Treatments for Epilepsy through Conventional/ Nano drug delivery system: A Comprehensive Review

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Abstract

The condition of epilepsy affects 70 million people worldwide. Unfortunately, most patients do not obtain the proper care, which results in fatal conditions. The term epilepsy was derived from the Greek word Epilepsia which meant to take hold of. It was considered a disease only after 2014. In this review, the history of epilepsy from ancient times, several categories, including ILAE, and general classification, are discussed. The pathophysiology of epilepsy is also covered after discussing the various medications and therapy options. Numerous treatment plans are available, but the main problem is that very little of the drug reaches the targeted location and fails to release the drug for a long time at the site of action. Researchers have developed several drug delivery methods based on nanotechnology to address these issues for better therapy targeting and efficacy.

Keywords: *Epilepsia; anti-epileptics; ILAE; conventional; nano-formulation.*

1. Introduction

Epilepsy is the most well-known neurological condition that fundamentally affects individuals, influences personal fulfillment, and represents well-being and a financial burden on society [1]. Epilepsy affects around 70 million people worldwide. In India, the prevalence of epilepsy is 6-10 per 1000 people [2]. Roughly 85% of these people don't get appropriate therapy because of financial, cultural, societal, and governmental barriers, compounded by pharmaceutical organizations' lack of interest because medicine conveyance isn't profitable. Those with epilepsy who are not treated risk devastating social repercussions such as shame and segregation and may even die from seizures. Making effective anti-epileptic medicine widely available is necessary to reduce the depressing and premature mortality associated with epilepsy and the significant financial burden the infection places on healthcare systems [3]. Definitions of epilepsy have always been problematic [4-8].

Epilepsy is not a single problem; instead, it is syndromic with several symptoms, including rapid abnormal electrical activity in the brain. A particular class of medications called anti-epileptic medicines is used to treat epileptic seizures. The primary function of an anti-epileptic drug is to slow the progressive death of the neuron that triggers attacks. The most common and important cause of death directly linked to epilepsy is a sudden unexpected death in epilepsy (SUDEP), which also accounts for a large portion of mortality in chronic uncontrolled epileptic patients [9]. Numerous new anti-epileptic drugs (AEDs) and modified versions of more well-established drugs are now available to treat epilepsy. Few of these novel AEDs are frequently recommended due to their actual outcomes.

The most significant information, including history, classification, currently available AEDs with restrictions, and nano-formulations to address issues with these medications, is included in this review.

2. History

The oldest knowledge on epilepsy can be found on a Babylonian table at the British Museum. It is a 40-tablet package of Babylonian medicine used around 2000 BC. The ancient Romans thought that epilepsy was a disease brought on by evil and could only be cured by touching or breathing on a person with epilepsy. People would spit at Satan if this happened. They would therefore have to live alone because they believed that epilepsy was unavoidable.

It was known as "The Sacred Disease" by the Babylonians. Hippocrates held a progressive perspective on epilepsy, acknowledging that it is a mental health issue rather than a sacred illness. He offered physical treatments for the infection and said that he couldn't treat the disease if it continued.

The concept of epilepsy became widely accepted in both Europe and North America in the nineteenth century. In 1857, Sir Charles Locock announced Bromide as the first effective anti-epileptic drug. A medical facility for the "paralyzed and epileptic" was established in London in that exact year. Sensory system expert Hughlings Jackson suggested that the seizure owing to the abrupt electro-substance of essentialness in the psyche character of the convulsions dependent upon the space and limit of the seat of the deliveries in 1873.

While researching in Germany in the 1920s, Hans Berger developed an electroencephalograph (EEG) that records brainwaves and has essential applications in studying epilepsy [10]. EEG revealed the existence

of electrical discharges in the mind and provided several examples of brainwave discharges associated with different seizure types. The EEG helped locate the seizure release site and increased the potential effectiveness of neurosurgical medications [11,12].

Phenobarbitone and phenytoin alone were the only treatments used to treat epilepsy between 1912 and 1938 in the middle of this century [13]. For the 80% of people with epilepsy who reside in developing nations, most development indicators have almost no meaning. The International League Against Epilepsy, a general master affiliation founded in 1909, has members from 60 countries and is expanding quickly. The analogous lay organization, the International Bureau for Epilepsy, was founded in 1962 and had 50 public components. It is also growing swiftly [14, 15].

These two organizations collaborated with the World Health Organisation in the Global Anti-Epilepsy Campaign in 1997, which aimed to improve stigma, care, and organizations for people with epilepsy while bringing attention to the conflict and its sufficiency [16].

3. Classification of Epilpesy

In 2014, the Global Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) recommended treating epilepsy like a disease. The following is included in the new clinical definition of epilepsy as a disease: (A) approximately two unwarranted (or reflex) seizures occurring more than 24 hours apart; (B) one unwarranted (or reflex) seizure and a likelihood of subsequent seizures similar to the overall repeat risk (roughly 60%) after two unwarranted seizures occurring over the next ten years; or (C) the cessation of an epilepsy disorder [17].

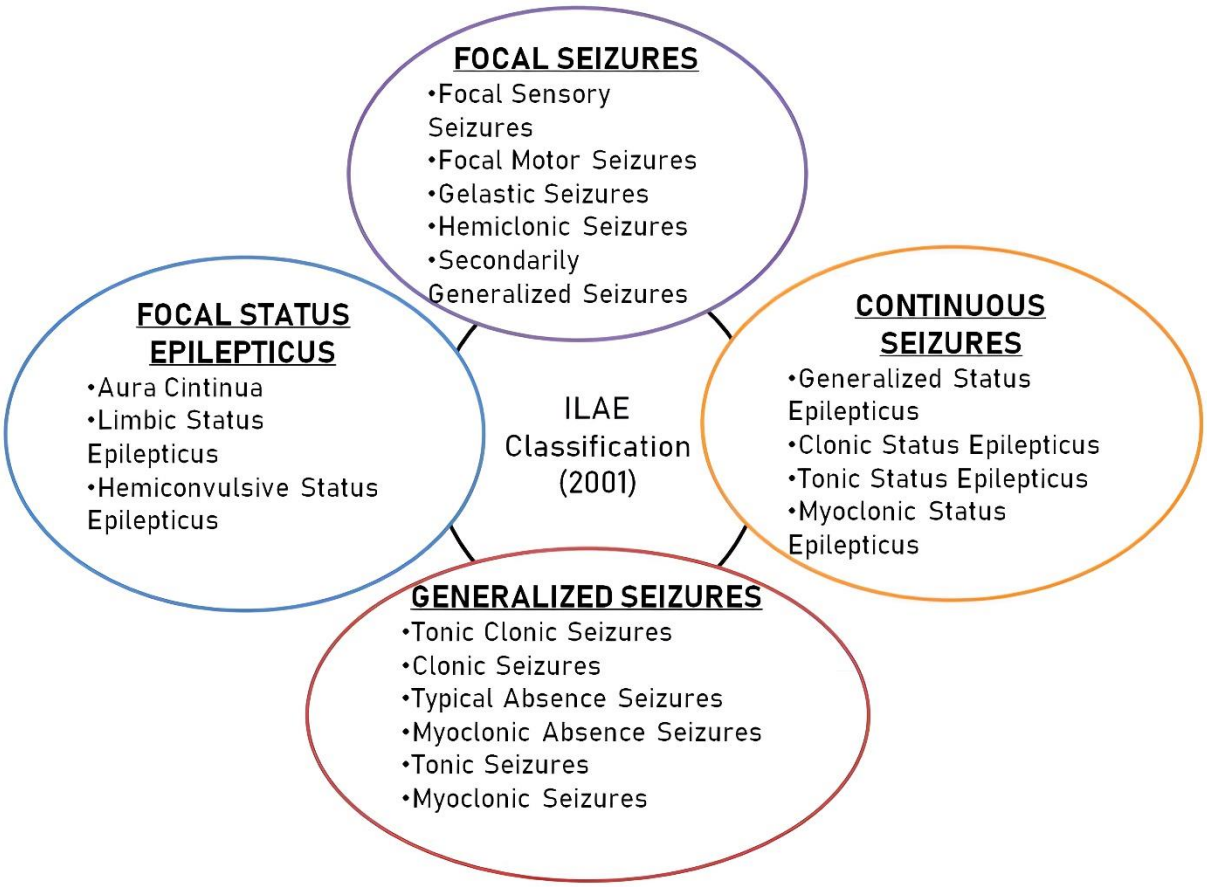


Figure 1: ILAE Classification of Epilepsy (2001)

When seizures and epilepsy are organized and grouped into comparable substances, better analysis and the board of seizures and epilepsy are done since diverse pharmaceuticals are often beneficial for various seizure types [18]. The most recent seizure and epilepsy arrangement was the International League Against Epilepsy (ILAE), released in March 2017. This new sequence is more in sync with a logical explanation of phrasings and includes several additional seizure categories. The current ILAE classification of epilepsy clinical conditions is divided into three levels: seizures, epilepsies, and epilepsy disorders. At each level, emphasis has been placed on etiology and co-morbidities [19]. Furthermore, epilepsy has been declared a treatable infection rather than a problem. It is expected to be settled after ten years of seizure-free time, with the most recent five years spent without medicines, or the patient is no longer at risk for age-related epilepsy [20].

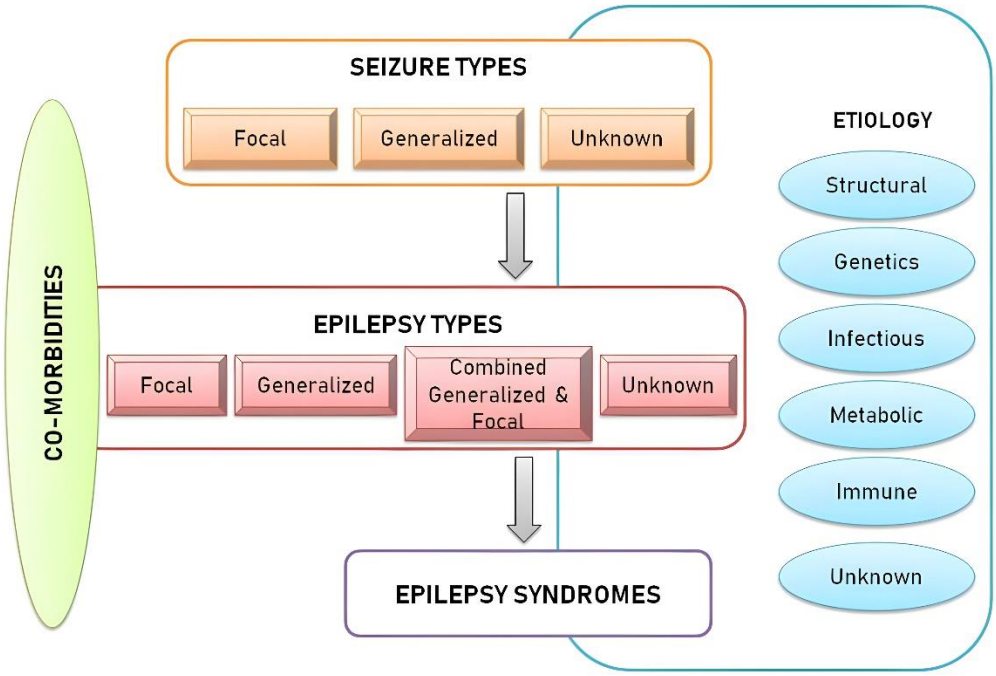


Figure 2: ILAE Classification of Epilepsy (2017) [12].

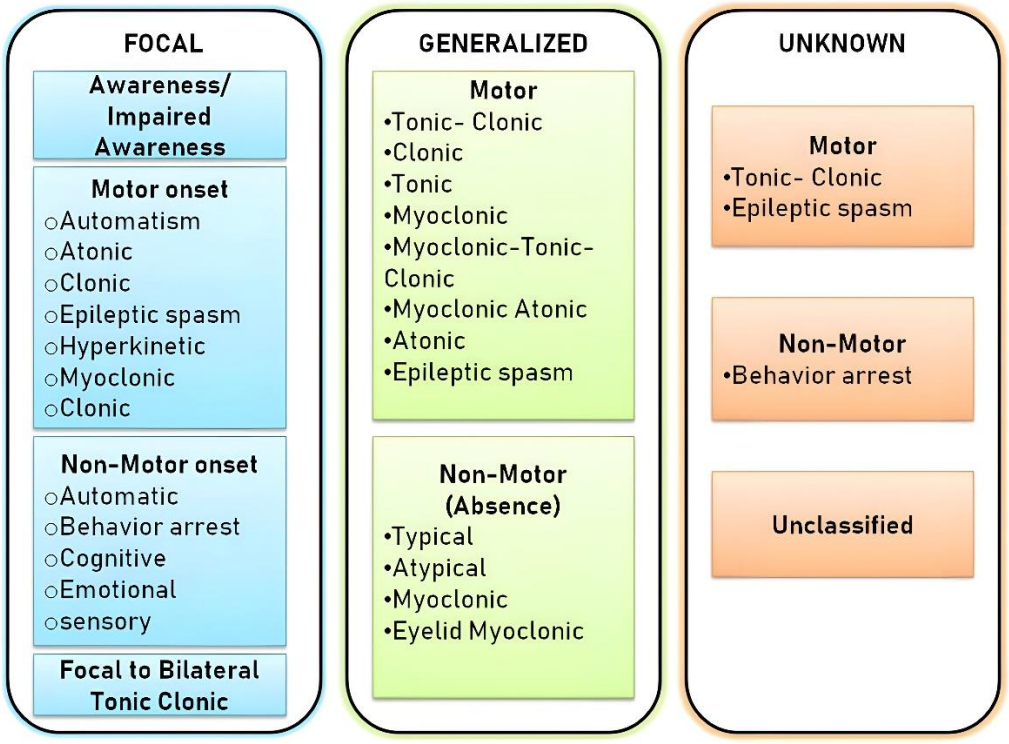


Figure 3: General Classification of Epilepsy [22].

Table 1: Types of seizures [20, 23-25]

Seizure types		Definition
Focal Motor Seizures	Focal Automatism Seizure	Repeated motor activity usually occurs under impaired awareness and is sometimes followed by amnesia and characterized by repeated action, such as saying something repeatedly, lip-smacking, rubbing, or wandering. It is a common feature of focal impaired awareness seizures. It is commonly misdiagnosed and disregarded as a seizure.
	Focal Atonic Seizures	Seizures with loss of muscle tone occur suddenly and last for a few seconds. It can occur on one side of the body or in one limb. Awareness is usually retained.
	Focal Tonic Seizures	Seizures with a sustained increase in muscle contraction that lasts for a few seconds or minutes and present clinically as stiffening of a limb or the neck.
	Focal Clonic Seizures	It has sustained rhythmical jerking of a group of muscles that occur either symmetrically or asymmetrically.
	Focal Epileptic Spasms	Sudden uncontrolled and sometimes painful muscle contractions commonly occur in children. Clinically present as sudden flexion of the waist and flexion or extension of the arms and legs, which may occur in clusters and can be focal, generalized, or of unknown onset. It is usually diagnosed by video-EEG. When it occurs in infants, it is called Infantile Spasm. Awareness is generally retained.
	Focal Hyperkinetic Seizures	Seizures are associated with exaggerated and often uncontrolled muscle activities such as agitated kicking, thrashing, and peddling during the seizure.
	Focal Myoclonic Seizures	It may be similar to clonic seizures but are usually brief, unsustained muscle contractions that occur suddenly and last for a few seconds or even less than a second or just an irregular jerking in one part of the face or body. Awareness is usually retained.
Focal Non-motor Seizures	Focal Non-motor Autonomic Seizures	These are seizures affecting the autonomic nervous system and presenting with symptoms like rising sensation in the stomach, hot and cold feelings, a strange taste or smell, etc
	Focal Non-motor Behavior Arrest Seizures	These are seizures presenting with the cessation of all activities and unresponsiveness for the entire seizure event.
	Focal Non-motor Cognitive Seizures	When there are hallucinations, illusions, deja vu, or impaired speech during the seizure, the patient is said to have had cognitive seizures.
	Focal Non-motor Emotional Seizures	These non-motor seizures begin with panic, anxiety, fear, joy, crying, depression, or other emotions.
	Focal Non-motor Sensory Seizures	These seizures present with abnormal sensations such as visual, olfactory, auditory, gustatory, somatic hallucination, or vertigo.
Tonized Motor	Myoclonictonic-clonic seizures	This seizure is usually observed in individuals with juvenile myoclonic epilepsy. It is characterized by arms jerking, tonic stiffening, and clonic rhythmical jerking.

	Myoclonicatonic seizures	This seizure is commonly seen in patients with Doose syndrome and was previously referred to as myoclonic Astatic seizures. It is characterized by the brief jerking of limbs or trunks, followed by a limp drop.
Generalized Non-motor Seizures	Typical Absence Seizures	These seizures are characterized by interruption of activities that occur suddenly with a blank stare and are occasionally associated with deviation of the eyes that lasts for a few seconds to half a minute with subsequent rapid recovery. It may be related to the flicking of eyelids.
	Atypical Absence Seizures	It has a slow onset with significant muscle tone changes that are more pronounced than in a typical absence. It has slow spike waves at EEG, usually less than three per second.
	A myoclonic absence seizure	This seizure starts with a few rhythmical jerks, followed by a staring spell.
	Eyelid myoclonia	In this seizure, the sudden forceful upward jerking of eyelids may be associated with the staring spell (absence seizure). The closure of the eyes usually stimulates it.

4. Pathophysiology of epilepsy

The brain is made up of nerve cells, and these nerve cells communicate and link with one another via axons by producing tiny electrical impulses. The unusual, hyper-simultaneous release of neurons begins in a specific brain region and then extends to neighboring areas. These activated neurons emit top-down eruptions of activity potential or electrical energy. The pathophysiology of epilepsy comprises the transition of a typical organization into a highly edgy network. It is associated with cycles that disrupt extracellular particle homeostasis, alter energy digestion, alter receptor function, and alter transmitter take-up.

Along with nerve cells, the brain deals with electrical phenomena. The arrival of artificial substances known as neurotransmitters from the axon end, which links with the subsequent cell, results from these electrical driving impulses. These synthetic components (synapses) can act excitatory or inhibitory. To maintain the capacity of neurons for activity, the balance of these excitatory and inhibitory driving factors is essential [26, 27]. NMDA receptors are overactivated by releasing extremely excitatory glutamate, which results in an excessive influx of Ca2+ ions. The extreme levels of Ca2+ led to a condition known as crumble, which activates cytoplasmic proteases (such as calpain I) that break down various proteins, including cytoskeletal proteins [28], neuronal nitric oxide synthase (nNOS), which increases nitric oxide production, producing the free radical peroxynitrite that damages DNA [29], ultimately leading to neuronal cell death.

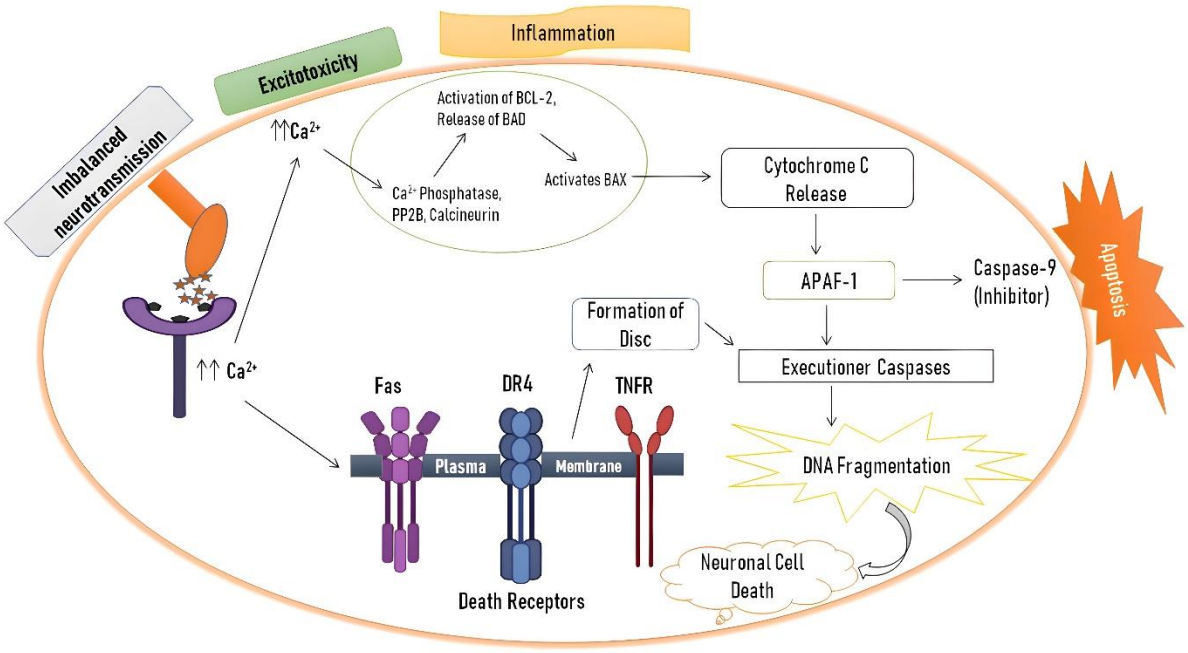


Figure 4: Pathophysiology of Epilepsy.

5. Treatments for epilepsy

5.1 Epilepsy surgery:

The doctor may suggest a medical procedure if the seizures cannot be controlled by medication alone and there is a reasonable diagnosis of a specific seizure type and disorder [30]. In epilepsy surgery, experts identify the region of the brain housing the unique tissue where seizures start from and remove it. But before choosing to undergo surgery, weigh the risks against the anticipated benefits because it's not sure that the body will desire to regulate seizures completely.

5.2 Vagus nerve stimulation:

The vagus nerve stimulator (VNS), a device inserted beneath the skin in the chest, can reduce the frequency of seizures by sending regular electrical signals to activate the vagus nerve. This cranial nerve transmits essential signals from the body to the brain. The VNS functions physically and organically; patients can "turn it on" if they suspect they are about to suffer a seizure. It might be frequently used in conjunction with AEDs.

5.3 Ketogenic diet:

The ketogenic diet is a high-fat, low-carb eating regimen that encourages the body to burn fat for energy instead of glucose. It has been shown to help some people with epilepsy by reducing their seizure frequency. The ketogenic diet can also help adults with epilepsy experience fewer seizures, although many people find it difficult to follow. Typically, doctors recommend a ketogenic diet to children whose seizures haven't responded well to medication alone. This eating plan should only be followed under the guidance of a doctor and a nutritionist because it may be challenging to adhere to, given how restrictive and explicit it is.

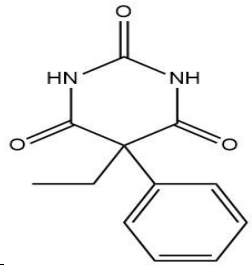
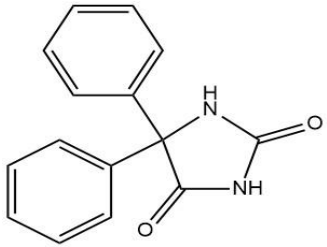
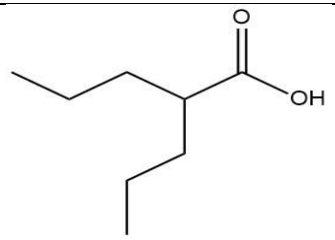
5.4 Lifestyle changes:

Although lifestyle modifications alone cannot control seizures, they are a helpful means of managing problems outside of the doctor's office. Getting enough sleep, regular exercise, and avoiding epileptic triggers like alcohol, smoking, and bright lights are all easy strategies for a patient to manage the illness at home. Another fantastic tool for managing the disease is keeping a seizure record of helping with tracking causes and seizure occurrences.

5.5 Anti-epileptic drugs:

The most well-known and effective method of preventing seizures is using anti-epileptic drugs (AEDs), also known as anti-seizure drugs (ASD), which are used to avoid seizures in individuals with epilepsy [31, 32]. AEDs don't treat epilepsy; instead, they operate to reduce the amount of electrical activity in the brain, which prevents seizures from starting in the first place. There are more than 20 types of anti-epileptic medications, each with a different combination of potential benefits and unintended side effects, so ask a doctor which medications are appropriate for the patient's particular type of seizure [33]. Many people must try multiple medications before finding the one that works best for them [34]. Furthermore, it shouldn't come as a surprise if the treatment necessitates a few adjustments to measures and prescriptions.

Table 2: First Generation Anti-epileptic drugs (FDA approval year), chemical structure, their mechanism of action, clinical uses, dose and available formulations:

Drugs	Structure	Mechanism of action	Clinical uses	Dose		Formulations	Ref
				Starting dose/ day	Maintenance dose/ day		
Phenobarbital (1912)		GABA facilitatory, GABA-mimetic, anti glutamate, Ca^{2+} entry reduction	Partial and generalized seizures (ineffective against absence seizures), status epilepticus	3 mg/kg	3-6 mg/kg	Suspension, Pills, IV.	35, 36-42
Phenytoin (1937)		Na^{+} channel blocker	Partial seizures, generalized tonic-clonic seizures, status epilepticus, (ineffective against absence and myoclonic seizures)	4 mg/kg	4-8 mg/kg	Suspension, Capsule, IV.	36-38, 43-46
Valproic acid (1978)		Na^{+} channel blocker, weak attenuation of Ca^{2+} mediated T current, augmentation of release of GABA	Partial and generalized seizures	15 mg/kg	15-45 mg/kg	Sprinkle capsules, Tablets, Suspensions, IV.	35-38, 47-52, 53

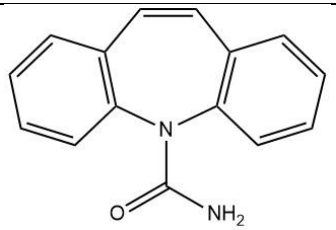
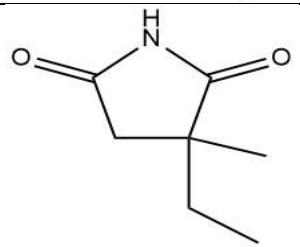
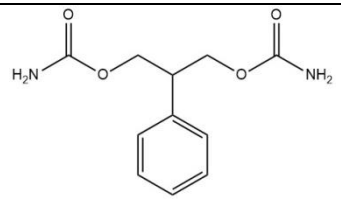
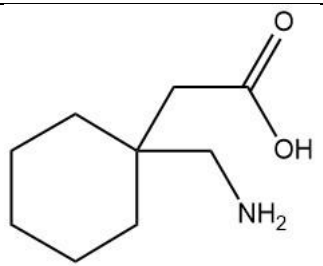
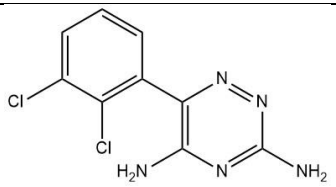
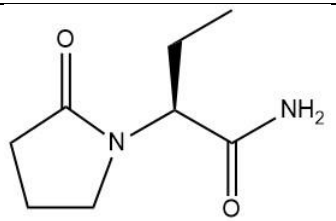
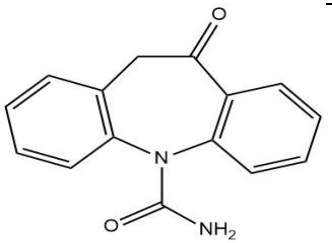
Carbamazepine (1974)		Na^+ channel blocker	Partial seizures, generalized tonic-clonic seizures, (ineffective against absence and myoclonic seizures)	10 mg/kg	10-35 mg/kg	Suspension, Capsule.	35-38, 54-58
Ethosuximide (1960)		Ca^{2+} blocker	Absence seizures	15 mg/kg	15-40 mg/kg	Liquid, Capsule	35-38, 53, 58-59

Table 3: Second Generation Anti-epileptic drugs (FDA approval year), chemical structure, their mechanism of action, clinical uses, dose and available formulations:

Drugs	Structure	Mechanism of action	Clinical uses	Dose		Formulations	Ref
				Starting dose/ day	Maintenance dose/ day		
Felbamate (1993)		Positive modulator of GABA, blocker of NMDA receptors	Severe and/or refractory epilepsies including Lennox-Gastaut syndrome	15 mg/kg	15-45 mg/kg	Suspension, Pills.	36-38, 60-65

Gabapentin (1993)		Ca^{2+} blocker (α28 subunit)	Adjunct for partial seizures (ineffective against absence and myoclonic seizures)	10 mg/kg	25-50 mg/kg	Suspension, Capsule, IV.	35-38, 54-55, 60, 66-72.
Lamotrigine (1995)		Na+ channel blocker	Adjunct for partial and generalized seizures (may aggravate severe myoclonic the epilepsy of infancy), Lennox-Gastaut Syndrome	0.15- 0.5 mg/kg	5-15 mg/kg	Pills (Chewable and dispesble)	35-38, 53, 60-61, 66, 73-76
Levetiracetam (1999)		Modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain.	Partial-onset, myoclonic, or tonic-clonic seizures	10 mg/kg	40-100 mg/kg	Pills, Liquid, IV.	36-38, 73, 77-82.
Oxcarbazepine (2000)		Na+ channel blocker	Partial seizures, generalized tonic-clonic seizures (ineffective against absence and myoclonic seizures)	8-10 mg/kg	30-46 mg/kg	Pills, Suspension.	35-38, 73, 77-78, 83-85.

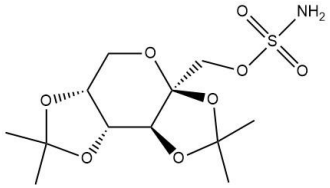
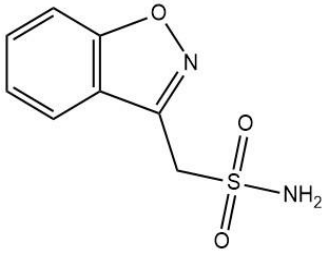
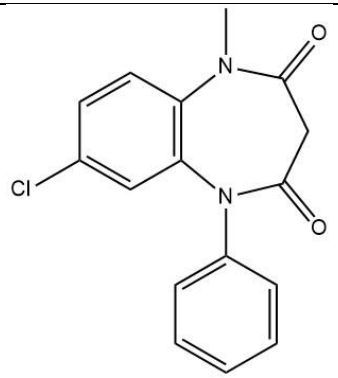
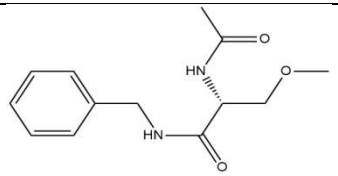
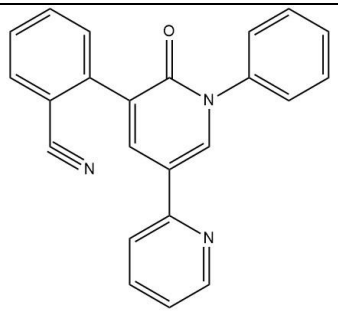
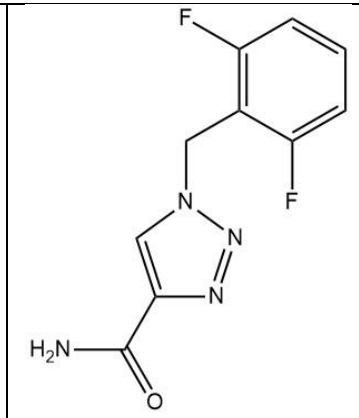
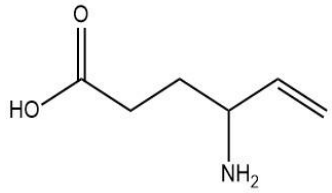
Topiramate (1997)		Multiple (GABA potentiation, glutamate [AMPA] inhibition, sodium and calcium channel blockade)	Adjunct for partial and generalized Seizures	1-3 mg/kg	5-9 mg/kg	Pills. Sprinkle capsule.	36-38, 60, 73, 77-78, 86-88.
Zonisamide (2000)		Na+ channel blocker	Partial and generalized seizures	2-4 mg/kg	4-12 mg/kg	Capsule.	36-38, 61, 73, 77-78, 89-91.

Table 4: Third Generation Anti-epileptic drugs (FDA approval year), chemical structure, their mechanism of action, clinical uses, dose and available formulations:

Drugs	Structure	Mechanism of action	Clinical uses	Dose		Formulations	Ref
				Starting dose/ day	Maintenance dose/ day		
Clobazam (2011)		Potentiation of GABAergic neurotransmission resulting from binding at a benzodiazepine site at the GABA(A) receptor.	Adjunctive treatment in patients with Lennox-Gastaut syndrome.	5 mg/kg	20- 40 mg/kg	Pills, Suspension.	36-38. 61, 92.
Lacosamide (2008)		Enhanced slow inactivation of voltage gated Na+ channels	Use (IV) for focal and generalized seizures with focal onset; no clinical hepatotoxicity	1 mg/kg	2-8 mg/kg	Pills, Oral. Solution, IV.	36-38, 73, 93-96.
Perampanel (2008)		Glutamate (AMPA) antagonist	Use for focal and generalized seizures with focal onset	2 mg/kg	8-12 mg/kg	Pills.	36-38, 97.

Rufinamide (2008)		Na+ channel blocker	Use for seizures in Lennox- Gastaut syndrome; no clinical hepatotoxicity	10 mg/kg	45 mg/kg	Suspension, Pills	36-38, 73, 93, 98-100.
Vigabatrin (2008)		GABA potentiation	No clinical hepatotoxicity; use for infantile spasms, focal and generalized seizures with focal onset	50 mg/kg	50-159 mg/kg	Powder, Pills.	35, 38, 60, 73, 78,101-102.

5.5.1 Limitation with AEDs

Anti-epileptic drug use is restricted due to adverse effects, withdrawal symptoms, hazardous interactions with other medications, and cost load, especially in developing countries [73]. The readily available anti-epileptic drugs are insufficient, negatively affect their use, and are difficult to comprehend when administered. Anti-epileptic drugs only help with already occurring seizures; they have no effect on epileptogenesis [103].

6. Nano-drug delivery systems for the treatment of epilepsy

Nanoformulations are innovative, hopeful, and a cutting-edge method for delivering neurotherapeutics across the BBB. Due to their wide spectrum of nanosizes, fascinating physical-substance features, and ability to utilise surface-engineered biocompatible and biodegradable nanomaterials, nanomedicines have recently demonstrated amazing potential for CNS drug delivery [104]. Anti-epileptic drug nanoformulations are a beneficial technique that can be utilized to get around the issues with traditional drug delivery systems.

Table 5: Recent nanoformulations to treat Epilepsy.

Si No.	Drug	Type of nanoparticles	Route of administration	Year	Reference
1.	Phenytoin Sodium	Nano Lipid carriers	Intranasal	2021	105
2.	Lamotrigine	PLGA nanoparticles	Intranasal	2021	106
3.	Oxcarbazepine	PLGA nanoparticles	Intranasal	2018	107
4.	Carbamazepine	Solid Lipid nanoparticles	IP	2018	108
5.	Gabapentin	Chitosan nanoparticles	Intranasal	2021	109
6.	Thymoquinone	PLGA nanoparticles	Intranasal	2020	110
7.	Carbamazepine	PEG nanoparticles	IV	2021	111
8.	Curcumin	Chitosan-alginate nanoparticles	IP	2020	112
9.	Rosuvastatin	Liquid crystalline nanoparticles	Intranasal	2020	113
10.	Catechin hydrate	Chitosan-PLGA nanoparticles	Intranasal	2020	114
11.	Levetiracetam	Albumin nanoparticles	IV	2020	115
12.	Phenytoin	Lecithin-chitosan nanoparticles	Intranasal	2021	116
13.	Carbamazepine	Carboxymethyl chitosan nanoparticles	Intranasal	2018	117
14.	Epigallocatechin-3-gallate	PEGylated PLGA nanoparticles	IP	2018	118
15.	Lamotrigine	Polymeric nanoparticles	Oral dissolving fims	2020	119

Multi-drug resistance transporters and p-glycoprotein presence in the blood-brain barrier prevent the entry of anti-epileptic drugs into the brain, causing drug-resistant epilepsy. Therefore, the intranasal delivery route is the most exploited for the drugs targeting the brain. Nanosized phenytoin sodium NLCs were

found to have better delivery of Phenytoin sodium with <50nm particle size within 5 minutes after intranasal administration identifying phenytoin sodium loaded NLC assuring nose-to-brain-direct delivery for the treatment of acute epileptic seizures [105].

Lamotrigine (LTG) loaded PLGA nanoparticles developed through emulsification-solvent evaporation technique displayed a pattern of biphasic release found in the brain in greater amounts after intranasal delivery when compared to LTG-SOL with features like the prolonged-release, higher availability and better brain target bypassing BBB reducing the dose, dose frequency, dose-related adverse effects, cost and proper treatment of epilepsy than LTG-SOL does [106].

Further study on carbamazepine in four different nanoformulations was sketched and prepared using homogenization and ultrasonication methods. Physicochemical and microscopic characterization of the four formulations identified the presence of spherical shape nanoparticles with around 160nm diameter entrapped with carbamazepine in the amorphous state, and *in vivo* experiments of seizure in a mice model showed effective CBZ-NLC for at least two h after intraperitoneal administration that treats refractory epilepsy [108].

Different formulations of Gabapentin (GBP)-loaded chitosan nanosized particles obtained using nanospray drying technique found a formulation with particle size 107 ± 13 nm showing high drug entrapment efficiency, cumulative drug release, and increased brain tissue penetration resulting in reduced neuroinflammation, seizure score, elevated EAAT 2 and GABA, TNF-α, and TGF-β and decreased pyramidal neurons degeneration than the marketed Conventin® capsules [109].

Through the emulsion solvent evaporation method, five different thymoquinone (THQ) PLGA-NPs have a particle size ranging from 97.36 ± 2.01 nm with low PDI, DL, and EE. Bioanalytical validation by UHPLC-PDA exhibited improvement in THQ-brain-bioavailability and seizure threshold treatment [110].

With acceptable polydispersity index, Lipoprotein-coated e-caprolactone (e-CL) nanoparticles (NPs) loaded with Carbamazepine having an average particle size of 96nm showed fluorescence of rhodamine B isothiocyanate-labeled e-CL NPs post-injection ranging from 2 h to 24 h, indicating it to be an ideal method of administration from the conventional methods [111].

Curcumin, with several medicinal values, was not exploited due to its lower solubility. Chitosan (CS)-alginate (ALG) - sodium tripolyphosphate (STPP) nanoparticles (NPs) loaded with curcumin assessment proved curcumin possessed anti-convulsive effect and preventing cognitive impairment through histological evaluation of the brain tissues for Nissl staining indicating a reduced level of cell death and for immunostaining method performed against NeuN and GFAP/Iba1 indicating decreased neuronal density and glial activation respectively on comparison to the free curcumin administration [112].

A dose titration study of rosuvastatin liquid crystalline nanoparticles (Ros-LCNPs) indicated that lower dose rosuvastatin was more effective when given intranasally than oral and intraperitoneal. Furthermore, Ros-LCNPs developed by hydrotrope method using glyceryl monooleate revealed Ros-LCNPs to be cubic and multivesicular with higher entrapment efficacy and biphasic release with no impairment in cognitive functions [113].

Through the double emulsion solvent evaporation method, chitosan (CS)-coated–PLGA–nanoparticles (NPs) loaded with catechin hydrate (CH) was prepared, and the values of dependent variables such as

polydispersity index (PDI), particle size, and zeta potential were calculated based on the composition of PLGA (50.0 mg), sonication time (90.0 s), PVA (1.10%) and temperature (25.0 °C) exhibiting excellent mucoadhesive-nature of CS–CH–PLGA–NPs [114].

Levetiracetam-loaded albumin nanoparticles (LEV-NPs) formulated by desolvation were targeted into the brain. *Invitro* studies done by dialysis indicated a biphasic drug release pattern, and the biodistribution study showed an enhanced concentration of levetiracetam in the brain, 3.51 folds than the normal levetiracetam administered [115].

Intranasal administration of lecithin–chitosan nanoparticles ($L_{10}C_i^+$) loaded with phenytoin (PHT) detected PHT in the brain after 5 minutes with a maximum of 11.84 ± 2.31 %ID g^{-1} after 48 hours and found lower accumulation of PHT in spleen and liver, avoiding the intrinsic side effect of PHT-IP. Furthermore, higher drug targeting efficiency and drug targeting percentage, $L_{10}C_i^{+,}$ was found to suppress the seizure entirely after 4 hours of administration with an 8-fold scaling down of the encapsulated dose compared to the PHT-IP dose required to attain a complementary inhibition due to systemic loss [116].

Carboxymethyl chitosan nanoparticles were used to bypass the blood-brain barrier to deliver carbamazepine (CBZ) intra-nasally. This intro drug release profile followed the Korsmeyer-Peppas model showing increased brain drug concentration and treatment efficacy in small particle size (218.76 ± 2.41 nm), around 35% drug loading, and 80% entrapment efficacy indicating enhanced bioavailability and brain targeting characteristics. On the other hand, Epigallocatechin-3-gallate, a multi-therapeutic agent, was least exploited because of its instability [117].

To deal with the instability, Epigallocatechin-3-gallate was loaded with PEGylated-PLGA nanoparticles using the double emulsion method to protect the drug and hence to improve brain delivery. As a result, these nanoparticles exhibited an average size of 169 nm, negative surface charge, monodisperse population, 95% encapsulation efficiency and a sustained drug release profile, and no cytotoxicity, decreasing the number of epileptic episodes and intensity of temporal lobe epilepsy [118].

Poor solubility and low dissolution of Lamotrigine resulted in frequent drug dosing against neurological diseases and anti-epileptic therapy. However, the composite oral matrix films mixed with polyvinyl pyrrolidone and polyvinyl alcohol (0.5:0.5) integrated with the polymeric nanoparticles showed more than 64% drug release within two h, indicating 9-to-11-fold drug release than the pure drug hence improved therapeutic efficacy and bioavailability with fewer side effects and cytotoxicity [119].

7. Conclusion

Most people experience epilepsy, a condition of the central nervous system, at some point in their lives. Anti-epileptic medications, divided into first, second, and third generations, treat epilepsy. The biggest issue with anti-epileptic drugs is that they are only offered in standard dosage forms. As a result, the patients have drug resistance and difficulties connected to dosage. Nano-drug delivery systems can be used in place of conventional drug delivery methods to solve their challenges. In the modern period, scientists are working to reduce the dose and circumvent physiological barriers that prevent the medicine from reaching the site of action or target site, which will be accomplished through nano-drug delivery systems.

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