new antiepileptic drugs (AEDs) is the substantial expense involved in the long and complicated clinical trial process. This is largely due to the complex nature of epilepsy, which requires thorough evaluation of the drug's effectiveness and potential side effects. These factors make it financially challenging for pharmaceutical companies to commit to investing in new AED research (Corrales-Hernández *et al.*, 2023, 2023; Schwabe, 2002). Development of new antiepileptic drug is a costly and risky process, with a success chance of approval by regulatory authorities been only 1 in 10. Even after approval, due to lack of safety and efficacy data, numerous antiepileptic drugs have been taken off from market in past, highlighting financial risks of companies in case of failures. Some drugs that were withdrawn from market include phenthenylate, benzchlor-propamide and aminoglutethimide (Wahab, 2010).

Future Perspectives and Directions

There has been a number of improvements going on in many areas leading to some advanced outcomes, likely to come in very near future. With advancements in technology, it may be possible to integrate technological tools in epilepsy management. Smartphone applications are already available for management of epilepsy (Le Marne *et al.*, 2018). Applications for assisting healthcare professionals in non-speciality settings can be developed for early diagnosis of epilepsy (Patterson *et al.*, 2015, 2018). Applications that are focused on patient adherence to the treatment may allow better management of the disease (Mirpuri *et al.*, 2021). Technology advancement may also aid in selection of antiepileptic treatment regime. AI based approaches combining with genetic and clinical data may predict response to treatment regime in future.

Genetics of epilepsies have also received significant advancements in last decade. Data on genetic mutations causing epilepsy is permitting to establish precision-therapy medicines. Advancements in technologies is strengthening genetic based data for the disease, allowing to develop new drug candidates and to also re-purpose existing drugs in precision therapies. With development of more treatments, precision therapies for management of epilepsies will likely expand (Perucca, 2021).

Biomarker-guided therapies hold significant potential in epilepsy management by enhancing diagnostic accuracy, predicting treatment response, and assessing adverse drug effects. Biomarkers can stem from genetic, molecular, imaging, or electrophysiological measures (Kobylarek *et al.*, 2019). Notable examples include the HLA-B*15:02 antigen, used to determine who is susceptible to negative responses caused by carbamazepine (C.-J. Chang *et al.*, 2020). Biomarkers could identify high-risk individuals' post-epileptogenic insults, guide the initiation or withdrawal of anti-seizure medication (ASM), and predict favourable responses to specific treatments. This approach could transform treatment paradigms, such as using predictive biomarkers to enhance the efficacy of ASMs in pharmacoresistant epilepsy. Single biomarkers are unlikely to provide comprehensive solutions; instead, combinations of biomarkers analysed via algorithms or AI tools may yield breakthroughs. By enabling precision medicine,

biomarker-based strategies could improve clinical trial outcomes, optimize drug efficacy, and minimize adverse effects, paving the way for a personalized approach to epilepsy treatment (Perucca, 2021). The development of novel and disease-modifying therapies for epilepsy focuses on targeting underlying etiologies rather than merely suppressing seizures. Advances in understanding epileptogenesis, pharmacoresistance, and disease mechanisms have led to innovative drug discovery paradigms, including the use of disease-specific models [53,60]. Investigational therapies include novel small molecules, repurposed drugs, gene therapy, and antisense oligonucleotides [63,64]. Compounds with antiepileptogenic and neuroprotective effects, such as phytocannabinoids, melatonin, and metformin, are being explored for their potential to prevent epilepsy, inhibit disease progression, or mitigate comorbidities like cognitive impairment (Frajewicki *et al.*, 2021; Murugan & Boison, 2020; Rahman *et al.*, 2021; Stone *et al.*, 2020; N. Yang *et al.*, 2020). Precision treatments aim to modulate specific pathways, though single-pathway interventions may not address complex comorbidities (Kearney *et al.*, 2019). Biomarkers are pivotal for early detection of epileptogenesis, patient selection, and treatment monitoring (Kotulska *et al.*, 2021). However, proving true disease modification requires innovative trial designs that differentiate symptomatic effects from prevention or alteration of epilepsy's natural course. These approaches represent a significant shift in epilepsy therapeutics (Perucca, 2021; Schwabe, 2002).

Conclusion

Recent advancements in epilepsy management and treatments are focused on addressing challenges of this complex neurological disorder. Innovations such as targeting therapies to specific ion channels and neurotransmitter pathways, while also applying non-invasive techniques such as dietary interventions is providing new hope for improved seizure control. Cutting-edge approached such as, advancements in gene and cell based therapies have potential to address genetic causes of disease directly, highlighting the potential scope of precision medicines customized for individual patients. Technological integration via AI is also revolutionizing epilepsy management, allowing real-time seizure predictions, personalization of treatments and wearable monitoring systems. NDDS are also contributing in improvising bioavailability, minimizing adverse effects and ensuring better patient compliance and outcomes. There are few challenges, such as high costs, regulatory barriers and limited accessibility, that underscores the importance of continued research and innovation. Future breakthroughs in biomarkers, precision medicine, and epigenetic therapies may overcome these limitations. Ongoing efforts to expand accessibility and affordability of next-generation treatments will significantly impact global epilepsy care.

Abbreviations

AEDs: Antiepileptic Drugs; *AI*: Artificial Intelligence; *ASM* : Anti-Seizure Medication; *BDNF*: Brain-Derived Neurotrophic Factor; *CD*: Cluster of Differentiation; *DRE*: Drug-Resistant Epilepsy; *EEG*: Electroencephalography; *ER*: Extended Release; *GABA*: Gamma-Aminobutyric Acid; *IGEs*: Idiopathic Generalized Epilepsies; *IR*: Immediate Release; *KD*: Ketogenic Diet; *MAD*: Modified Atkins Diet; *MCT*: Medium Chain Triglyceride; *miRNA*: MicroRNA; *MSC*: Mesenchymal Stem Cells; *NDDS*: Novel Drug Delivery Systems; *NGS*: Next-Generation Sequencing; *PET*: Positron Emission Tomography; *rTMS*: Repetitive Transcranial Magnetic Stimulation; *SCN*: Sodium Channel; *SNP*: Single Nucleotide Polymorphism; *TLE*: Temporal Lobe Epilepsy; *TDDS*: Transdermal Drug Delivery Systems; *TMS*: Transcranial Magnetic Stimulation; *VNS*: Vagal Nerve Stimulation

Declarations

Author contributions

All the listed authors have actively participated in the preparation of the manuscript. CPJ drafted the original manuscript, SA, LSC and SS compiled the information and reviewed literature, JP conceptualised and AB reviewed the manuscript. All authors approved the final submission. The authors confirm that no paper mill and artificial intelligence was used.

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Data availability

All source data for this work (or generated in this study) are available upon reasonable request.

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Competing interest

The authors declare no competing interests.

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