A Review on the use of Ganaxolone in the Treatment of Epilepsy

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
March, 2024

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled “A review on the use of ganaxolone in the treatment of epilepsy” submitted by Dibbo Protim Ghosh (20146027) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March, 2024.

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Ethics Statement

This study does not involve any animal or human trial.

Abstract

Epilepsy currently affects about 50 million people and approximately 10% of the population will have at least one seizure during their lifetime yet very little is known about this condition. This condition can occur as a result of various causes and has multiple proposed pathogenesis. There are multiple types of epilepsy and as of now there is no cure. Even treatment for many types of epilepsy is not available. Ganaxolone is a new anti-seizure medication which has been approved by the USFDA for the treatment for CDD associated epilepsy, it is a first drug in its class. It has shown great promise in the clinical trials as it is effective against treatment resistant epilepsy and exhibits lower side effects and drug interactions. In this review, the clinical trial data of ganaxolone is analyzed and an evaluation of its effectiveness over currently available treatment is provided which can be used to unravel the full potential of this drug in the future.

Keywords: epilepsy; ganaxolone; ganaxolone clinical trials; CDKL5 deficiency disorder: PCDH19 related epilepsy; status epilepticus.

Dedication

Dedicated to those who have been suffering from epilepsy.

Acknowledgement

First of all, I want to give thanks and appreciation to God for granting me good health as well as patience, dedication and knowledge I needed to finish the thesis.

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List of Acronyms

ILAE	International league against epilepsy
WHO	World Health Organization
DNA	Deoxyribonucleic acid
GABA	Gamma-aminobutyric acid
NMDAR	N-methyl-D-aspartate receptor
LGI-1	Leucine rich glioma inactivated protein I
ANNA-A	Anti-neuronal nuclear antibody type 1
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
GABA-B	Gamma-aminobutyric acid B
mGluR5	Metabotropic glutamate receptor 5
MRI	Magnetic resonance imaging
EEG	Electroencephalogram
AMPA	Alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid
NMDA	N-Methyl-D-aspartic acid
mGlu1	Metabotropic glutamate receptor 1
mGlu5	Metabotropic glutamate receptor 5
mGlu2	Metabotropic glutamate receptor 2
mGlu3	Metabotropic glutamate receptor 3

mGlu4	Metabotropic glutamate receptor 4
mGlu6	Metabotropic glutamate receptor 6
mGlu7	Metabotropic glutamate receptor 7
mGlu8	Metabotropic glutamate receptor 8
HLA	Human leukocyte antigen
CDKL5	Cyclin-dependent kinase-like 5
CYP	Cytochrome P450
CDD	Cyclin-dependent kinase-like 5 deficiency disorder
PCDH19	Protocadherin 19
LGS	Lennox-Gastaut syndrome
CSWS	Continuous spikes and waves during sleep
SE	Status epilepticus
IV	Intravenous
miRNA	Micro ribonucleic acid
RNA	Ribonucleic acid
mRNA	Messenger ribonucleic acid

The use of Ganaxolone in the Treatment of Epilepsy

Chapter 1: Introduction

1.1 Introduction to epilepsy

Fisher et al. (2005) have described epilepsy as a brain disorder which is primarily distinguished by recurring and random disturbances in normal brain function, known as epileptic seizures. Falco-Walter (2020) differentiates between seizure and epilepsy using the definitions set by the International League Against Epilepsy (ILAE), a seizure is a brief manifestation of signs and symptoms as a result of excessive or synchronous neuronal activity occurring in the brain and the time span is usually less than two minutes. On the contrary, in epilepsy a person has multiple seizures (usually two or more) which are unprovoked or reflex seizures and they are more than 24 hours apart or one unprovoked or reflex seizure and a 60% or greater risk of having another seizure within the next 10 years or epilepsy syndrome is present. It is a noncommunicable chronic disorder and Falco-Walter (2020) mentions that about 10% of the population will have one seizure during their lifetime but people having a single seizure may not necessarily have epilepsy. Epilepsy is one of the most commonly occurring chronic disorders which affect people of all ages in the population. According to the World Health Organization (WHO) (2023), epilepsy is classified as a frequently occurring neurological disorder which currently affects about 50 million people around the world. Frequency of new cases of epilepsy (WHO, 2023):

Total new cases per year	***About 5,000,000***
New cases in high income countries per year	***49 per 100,000 of the population***
New cases in low income countries per year	***139 per 100,000 of the population***

Figure 1: WHO statistics on epilepsy

The rate of incidence is higher in low-income countries compared to high income countries.

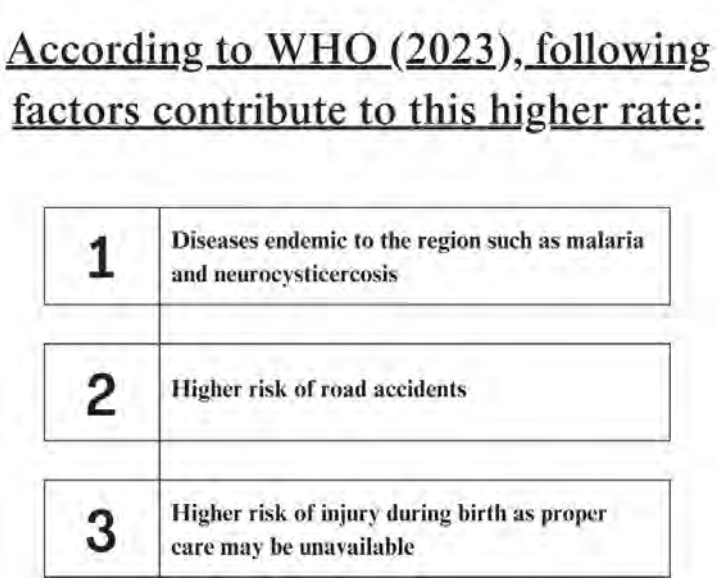

Figure 2: Factors leading to a higher rate of epilepsy in low-income countries

1.2 Etiologies of epilepsy

The knowledge regarding the etiology of epilepsy is regularly evolving and so is the classification of etiology of epilepsy. Pack (2019) discusses the evolution of etiological classification of epilepsy starting from the initial ILAE classification in 1981 which classified epilepsy into either partial or generalized seizures. This was modified in 1985 to idiopathic or symptomatic epilepsies. Cryptogenic epilepsy which are probably symptomatic but the cause cannot be identified were added to the 1985 classification in 1989 by the ILAE. Genetic

abnormalities account for majority of the cases of childhood epilepsy. The other leading causes are brain injury due to perinatal insults and improper cortical development. Barring genetic predisposition, common causes of seizure in adults are encephalitis, meningitis, brain tumors or traumatic brain injury. Neurodegenerative disorders are the primary cause of epilepsy in the elderly, tumours in the brain and head injury may also cause epilepsy in the elderly (Falco-Walter, 2020). The most recent classification of etiology was published by the ILAE in 2017 and is the most updated version as of right now. A proper classification of etiology is required to carry out a smooth diagnosis in clinical setting. Identifying the cause can help in choosing the course of treatment, prognosis and clinical course (Shorvon, 2011). The current classification by the ILAE is divided into the following six categories (Figure 3):

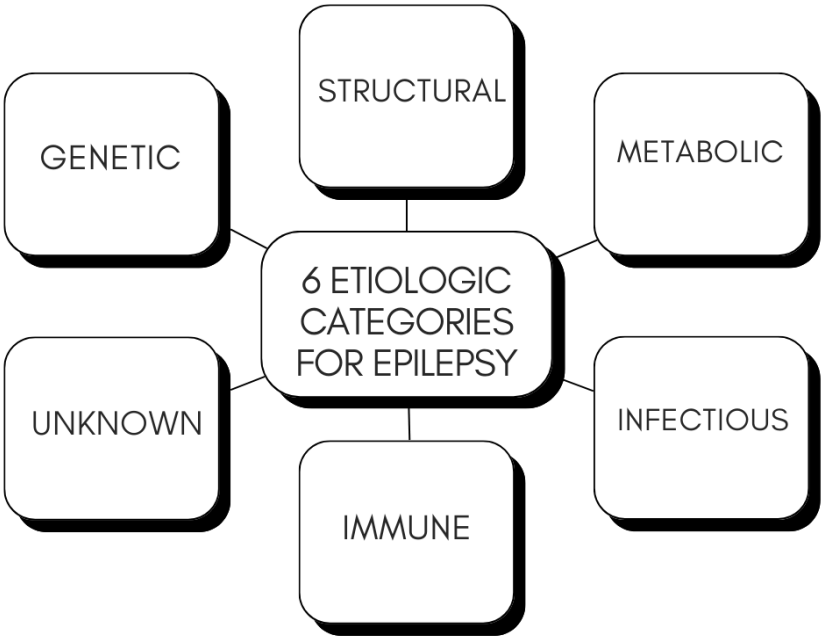

Figure 3: The etiological classification of epilepsy

Genetic etiology: an epilepsy is classified under this etiology if an epilepsy causing gene is known to be present or predicted to be present in the genome. Wang et al. (2017) have identified 977 genes that may be responsible for causing epilepsy. Wang et al. (2017) have further

grouped these genes into 4 categories based on the expression of epilepsy in phenotypes. The categories are:

- Epilepsy genes: they are responsible for causing epilepsy or may cause syndrome where epilepsy is the core symptom.
- Neurodevelopment-associated epilepsy genes: they can cause abnormalities in brain development and can cause epilepsy.
- Epilepsy-related genes: physical and systemic defects are observed and epileptic seizures may be observed.
- Putatively associated with epilepsy: these are genes which need further verification.

Infectious etiology: If the central nervous system becomes infected, they may cause epileptic seizures. In places, where endemic diseases are present, this may be one of the most distinguishable causes. Seizures here are formed due to changes caused in the brain by the infectious agent. Cysticercus, human immunodeficiency virus, cytomegalovirus, toxoplasma gondii, mycobacterium tuberculosis and plasmodium falciparum are some of the most common infectious agents (De Vera-González, 2022). Each of these infectious agents are responsible for different type of damage to the central nervous system. Many viruses are known to cause cortical necrosis; cerebral malaria is likely to lead to hypoxic-ischemic injury and likewise each infectious agent is associated with a specific type of brain damage. A pro-inflammatory response is initiated in the brain in response to these infectious agents and it can damage the blood brain barrier, lead to death of neurons and cause constant overexcitation of neurons. Immune response is initiated against these infectious agents and that can modify blood brain barrier integrity by the release of cytokines, this leads to hyperexcitability of neurons.

Metabolic etiology: seizures are caused by metabolic abnormalities. A brief metabolic abnormality causing seizure would not be called epilepsy as this seizure is provoked. Some metabolic malfunctions are caused by genetic defects and these are observed as cellular

degeneration and dysmyelination to disorders of neuronal migration, making the person more susceptible to seizures. These disorders will be classified by the faulty molecule or mechanism and categorized as small or large molecule disorders. Small-molecule disorders refer to the involvement of amino acids, organic acids, fatty acids, neurotransmitters and their metabolites, urea cycle products, vitamers and cofactors. List of small and large molecule disorders are given below (De Vera-González, 2022):

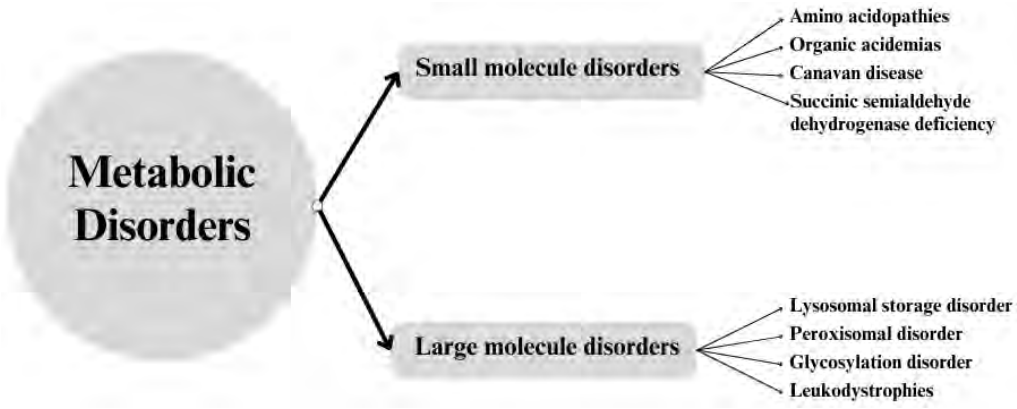

Figure 4: Classification of metabolic disorders

Most of the metabolic epilepsies have a genetic origin but pyridoxine dependent seizures and cerebral folate deficiency are cases where the epilepsy is acquired.

Structural etiology: they may be genetic or acquired. The genetic and acquired causes are classified below:

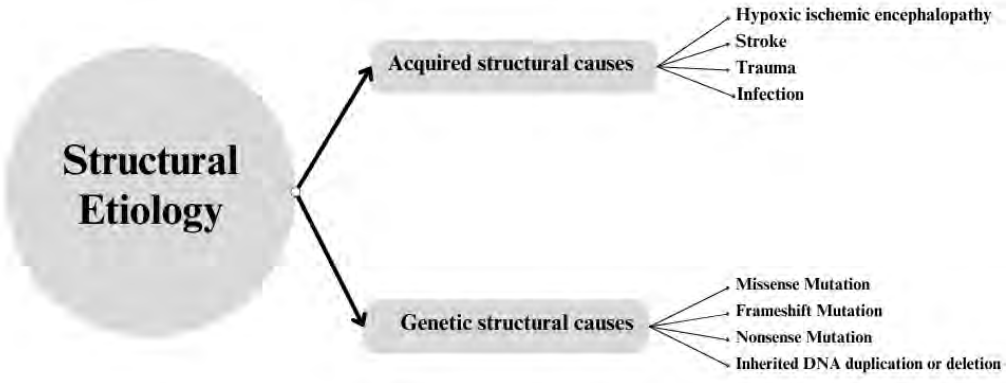

Figure 5: Classification of structural etiology

Hippocampal sclerosis is observed frequently in mesial temporal lobe seizure. As a result, pyramidal neurons are lost in specific regions of the brain. It causes the loss of GABAergic neurons. This leads to neuronal and synaptic reorganization in the brain which is responsible for epileptogenesis.

Immune etiology: this includes autoimmune diseases. Antibody-mediated limbic encephalitis is a common cause of epilepsy (Falco-Walter, 2020). Additionally, several receptor and proteins have been identified by Toledano and Pittock (2015), whose inflammation due to autoimmune reasons are predicted to cause epilepsy, some of them are:

- N-methyl-D-aspartate receptor (NMDAR)
- Leucine rich glioma inactivated protein I (LGI-1)
- Anti-neuronal nuclear antibody type 1 (ANNA-A)
- Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)
- Gamma-aminobutyric acid- B (GABA-B)
- Metabotropic glutamate receptor 5 (mGluR5).

Identifying this etiology is very important and the course of treatment will be different. To treat epilepsy with this type of etiology, immunologic agents such as steroids, immunoglobulins, plasmapheresis, rituximab are used.

Unknown etiology: this is assigned to patients whose cause cannot be fully determined.

Often identifying the etiology of epilepsy is difficult. This is because epilepsy in most cases is multifactorial. Most epilepsies don't only have a genetic element but an acquired element as well. This makes it very difficult to assign a cause of epilepsy. The factor which contributes the most to the disease is usually taken as the cause, and this assigning of cause may be clinically important. Furthermore, we do not have complete knowledge about epilepsy, otherwise classifying the etiology according to the molecular mechanism would be the ideal

approach (Shorvon, 2011). Lastly, with advancement in technology, it is possible to narrow down the cause further. It is now possible to identify a hippocampal sclerosis with an MRI and the new techniques is genomics now enables us to diagnose any genetic causes that leads to epilepsy.

1.3 Signs, symptoms and prodromes

Prodromes are early early symptoms that indicate the forthcoming of a disease or illness. In this case, they are symptoms that signal that a seizure may be occurring soon. Besag and Vasey (2018) have reviewed 8 studies and reported an overall prodrome frequency of 21%. Out of 1843 subjects, 404 of them have reported of prodrome symptoms. Most common prodrome symptoms are:

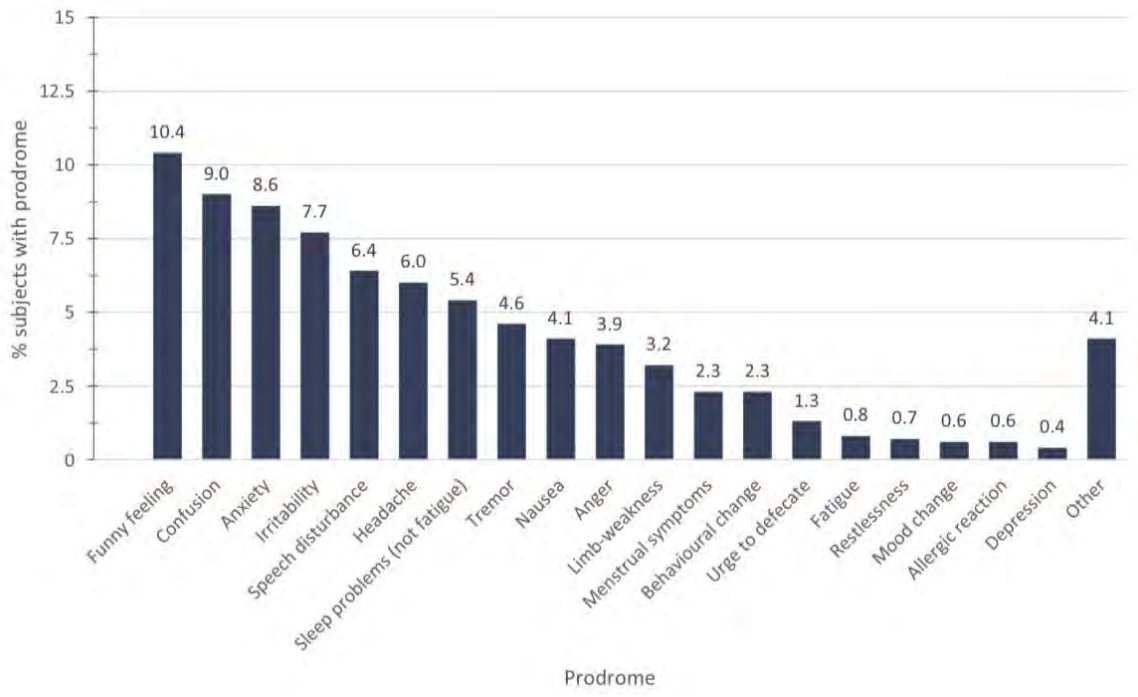

Figure 6: Frequency of prodrome symptoms (Besag and Vasey, 2018)

Signs and symptoms are a major part of an epileptic seizure as it is a clinical event and primarily defined by the signs and symptoms. Most of the times it is not possible to accurately identify all the signs and symptoms as there is a large range of clinical manifestations. The clinical

manifestation of seizures can depend on various factors such as location of seizure generation in the brain, method of propagation, maturity of the brain, unpredictable pathogenesis, sleep-wake cycle, drugs and many other factors. Seizures can affect a wide range of functions, such as motor, sensory and autonomic functions, additionally, consciousness, emotional state, cognition and behaviour may be altered. Change may be observed in many of these factors during a seizure. Somatosensory, auditory, visual, olfactory, gustatory and vestibular senses are primarily grouped as sensory manifestations (Fisher et al. 2005). It also may include more complex sensations with rather complex perceptual distortions. During seizures, problems may arise with perception, attention, emotion, memory, execution, praxis and speech, these are called cognitive deficits. Memory distortions are further classified into negative and positive. If memory formation is inhibited or retrieval is difficult, it is called negative symptom whereas, the introduction of an inappropriate memory is called a positive symptom. Positive memory symptoms are responsible for déjà vu and forced memories during a seizure. Often seizures are characterized by extreme emotional states such as fear, elation, satisfaction or anxiety.

1.4 Classification of epilepsy

The types of epilepsy are as follows:

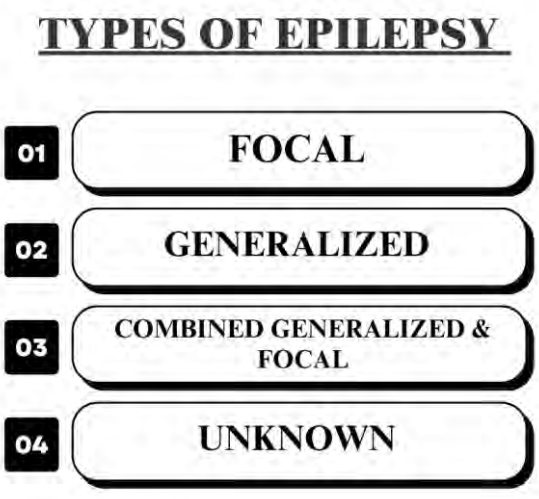

Figure 7: Types of epilepsy

To classify an epilepsy as generalized epilepsy, the patient typically exhibits spike-wave on the electroencephalogram (EEG). Patients with generalized epilepsy may have various types of seizures such as absence, myoclonic, atonic, tonic and tonic-clonic seizures. The diagnosis is based on clinical evidence from the EEG. Care has to be taken for patients with generalized tonic-clonic seizure but present a completely normal EEG (Scheffer et al., 2017). Further evidence such as a family history or myclonic jerks has to be present to confirm a diagnosis in that case.

Focal epilepsies consist of unifocal and multifocal disorders and additionally it concerns with seizures occurring in one hemisphere. Focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures and focal to bilateral tonic-clonic seizures are characteristic of this type of epilepsy (Scheffer et al., 2017). This form of epilepsy is diagnosed based on clinical evidence and EEG data. EEG data usually contains epileptiform discharges.

The combined generalized and focal epilepsy is a form of epilepsy in which the patient exhibits both generalized and focal epilepsies. Diagnosis is done based on clinical manifestations and EEG data. EEG data collected between two seizures commonly shows generalized spike-wave as well as focal epileptiform discharges. Dravet syndrome and Lennox-Gastaut syndrome are two examples where both focal and generalized seizures are observed. It is also the final diagnosis that is possible where an accurate diagnosis of the syndrome is not possible.

Unknown epilepsy is designated to those epileptic conditions in which the physician is not able to assign a type due to lack of clinical evidence. This usually occurs when an EEG is not available or the EEG data was insufficient.

1.5 Pathophysiology

Epilepsy is a heterogeneous disease which means different stimulus may initiate epileptogenesis. This epileptogenesis may consist different biological pathways and processes.

It can involve structural and functional modifications. Epileptogenesis can occur via neurotransmission signalling pathway, molecular and genetic mechanism, neurogenesis and rewiring pathways, immunological and inflammatory pathway and apoptotic pathway (Hui Yin et al., 2013). Among these, pathogenesis based on neurotransmission signalling pathway is the most studied and widely accepted.

Neurotransmission signalling pathway describes epileptogenesis by the imbalance of neurotransmitters. Glutamate and gamma-aminobutyric acid (GABA) are the two major neurotransmitters of the central nervous system. Glutamate and GABA are excitatory (causes excitation by depolarizing neurons) and inhibitory neurotransmitters respectively. These are also two neurotransmitters which are extensively studied for epilepsy. Glutamatergic and GABAergic systems are vital in the formation of epilepsy. Imbalance in the excitation caused by glutamate and inhibition caused by GABA is thought to be the major mechanism of seizure formation. The imbalance results in neuronal hyperexcitability.

Glutamate receptors are classified into ionotropic (ligand-gated cation channels) receptors and metabotropic (G protein-coupled) receptors. Ionotropic receptors include alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), N-methyl-D-aspartic acid (NMDA) and kainate. Metabotropic receptors include three families of receptors, group I: mGlu1 and mGlu5; group II: mGlu2 and mGlu3; group III: mGlu4, mGlu6, mGlu7 and mGlu8 (Meldrum et al., 1999).

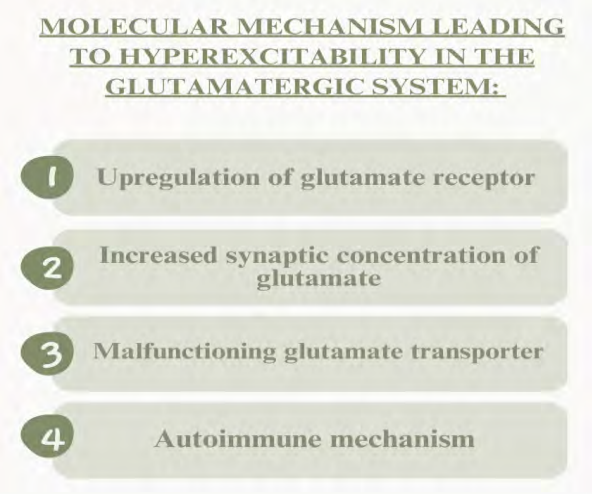

Figure 8: Mechanisms causing hyperexcitability in glutamatergic system.

Hui Yin et al. (2013) mention four mechanisms (as shown in Figure 8) that can possibly be involved in the initiation and progression of epilepsy. These mechanisms lead to increased glutamate activity and as a result hyperexcitation forms leading to epilepsy.

On the contrary, GABA is responsible for inhibition and does so by causing hyperpolarization in neurons. GABA can counter the effects of the glutamatergic system and prevent epileptogenesis. $GABA_A$ and $GABA_B$ are the two types of GABA receptor and they are ligand-gated ion channels and G protein-coupled receptors respectively. $GABA_A$ activation increases influx of chloride ions and $GABA_B$ activation causes increase in potassium conductance and decrease in calcium entry (Treiman, 2001). In case of a loss in GABA mediated inhibition, the chance of excitatory potential formation increases. This may cause epileptogenesis. Molecular mechanisms regarding the GABAergic system leading to hyperexcitability described by Hui Yin et al. (2013) is summarized in Figure 9.

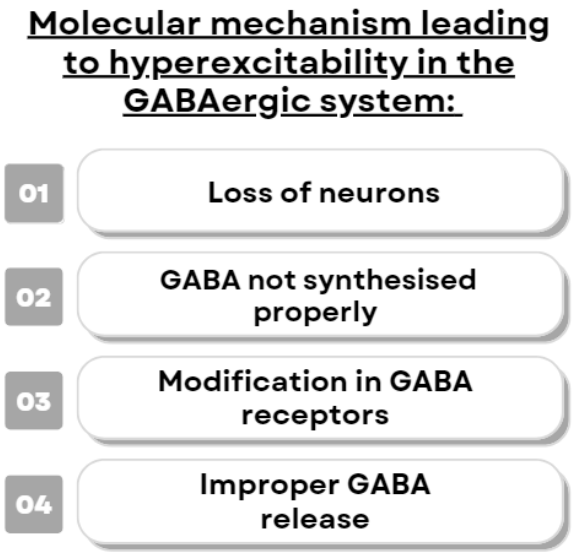

Figure 9: Mechanisms causing hyperexcitability in GABAergic system.

In addition to glutamate and GABA, several experiments have shown that serotonin, noradrenaline and dopamine may also contribute to epileptogenesis.

1.6 Existing treatments

There is no existing cure for epilepsy. The primary aim of currently available treatments is to help patients live an unrestricted life by managing the seizures in the ways mentioned in Figure 10.

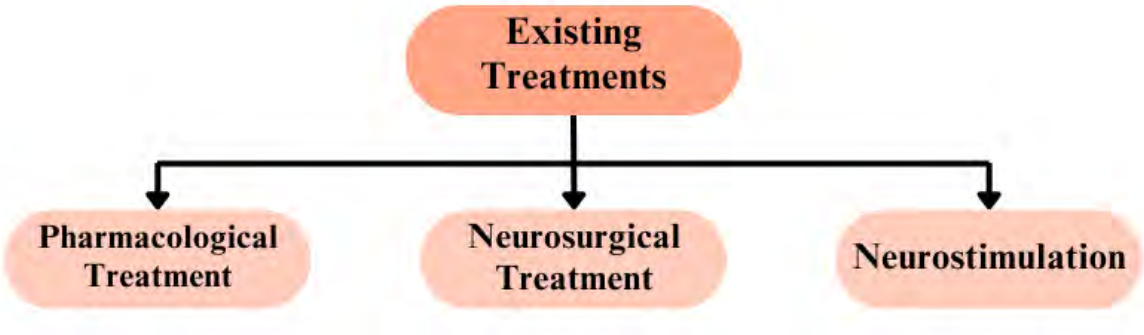

Figure 10: Existing treatments of epilepsy

Antiepileptic drugs mainly work by inhibiting the overexcitation of neurons. As a result, the initiation or propagation of seizures are inhibited. The antiepileptic drugs can be classified based on generations:

Classification of anti-seizure medication

First-generation drugs	Second-generation drugs	Third-generation drugs
• Phenobarbital	• Clonazepam	• Tiagabine
• Phenytoin	• Valproate	• Gabapentin
• Ethosuximide	• Carbamazepine	• Felbamate
• Phenacemide	• Diazepam	• Vigabatrin
• Trimethadione	• Sulthiame	• Levetiracetam

Figure 11: Generations of antiepileptic drugs

The evolution of antiepileptic drugs over the years is shown in Figure 12.

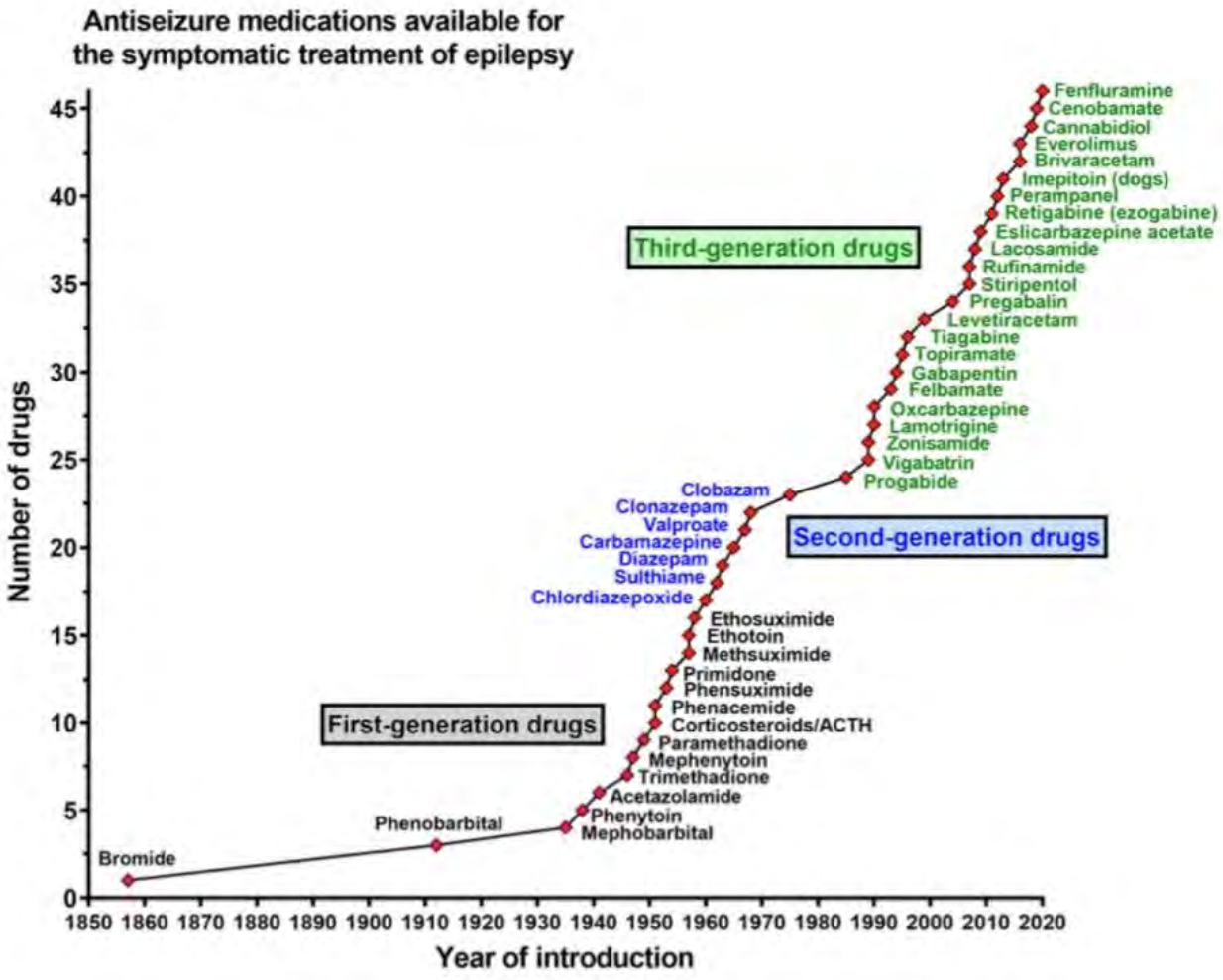

Figure 12: Evolution of antiepileptic drugs (Löscher & Klein, 2021)

A classification based on mechanism of action is provided below:

Mechanistic classes of antiseizure medications	Antiseizure medications that belong to this mechanistic class
Modulators of voltage-gated sodium channels	
Increase of fast inactivation (transient sodium current; I_{NaT})	Phenytoin, fosphenytoin[a], carbamazepine, oxcarbazepine[b], eslicarbazepine acetate[c], lamotrigine; possibly topiramate, zonisamide, rufinamide, brivaracetam
Increase of slow inactivation	Lacosamide
Block of persistent sodium currents (I_{NaP})	Cenobamate, lacosamide, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, topiramate, valproate, gabapentin, cannabidiol
Blockers of voltage-gated calcium channels (T-type)	
High-voltage activated	Phenobarbital, phenytoin, levetiracetam
Low-voltage activated T-type (Ca_v3)	Ethosuximide ($Ca_v3.2 > Ca_v3.1$), methsuximide, eslicarbazepine ($Ca_v3.2$); possibly valproate
Activators of voltage-gated potassium channels (K_v7)	Retigabine (ezogabine)
Modulators of GABA-mediated inhibition	
Allosteric modulators of $GABA_A$ receptors	Phenobarbital, primidone, stiripentol, benzodiazepines, (including clonazepam, clobazam, diazepam, lorazepam, and midazolam), topiramate, felbamate, retigabine (ezogabine), cenobamate
Inhibitors of GAT1 GABA transporter	Tiagabine
Inhibitors of GABA transaminase	Vigabatrin
Activators of glutamic acid decarboxylase	Possibly valproate, gabapentin, pregabalin
Inhibitors of ionotropic glutamate receptors	
Antagonists of NMDA receptors	Felbamate, topiramate, possibly valproate
Antagonists of AMPA receptors	Perampanel, phenobarbital, levetiracetam
Modulators of the presynaptic release machinery	
SV2A	Levetiracetam, brivaracetam
α2δ subunit of calcium channels	Gabapentin, pregabalin
Inhibitors of carbonic anhydrase	Acetazolamide, sulthiame, topiramate, zonisamide; possibly lacosamide
Serotonin-releasing agents	Fenfluramine
Disease-specific modulators	
Inhibitors of mTORC1 signaling[d]	Everolimus
Lysosomal enzyme replacement[e]	Cerliponase alfa (recombinant tripeptidyl peptidase 1)
Mixed/unknown	Valproate, felbamate, topiramate, zonisamide, rufinamide, adrenocorticotrophin, cannabidiol, cenobamate, potassium bromide

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *GAT* GABA transporter, *mTORC1* mechanistic target of rapamycin complex 1, *NMDA* N-methyl-D-aspartate, *SV2A* synaptic vesicle protein 2A

[a]Fosphenytoin is a prodrug for phenytoin

[b]Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly S-licarbazepine (eslicarbazepine)

[c] Eslicarbazepine acetate is a prodrug for S-licarbazepine (eslicarbazepine)

[d]In patients with epilepsy due to tuberous sclerosis complex

[e]In patients with epilepsy due to neuronal ceroid lipofuscinosis type 2

Figure 13: Molecular mechanisms of antiepileptic drugs (Löscher & Klein, 2021)

Patients who are resistant to treatment with antiepileptic drugs could be advised a neurosurgical procedure. Removal or disconnection of a particular brain region in these patients may help to control seizures (De Vera-González, 2022). Lesional epilepsies that form as a result of developmental abnormalities, vascular malformations, trauma or tumor need to undergo the resection procedure. Temporal lobe epilepsy is primarily treated surgically via temporal lobectomy with hippocampectomy. If a particular epileptogenic lesion is identified then, it can

also undergo resection surgery. Epilepsy that concerns a large part of the brain will be advised with a subtotal or total hemispherectomy. As a consequence, for surgical treatment to be successful, the type of epilepsy and the affected brain region has to be carefully identified through neuroimaging diagnostic techniques and neurophysiological examinations. 50-80% success rate is observed among distinct groups that have undergone surgery (Ryvlin et al., 2014).

Neurostimulation techniques can be used as a last-line treatment when surgery and medication has not worked, especially in palliative patients. By applying electrical impulses to the peripheral nerves or to a particular region of the brain, it is possible to stop seizure formation.

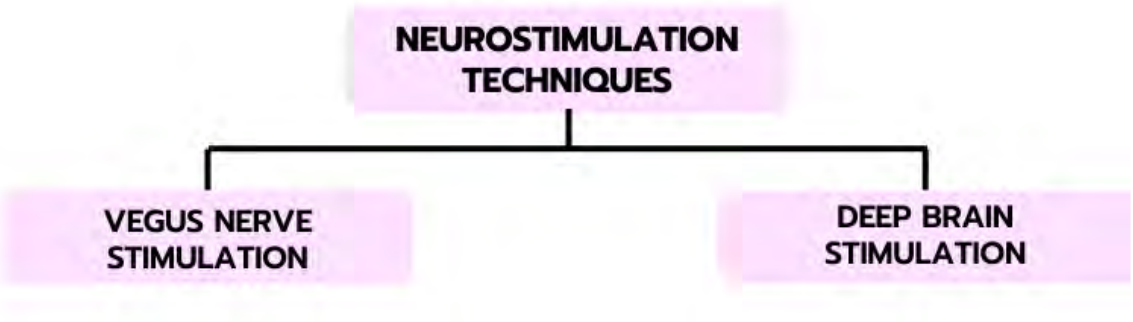

Figure 14: Neurostimulation techniques

The two well-known neurostimulation techniques as shown in Figure 11 are vagus nerve stimulation (vagus nerve stimulator was the first approved device for epilepsy) and deep brain stimulation which is done by implanting electrodes in the anterior nucleus of the thalamus (De Vera-González, 2022). Regular vagus nerve stimulation reduces seizure frequency by half in about one third patients and improves quality of life (Thijs et al., 2019).

1.7 Aims and objectives

This article aims to analyse the clinical trial data of the new antiepileptic drug ganaxolone. The analysis of clinical trial data of ganaxolone would yield significant results and then it can be compared to the standard treatment that is already available for epilepsy. This comparison will be used to evaluate whether or not the new drug has better efficacy, whether the potential benefits of this drug outweigh the risks. Which drug exhibits less adverse effects is also a point to be discussed. The ultimate goal is to provide a concise and effective summary of this drug in terms of its treatment potential in different types of epilepsy, this will be done by comparing different clinical trial data collected from various sources and based on this a conclusion will be reached on the potential of this new drug.

Chapter 2: Novel drug for epilepsy

2.1 Reasons for developing new drugs

According to Abou-Khalil and Schmidt (2012), following are the limitations to the existing treatments of epilepsy:

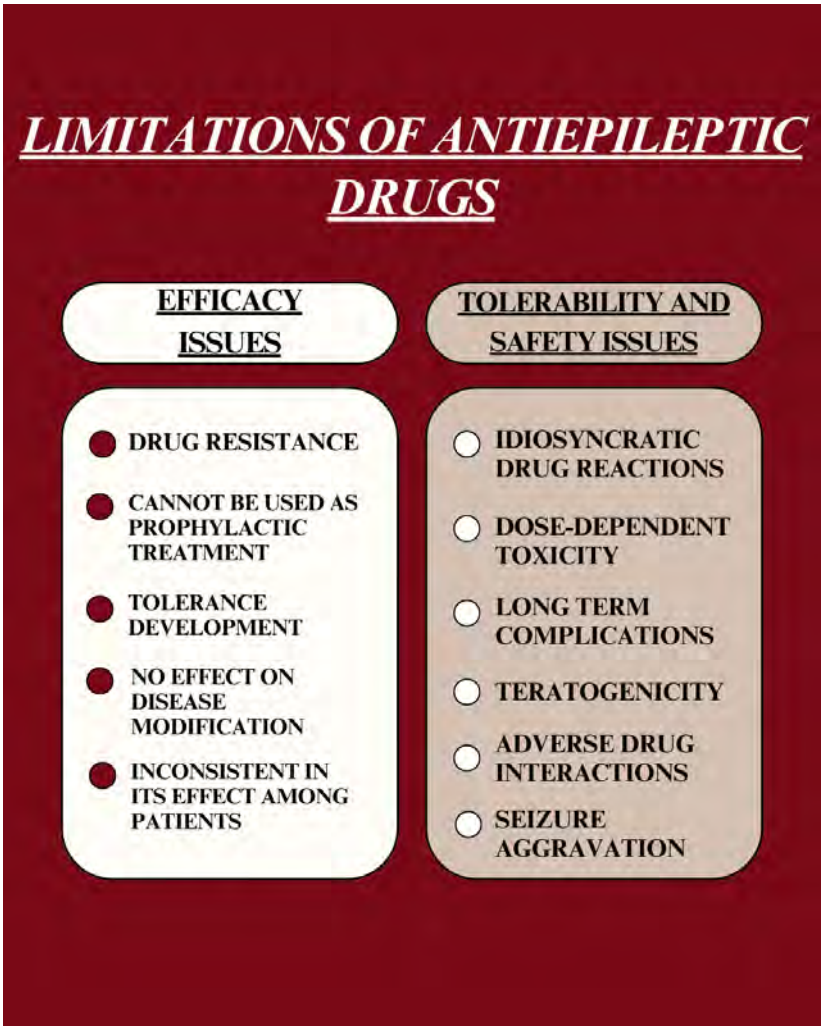

Figure 15: Limitations of existing treatment for epilepsy

According to Kwan and Brodie (2000), more than 30% patients will not respond appropriately to anti-epileptic drugs. A patient is considered resistant to antiepileptic dugs if they do not respond to at least six medications and it is found that with a change in treatment regimen about 16.6% of patients become seizure free (Schiller and Najjar, 2008). Drug transporter hypothesis, drug target hypothesis and a new theory called the inherent severity model of epilepsy are

theories that try to explain the mechanism of drug resistance but none of them convincingly do so.

Following a brain trauma, there is always high risk of posttraumatic epilepsy. This risk is quite high for a long duration of time which provides the opportunity for prophylactic treatment. A combination therapy of Phenobarbital and phenytoin has looked promising in the past but there is limited data available. Prophylactic measures with antiepileptic medications may prevent the initial development of posttraumatic seizures but it is ineffective in the long term and permanent posttraumatic epilepsy may develop later (Abou-Khalil and Schmidt, 2012).

If a drug is taken over a long period of time, then the body will produce an adaptive response and a diminished effect of the drug will be observed. How quickly tolerance is developed may vary from person to person. Therapeutic efficacy as well as side effects will be reduced. This effect is reversible if the particular drug therapy is stopped. Two types of tolerance are observed: Pharmacokinetic tolerance which is exhibited by most first-generation antiepileptic drugs and pharmacodynamic tolerance where receptor sensitivity is lost (Abou-Khalil and Schmidt, 2012). Pharmacodynamic tolerance can cause complete loss of therapeutic activity and cross-tolerance may arise. Many treatment regimens therefore fail or are ineffective due to the development of drug tolerance.

Prompt treatment with antiepileptic dugs may decrease the frequency of seizures for a couple of years but it has no effect on the long-term remission in people of infrequent seizures (Marson et al., 2005). In low-risk patients (patients with only one seizure), the benefit of immediate treatment is negligible but in medium to high-risk people (more than three seizures) it may be beneficial (Kim et al., 2006). In general, antiepileptic drugs lower the chance of any further seizures but no evidence clearly suggests that it is able to modify the underlying disease.

Due to different genetic profile among patients, drugs may show different efficacy. Genetic variability has been reported to affect the biotransformation of phenytoin, hence affecting its efficacy. Asian patients carrying a certain human leukocyte antigen (HLA) allele also are more susceptible to developing Stevens-Johnson syndrome while being on Carbamazepine.

Toxicity and/or side effects are observed at higher doses for any drugs. Barbiturates may cause sedation and at higher doses it will form a state of anaesthesia or may even cause coma and death.

Some antiepileptic drugs may cause hypersensitivity reactions. Carbamazepine is example of a classical antiepileptic drug which can cause idiosyncratic drug reactions. It has been reported that carbamazepine may cause Lyell syndrome and Stevens-Johnson syndrome in some patients. It had affected 14 per 100,000 users of this drug (Chowta et al., 2011).

Some drugs can cause long term adverse effects which are irreversible. The popular antiepileptic drug vigabatrin is known to cause irreversible concentric visual field defects.

If taken during pregnancy, many epilepsy drugs such as valporate exhibit teratogenic activity. Valproate is responsible for causing birth defects if taken by pregnant women and the offspring may suffer from permanent cognitive impairment (Abou-Khalil and Schmidt, 2012)

A major limitation of the currently available drugs is seizure aggravation. For example: carbamazepine is able to aggravate juvenile myoclonic epilepsy. Myoclonic and absence seizures are generally aggravated by drugs for partial seizures (Abou-Khalil and Schmidt, 2012).

Antiepileptic drugs also exhibit many clinically relevant drug interactions which are summarized in the table below:

Simplified synopsis of drug interaction properties of common antiepileptic drugs (AEDs)

Anticonvulsive agent	Clinically relevant interactions when added to other drugs including AEDs	Clinically relevant interactions when other drugs are added
Clobazam (CLB)	No relevant change	No relevant change
Felbamate (FBM)	Increases plasma concentrations of VPA, PHT, PB, CBZ epoxide	Plasma concentration reduced by enzyme inducers
Gabapentin (GBP)	No relevant change	No relevant change
Levetiracetam (LEV)	No relevant change	No relevant change
Lacosamide (LCM)	No relevant change	Plasma concentration reduced by enzyme inducers
Zonisamide (ZNS)	No relevant change	Plasma concentration reduced by enzyme inducers
Topiramate (TPM)	No relevant change	Plasma concentration reduced by enzyme inducers
Carbamazepine (CBZ)	Lower plasma concentrations of LTG, TGB, VPA and lower efficacy of other drugs*	Plasma concentration increased by a variety of drugs, including erythromycin, propoxyphene, isoniazid, cimetidine, verapamil, diltiazem, fluoxetine
Ethosuximide (ETS)	Uncertain	Plasma concentration reduced by enzyme inducers
Lamotrigine (LTG)	No relevant change	Plasma concentration increased by valproate and reduced by enzyme inducers and by estrogen
Oxcarbazepine (OXC)	Lower plasma concentrations of LTG, PHT, TGB, VPA and lower efficacy of other drugs* at OXC doses of >900 mg*	Plasma concentration reduced by enzyme inducers
Phenobarbital (PHB)	Lower plasma concentrations of LTG, OXC, PHT, TGB, VPA and lower efficacy of other drugs*	Plasma concentration increased by valproate and felbamate
Phenytoin (PHT)	Lower plasma concentrations of LTG, PHT, TGB, VPA and lower efficacy of other drugs*	VPA competes for protein binding
Pregabalin (PGB)	No relevant change	No relevant change
Primidone (PRM)	Lower plasma concentrations of LTG, OXC, PHT, TGB, VPA and lower efficacy of other drugs*	Plasma concentration reduced by enzyme inducers
Rufinamide (RFM)	No relevant change	Plasma concentration increased by valproate and reduced by enzyme inducers
Valproate (VPA)	Higher toxicity of PHT, PHB, and PRM†	Plasma concentration reduced by enzyme inducers
Vigabatrin (VGB)	No relevant change	No relevant change

*Inducers of cytochrome P450 enzyme system.
†Inhibitor of uridin-diphosphate-glucuronyl-transferase system.
(Benedetti, 2000; Patsalos and Perucca, 2003)

Figure 16: Clinically relevant drug interactions of antiepileptic medications (Abou-Khalil and Schmidt, 2012)

2.2 CDKL5 deficiency disorder

Epilepsy can be caused by mutations in the CDKL5 gene. This form of epilepsy manifests itself very early in life, usually in the first 3 months. There is a lack of effective treatment for this type of epilepsy. This gene is found in the short arm of the X chromosome. The protein product is found throughout the body but primarily in the brain specifically in the cerebral cortex, hippocampus, cerebellum, thalamus and the brainstem. It plays a role in the neuronal formation and development. It is predicted that the protein is responsible for neuronal growth, neuronal migration, neuronal formation, proliferation (Bahi-Buisson & Bienvenu, 2011). Additionally,

it has a role in maturation and functioning of synapses. Appropriate concentration of CDKL5 in the cytoplasm determines the maturation of dendrites. 265 disease causing variants of this gene have been found so far (Jakimiec et al., 2020). Half of these were a result of point mutations. Deletion of this gene has also been observed in some cases. This genetic condition results in a drug-refractory form of childhood epilepsy which is generally the first symptom of this disease.

2.3 Drug of interest

The drug that is being studied is Ganaxolone as shown in Figure 17. It is classified as a neurosteroid and is a positive allosteric modulator of the gamma-aminobutyric acid $(GABA)_A$ receptor complex. Allopregnanolone is an endogenous neuroactive steroid and ganaxolone is its synthetic methyl analog. Its binding site is distinct from that of benzodiazepines and barbiturates. In low concentration (nanomolar) ganaxolone acts as a positive allosteric modulator of $GABA_A$ receptors, which means it will potentiate GABA-mediated inhibition. It does so by increasing the frequency and duration of channel opening (Gąsior et al., 2024). But direct activation of chloride flux was observed at higher concentration of ganaxolone (Nohria & Giller, 2007). Upon the administration of a ganaxolone oral suspension, it took 2-3 hours to reach maximum plasma concentration. When ganaxolone was administered after a high-fat meal instead of fasted condition, the C_{max} and AUC were found to be at least 3- and 2- fold higher. A bimodal elimination occurs with a terminal half-life that is set at 34 hours. Ganaxolone has a complex metabolism process, CYP3A4, CYP2B6m CYP2C19 and CYP2D plays a crucial role in its biotransformation. For example, if ganaxolone is taken together with a strong CYP3A4 inducer like rifampin, it was observed that the C_{max} of ganaxolone reduced by 57% and the AUC had reduced by 68% (De, 2024). It was approved by USFDA in March 2022 for the treatment of seizures caused by cyclin-dependent kinase-like 5 deficiency disorder (CDD). It can be used in patients of age 2 and above. It is the first approved treatment for

seizures associated with CDD and is being further investigated for the treatment of tuberous sclerosis complex-related epilepsy and other forms of epilepsy (Lamb, 2022).

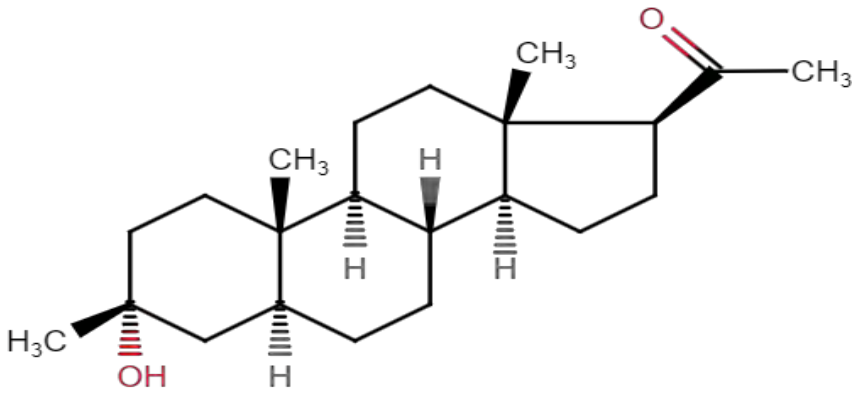

Figure 17: Chemical structure of ganaxolone

Chapter 3: Methodology

3.1 Study selection for introduction

For information collection for introduction portion of the article, multiple online databases were utilized. PubMed, ScienceDirect, Wiley Online Library and SpringerLink were the databases primarily used to extract information. The search for information took place in the month of January in 2024. CDKL5 deficiency disorder was first discovered in 2004 and the knowledge of epilepsy is constantly evolving, keeping this in mind, article published from 1999 were only considered. Articles in English were only considered for this study. The search strategy was based on searching for relevant information using the above-mentioned databases and the sub-headings used in this article were primarily used as search terms. The search terms included ‘epilepsy’, ‘etiology of epilepsy’, ‘symptoms of epilepsy’, ‘pathophysiology of epilepsy’, ‘types of epilepsy’, ‘existing treatments for epilepsy’, ‘limitations of current anti-epileptic drugs’, and ‘CDLK5 deficiency disorder’. From a large collection of articles, only the ones with most updated information and most relevant for the intended article were chosen.

3.2 Study selection for Ganaxolone clinical trial

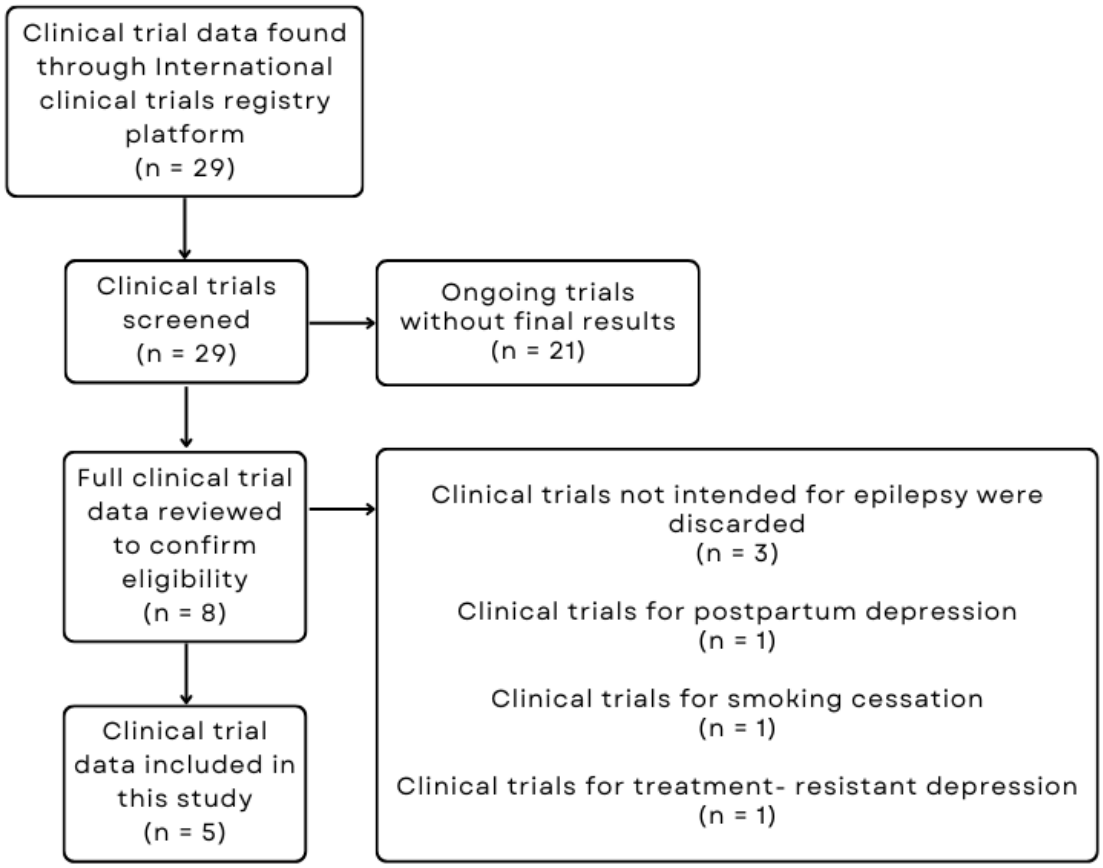

Figure 18: Search criteria for ganaxolone clinical trial data

The aim was to collect a minimum of five clinical trial data for the drug of interest which is ganaxolone. The international clinical trials registry platform was used and the search term 'ganaxolone' was used to search for available clinical trial data. The search strategy has been fully explained in Fig 17. Five clinical trial data was fulfilled the eligibility criteria and all five of them have been chosen. No further database was searched as the requirement for the number of clinical trial data was met.

3.3 Study selection criteria

3.3.1 Inclusion criteria

Clinical trials meeting the inclusion criteria have been selected for this study. Following are the inclusion criteria:

1. Patient from any age group regardless of any prior use of anti-epileptic medications.
2. A minimum of 10 patients administered with ganaxolone.
3. Full clinical trial data available.
4. Ganaxolone used as the therapeutic intervention.
5. Any dosage form can be used.
6. Efficacy of the drug tested for epilepsy.
7. Change in seizure frequency, time to cessation of seizure used as endpoints.

3.3.2 Exclusion criteria

Clinical trials falling under the exclusion criteria have been discarded and have not been used for this study. Following is the basis of exclusion:

1. Any use of combination therapy.
2. Use of the drug for any other indication than epilepsy.
3. Ongoing clinical trials, clinical trials stopped mid-way or clinical trials with partial data available.
4. Change in seizure frequency or time to cessation of seizure data not available.

Chapter 3: Results and discussion

3.1 Results

Table 1: Clinical trial data of ganaxolone

Patient No.	Disease	Intervention	Dose	Primary/ Secondary Endpoints	Side Effects	Reference
29 (10 patients given ganaxolone)	PCDH19-Related Epilepsy	Ganaxolone and placebo	50mg/ml	Primary endpoint: Median % change in number of seizures was -61.52. Median % change in number of seizures for subjects in the biomarker-positive stratum is -35.90.	Psychogenic seizure, constipation, dental caries, diarrhoea, eructation, fatigue, upper respiratory tract infection, increase in alanine aminotransferase, protein urine present, decreased appetite, somnolence, ataxia, lethargy, aggression, agitaton, behaviour disorder, insomnia, irritability, restlessness and papule.	https://clinicaltrials.gov/study/NCT03865732

				Secondary endpoint: 50% primary seizure reduction.		
17	Status epilepticus, epilepsy, convulsive status epilepticus and non-convulsive status	Placebo and Ganaxolone	500mg/day, 650mg/day and 713mg/day.	Primary endpoint: no participants required an IV anesthetic drug within the first 24 hours after giving the drug. Anesthetic drugs are a third line treatment for status epilepticus. Secondary endpoint: Number of patients without recurrence were counted. The median time to cessation was also	Sepsis, pneumothorax, sedation, loss of consciousness, intestinal perforation.	https://clinicaltrials.gov/study/NCT03350035

	epilepticus			counted – Low dose: 5 Medium dose: 5.580 High dose: 10.16 The seizure burden (%) baseline and percentage change from baseline by time point was given.		
26	Drug resistant partial onset seizure	Ganaxolone	Up to 1800mg	Primary endpoint: -41.86 and 44.913 are the mean and standard deviation respectively for the percent change from baseline in seizure frequency after 28 days.	Pulmonary embolism	https://clinicaltrials.gov/study/NCT02519439

				Secondary endpoint: 53.8% volunteers showed a 50% or greater decrease in seizure frequency.		
30 (7 in CDKL5 group)	PCDH19 epilepsy and other rare genetic epilepsies	Ganaxolone	N/A	Primary endpoint: at 91 days, there is a -31.23 (mean) percentage of change of frequency. It has a standard deviation of 41.438. Mean and standard deviation at week 26 were -20.55 and 60.588 respectively for percentage of change of frequency.	Seizures and rash.	https://clinicaltrials.gov/study/NCT02358538
101 (49 given ganaxolone)	CDKL5 deficiency disorder	Ganaxolone and placebo	50mg/ml 3x/day for 17 weeks.	Primary endpoint: 54.00 is the baseline median seizures per day and 17 week-post baseline the median is 45.03. For placebo, it was 49.17 and after 17 weeks, it was 55.50.	Bronchitis, rhinovirus infection, urinary tract infection, oxygen saturation decreased, food refusal, pneumonia aspiration, irritability and nervous system disorders such as somnolence, seizures and sedation.	https://clinicaltrials.gov/study/NCT03572933

				Secondary endpoint: at baseline, for ganaxolone the mean and standard deviation were 22.57 and 25.761 respectively for percent of seizure-free days. This changed to 32.29 and 30.615 after 17 weeks. For placebo, at baseline 30.32 was the mean and 27.070 was the standard deviation for percent of seizure-free days. It changed to a mean of 36.17 and a standard deviation of 30.932 at 17 weeks.		

3.2 Discussion of clinical trial results

A phase 2 clinical trial was conducted (ClinicalTrials.gov registration no. NCT038657320) on 25 female patients (21 were part of the baseline study) between the ages of 1 and 17 in whom a pathogenic variant of the PCDH19 gene was confirmed. It was a double-blind trial and the patients would go through a baseline period before they were randomized to receive either ganaxolone or a placebo for 17 weeks in addition to the medication they were already receiving for PCDH19 related epilepsy. The patients who qualified from this phase were then taken into the open label study. Reduction in seizure frequency was observed as the primary endpoint and non-seizure related endpoints were assigned as secondary endpoints of the study. At the end of the double-blind 17-week period, the median % change seizure frequency was -23.97 and -61.52 for placebo and ganaxolone respectively. The inter-quartile range for placebo was -88.24 to -4.89 and for ganaxolone it was -95.85 to -33.40. The secondary outcome tells us that 36.4% of the participants in the placebo group experienced a 50% or greater reduction in seizure frequency whereas, 50% participants experienced a 50% of greater reduction in seizure frequency in the ganaxolone group. From these observations, we can deduce that ganaxolone is considerably better at alleviating seizures which is a core symptom of epilepsy. In the placebo group, 45.45% exhibited serious adverse effects and only 10% participants had serious adverse effects from the ganaxolone group. Additionally, no deaths occurred during the trial.

Another phase 2 trial (ClinicalTrials.gov registration no. NCT03350035) was conducted on participants who were 12 years or older. Males and females both could participate in this trial. This study evaluated the safety, tolerability and efficacy of ganaxolone when it is administered by intravenous infusion (IV). It was a double-blind, randomized and placebo controlled clinical trial. The primary outcome of this study checked the number of patients who required an IV anaesthetic drug for the treatment of status epilepticus (SE). The key outcome which can be observed for this study was the secondary outcome that calculated the time to cessation of SE

which was observed up to 24 hours. The patients in this study were divided into three groups depending on the dose of ganaxolone. 5 patients were given a low dose which was 500mg/day, 4 patients were administered with a medium dose which was 650mg/day and a high dose of 713 was given to 7 patients. Participants were only included in the study if a seizure was confirmed. For low dose ganaxolone, the median time to SE cessation was 5 minutes with a range of 2.45 to 6.05 minutes. For medium dose ganaxolone, 5.580 minutes is the median time to SE cessation and a range of 4.18 to 22.25 is observed. Lastly, 10.16 minutes was the median time for SE cessation with high dose ganaxolone and a range of 1.34 to 241.00 was observed. A 40% all-cause mortality rate was observed in the low dose ganaxolone group and the rate was 12.5% for the high dose ganaxolone group. Serious adverse effects were faced by the participants in this trial, 40%, 50% and 25% patients respectively from the low, medium and high dose ganaxolone group suffered from it. Significant adverse effects were observed in this trial but ganaxolone was successful in bringing cessation to SE. It took least time for low dose ganaxolone to cause cessation of SE, which was 5 minutes. In addition, none of the dosage groups required any intervention with anaesthetics which is a third-line treatment for SE. This proves that ganaxolone may be used alone for the prevention and treatment of epilepsy and does not necessarily need to be an adjuvant drug as seen in the previous trial (ClinicalTrials.gov registration no. NCT038657320).

Contrary to the previously discussed trials, this is a phase 3 trial which was conducted (ClinicalTrials.gov registration no. NCT02519439) on 26 patients of the age 18 and above. This is a follow-on open label extension study which lasted for 2 years. The primary outcome of the study measured the percent change from baseline in 28-day seizure frequency and the secondary outcome measured the number of participants who showed a 50% or greater reduction in 28-day seizure frequency from baseline. The dose in this clinical trial was based on tolerability and response. According to the primary outcome, -41.86 was the mean change

in seizure frequency from baseline in 28 day and the standard deviation was 44,913. The secondary outcomes outline that 53.8% participants exhibited a 50% or greater reduction in 28-day seizure frequency from baseline. A reduction of 50% or more in seizure frequency was also shown in 50% of the participants in the clinical trial (ClinicalTrials.gov registration no. NCT038657320) for PCDH19 related epilepsy patients. On the other hand, this trial focusses on drug resistant partial onset seizures, it has a great seizure frequency reduction rate and it also provides evidence that ganaxlone is able to relieve different forms of seizures and has potential to treat different types of seizures. Serious adverse effects were only faced by 3.85% participants.

A trial was conducted on female children with a mutated variant of the PCDH19 gene. They exhibited types of genetic epilepsies. It was a phase 2 trial with a participant enrolment of 30. It is an open label trial where ganaxolone was used as an adjuvant. The participants may be male or female and their ages must be between 2 to 18. Their eligibility criteria were not only limited to PCDH19 gene related epilepsy but it also included CDKL5; Dravet Syndrome; Lennox-Gastaut Syndrome (LGS); Continuous Spikes and Waves during Sleep (CSWS). Participants were grouped based on the type of epilepsy they were affected by, 7 participants were in the CDKL5 group, 2 had CSWS, 10 had Lennox-Gastaut syndrome and 11 had PCDH19. For the primary outcome, they change in seizure frequency from baseline at day 91, week 26 and week 52 were measured in terms of mean and median. For the purpose of this study, the median changes in seizure frequency from baseline at 91 days will be considered. In the CDKL5 group, a median percent change in frequency of -47.34 was observed, -10.22 was the median percent change in frequency in the Lennox-Gastaut syndrome group, PCDH19 received a median percent change in frequency of -25.98. No data was available for CSWS. The full range for CDKL5, Lennox-Gastaut syndrome and PCDH19 were -80.9 to 36.8, -68.1 to 904.3 and -100 to 723.2 respectively. The mean percentage of seizure free days at day 91

from baseline was calculated as secondary outcome. For the CDKL5 group, the mean percentage change was 11.84 with a standard deviation of 18.472. The Lennox-gastaut group showed a mean percentage change of -1.12 with a standard deviation of 24.928. Lastly, the PCDH19 group had a mean percentage change of 7.87 with a standard deviation of 17.843. A total of 7 participants faced serious adverse effects, 1 from the CDKL5 group, 1 from the CSWS group, 2 from the Lennox-gastaut group and 3 from the PCDH19 group.

The last clinical trial of ganaxolone in this study is a phase 3 trial and an enrollment of 101 participants had occurred. It was a double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment that was carried out of participants between the ages 2 and 21 and who suffers from CDKL5 deficiency. 51 patients were given the placebo and 50 participants received ganaxolone. Both male and female participants took part in the study. Another eligibility criteria were that the patient must have tried 2 or more antiepileptic medications before which have failed to control their seizures. The primary outcome of this study measures the 28-day seizure frequency for major moto seizure types. The baseline median for placebo was 49.17 (seizures per day) with a 95% confidence interval of 32.20 to 60.67. The baseline median for ganaxolone was 54 and the 95% confidence interval for ganaxlone was 38.24 to 106.67. In the 17-week post baseline phase, the median number of seizures per day with placebo was 55.50 and with ganaxolone was 45.03. It can be seen that the number of seizures has reduced by the administration of ganaxolone hence indicating its effectiveness for the treatment of epilepsy related to CDKL5 deficiency. 9.8% participants from the placebo group sufferd serious adverse effects and the value was 12% from the ganaxolone group.

3.3 Evaluation of the usefulness of the drug

The use of IV ganaxolone in a phase 2 trial (ClinicalTrials.gov registration no. NCT03350035) in patients with refractory status epilepticus has been successful. Patients in this trial had previously used benzodiazepines and other medications which are considered second-line treatment but those treatment had failed. SE patients are administered with lorazepam, midazolam or diazepam initially but 30-57% patients fail to respond to these drugs. This means that the patient has established SE and a second-agent has to be tried. Fosphenytoin, valproate and levetiracetam are the drugs of choice but 53-55% of patients also do not respond to these drugs. These patients have refractory status epilepticus. These patients may be put in a coma with long stays in hospital and low chance of returning to baseline clinical function. With refractory status epilepticus, the mortality rate is 35% and among those who survive, neurological disorders are common. An IV anaesthesia would be the next choice but the risk of these drugs outweighs the potential benefits therefore, ganaxolone was used. Patients who have status epilepticus after 24 hours of IV anaesthesia administration, they are said to have super-refractory status epilepticus. 65% of the patients in this trial had nonconvulsive SE and used a median of three anti-seizure medication previously, all of which failed. The median time to cessation was 5 minutes after the administration of IV ganaxolone. No patients had to be injected with IV anaesthetics in this study. The deaths that had occurred during the trial, none were found to be related to the use of ganaxolone. Ganaxolone was able to rapidly control seizures in patients with refractory status epilepticus and it had also exhibited great safety and tolerability. It proved itself as a great alternative to IV anaesthetics which can cause complications such as infections, hypotension, organ failure and increased mortality. A new treatment option that immediately prevents status epilepticus and maintains any further seizures was needed as refractory status epilepticus treatment can be expensive, a third-line anaesthetic may be risky and to prevent super-refractory status epilepticus from forming. In pre-clinical

models, ganaxolone had shown anticonvulsant activity in treatment-resistant status epilepticus without developing any tolerance. Ganaxolone has great potential to be a drug of choice for patients with refractory status epilepticus with acceptable and better safety and tolerability profile compared to IV anaesthetics. The results of this trial are significant in that many patients in this trial had failed benzodiazepine and other second-line treatments but ganaxolone was about to cause seizure cessation within 5 minutes. The other significant clinical outcome is that no patient had to be put on anaesthetics which open new possibilities for safer treatments with greater efficacy which is not reduced with time. The adverse effects often can be serious with the use of anaesthetics, IV anaesthetics may cause respiratory depression, cardiac arrythmias, QT prolongation, propofol infusion syndrome among others (Vaitkevicius, Ramsay, Swisher, Husain, Aimetti, & Gąsior, 2022b).

A phase 3 trial with 101 eligible patients (ClinicalTrials.gov registration no. NCT03572933) was conducted. -30.7% was the median percentage change in 28-day major motor seizure frequency with ganaxolone and in the placebo group (p=0.0036) it was -6.9%. 27,1% was the Hodges-Lehmann estimate of median difference in responses between the two arms of the trial (95% Cl -47.9 to -9.6). Somnolence, pyrexia and upper respiratory tract infections occurred more often in the ganaxolone group and occurred at least in 10% of patients. CDD associated seizures have to approved treatments and this trial has shown that ganaxolone was able to greatly reduce the frequency of CDD associated seizures in comparison to placebo and showed great tolerance. Pestana-Knight et al. (2022) claims this to be the first clinical trial that suggests a potential clinical benefit of using ganaxolone in CDD associated seizures. This potential clinical benefit is being further investigated in an extension of this trial (Pestana-Knight et al., 2022).

Currently, there are limited publications are available discussing the total summary of the use of this drug. This article may help clinicians in the future and may act as a starting point. Within

the limited trials and results available, ganaxolone is showing great promise as an anti-seizure medication. Epilepsy is a heterogenous disease which consists of many types, analysing the results it can be concluded that ganaxolone has been shown to be effective against refractory status epilepticus, CDD associated seizure and PCDH19 related epilepsy. It also is a better alternative than some of the existing drugs such as anaesthetics which have life-threatening side effects. People who were resistant to multiple medications have responded to ganaxolone in the trials with adequate alleviation of seizures. Ganaxolone showed greater tolerability and its effects did not diminish with time. Ganaxolone also does not cause cognitive disabilities in patients who use them, this is a concern with some of the other anti-seizure medications (Yawno et al., 2017). Cognitive issues mean having trouble thinking, paying attention remembering and concentrating in daily activities and because of these reasons some patients may refuse to take anti-seizure medications (Mutanana et al., 2020). The older generation anti-seizure medications are highly susceptible to drug-drug interactions which is less of an issue with the later generations and ganaxolone (Johannessen & Landmark, 2010). Ganaxolone is indicated for CDD associated epilepsy and is a first drug in its class. Ganaxolone has also been used to treat neonatal seizures, replacing phenobarbitone. Phenobarbitone is used as there is a lack of other options but it has great potential to cause side effects. Often, the risks associated with phenobarbitone forces physicians to delay the use of the drug and this can cause further complications, the availability of ganaxolone can mitigate these risks and any risks associated with brain development (Yawno et al., 2017).

Chapter 4: Conclusion

4.1 Limitations

Following are the limitations of this study:

- There are not many clinical trial data available for this drug. Among those that are available, most are phase 2 clinical trial data. The participant count is very low for any phase 3 clinical trial data that is available.
- Epilepsy is a heterogenous disease which has various different causes and pathophysiology. Finding trials for the same type of epilepsy with the same baseline is not always possible.
- Multiple trials with the same endpoints cannot be found. This makes it difficult to directly compare different clinical trial data and make an analysis on their effectiveness.
- In some trials there is a lack of randomization and no comparator arms are available.
- Proper statistical analysis could not be conducted. A proper analysis with adequate data would ensure the reliability of results.

4.2 Future studies

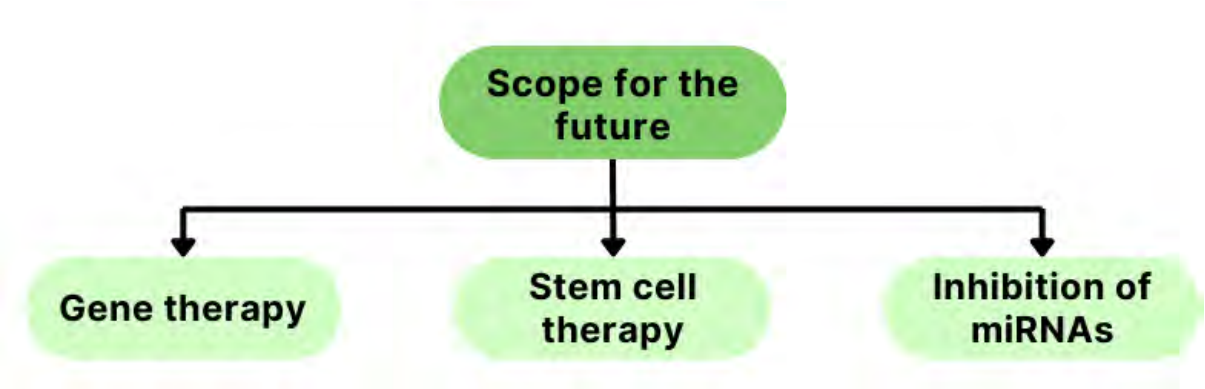

Figure 19: Scope for the future

More trials need to be carried out to find out whether this drug is broad-spectrum or a narrow-spectrum drug and trials including more participants also need to be conducted. More publications discussing and analysing the results of the clinical trials to establish its efficacy is also necessary. CDKL5 deficiency disorder is a disease that occurs due to a genetic defect. The epilepsy caused by this disorder has a genetic cause and therefore ganaxolone will only be a preventive method. Research in areas mentioned in Fig 18. could bring about groundbreaking change and help patients reduce seizure frequency drastically. A deep understanding of the pathogenesis of epilepsy along with continuous research in the mentioned area could shade some light in to the possible cure for this form of epilepsy.

Most of the current anti-epileptic drugs target ion channels or neurotransmitter systems. It is reported that about 30-40% patients will not respond appropriately to medication and 80% will face adverse effects due to the medication will cause them to stop the drug or non-adherence. As a result, there is a desperate need for novel therapeutic approaches to treat epilepsy and gene therapy has made great advances in the recent past. Gene therapy works by inserting genetic material into target cells and fixing the genetic defect which establishes normal physiological function. It is still far from gaining marketing approval but the following has had success in animal models: overexpressing inhibitory neuropeptides and modulating the expression of neurotransmitters or ion channels.

A second approach is through antisense oligonucleotides, it is used as an intracerebral injection to inhibit targeted MicroRNAs (miRNAs). miRNAs are small noncoding RNAs that are able to inhibit translation of mRNA and can be used a novel therapeutic approach for epilepsy. Currently, there are evidence of about 10-20 miRNAs being dysregulated which have a direct effect on seizures (De Vera-González, 2022).

Often prolonged seizures may cause neuronal damage, astrocyte activation, the formation of reaction oxygen species and mitochondrial dysfunction. In this case, stem cell therapy could be useful and it has been considered as a novel therapeutic strategy for treating epilepsy. Its regenerative properties are what makes it very promising and it is expected that this could provide patients with long term seizure control especially in patients who are considered to be drug resistant (Chang & Chang, 2022).

4.3 Conclusion

Ganaxolone is a new drug which has shown to be effective in certain types of epilepsy including CDD associated seizures, refractory epilepsy where patients suffered from drug resistant. Ganaxolone has reduced severity of epilepsy in patients where other medications had failed. This is the first drug which can be used against CDD associated seizures. The clinical trials showing promise were conducted in limited population. The sample size of the trials has to be increased and it has to be determined whether this drug can act as a broad-spectrum drug or not. Ganaxolone has exhibited greater efficacy in some cases and its safer than the standard drugs used to treat epilepsy. With more trials and safety and efficacy data, in the near future it may be able to replace drugs that carry considerable risks compared to its benefits.

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