ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR503

Anxiety and Epilepsy: Current Understanding and Future Perspectives

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Abstract:- Anxiety is characterized as an overwhelming sense of worry or fear for the future, while epilepsy is a chronic neurological condition. Both anxiety and epilepsy are prevalent conditions that impact individuals globally and are associated with diminished function and life quality. This review article explains about the treatment, etiology, pathophysiology, current advances and neurological relationship between anxiety and epilepsy. Previous research suggests that anxiety disorders are widespread and clinically relevant comorbid diseases in epilepsy patients because anxiety can cause seizures or seizures may cause anxiety. To treat anxiety and epilepsy, a thorough, multidisciplinary clinical assessment is required. Medication, lifestyle modifications, and psychotherapy are also required.

Keywords:- *Anxiety, Current Advances, Epilepsy, GABA (Gamma Amino Butyric Acid), Treatment, Pathophysiology.*

I. INTRODUCTION

Anxiety is a state that leads to a heightened sense of threat and a response to it that might include a variety of defensive behaviors [1]. When uncertain danger is imminent, anxiety is a physiological state of distress and restlessness [2]. Anxiety is thought to affect 4.05% of global population [3]. These are the mental health issues that are most common. Pathological anxiety disorders are caused by abnormalities in neural circuits involved in mood and anxiety due to inherited or acquired factors, such as stress. These disorders include five main types of generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder (PTSD), social phobia, and social anxiety disorders [1]. For at least six months, at least three of the following symptoms have been linked to anxiety: restlessness, which includes irritability, tense or agitated sensations, weariness fast, problems concentrating or losing your mind, impatience, tense muscles, and disturbed sleep [4].

II. TREATMENT

Monoamine reuptake inhibition is currently the most effective treatment for moderate to mild chronic anxiety [5]. Selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed family of antidepressants, are the first-line therapies for anxiety disorders; tricyclic antidepressants, buspirone, and pregabalin are also helpful [6]. Benzodiazepines are also frequently used to treat acute anxiety, even though they are useful for the majority of patients. Benzodiazepines do, however, appear to be linked to chemical, physical, and mental dependence. The degree of anxiety disorders determines how effective a treatment plan will be; therefore, it is critical to develop novel therapeutic strategies to lessen the negative effects of anxiety on society and the economic market [7][8][9][10]

- *Recent Advances*

Table 1 Recently Marketed Drugs for Anxiety

S.no	Drug	Treatment	Refs.
1	Agomelatine	Generalized anxiety disorder	11,12
2	Escitalopram	Generalized anxiety disorder	11,12
3	Vilazodone	Generalized anxiety disorder and social anxiety disorder	13
4	Gepirone	Anxiety	14, 15
5	Tandospirone	Generalized anxiety disorder	16
6	Psilocybin	Anxiolytic better in combination with psychotherapy	17, 18

Table 2 Novel Drugs in Clinical Phase [19]

S.no	Drug	Phase	Indication
1	MM – 120	2	General Anxiety Disorder
2	AVN – 101	2	General Anxiety Disorder
3	ACH 000029	1	General Anxiety Disorder
4	Darigabat	1	Panic Disorder
5	Aloradine	3	Social Anxiety Disorder
6	Cannabidiol	3	General Anxiety Disorder
7	RLS103	1b/2a	Social Anxiety Disorder
8	BNC210	2	Social Anxiety Disorder
9	VQW-765	2	Performance anxiety

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR503

➢ *Etiology*

Many biopsychosocial factors seem to contribute to anxiety disorders. Clinically important illnesses arise from the interaction of genetic vulnerability and stressful or traumatic circumstances. Few of the reason anxiety might be caused are as follows

- Prescription medications
- Substance abuse
- Alcoholism
- Trauma
- Early life events
- Stress
- Illnesses like diabetes and epilepsy
- Other comorbidities like depression can all make anxiety worse [20]

III. PATHOPHYSIOLOGY

In the central nervous system, dopamine, serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) are the primary neurotransmitters that cause anxiety. Most symptoms are mediated by the autonomic nervous system, particularly the sympathetic nervous system. The amygdala plays a crucial role in managing anxiety and fright. It has been discovered that the amygdala responds more strongly to alarming stimuli in patients with anxiety disorders. Pharmaceutical or psychological interventions can be used to correct anomalies in prefrontal-limbic activation since the prefrontal cortex is related to the limbic system and the amygdala (20).

Because the amygdala projects to the hypothalamus, which in turn controls the autonomic nerve system, it affects blood pressure, heart rate, and changes connected to stress.

The brain's medial temporal lobe contains the hippocampus, which regulates emotional actions, especially those related to anxiety, in addition to cognitive processes [6]. The diverse ways in which the hippocampus's dorso-ventral axis regulates anxiety and cognitive functions help to explain these unique roles [21]. There is mounting evidence that the ventral hippocampus plays a major role in the processing of anxiety. Higher levels of anxiety and higher levels of hippocampus activity have been linked in previous research [6].

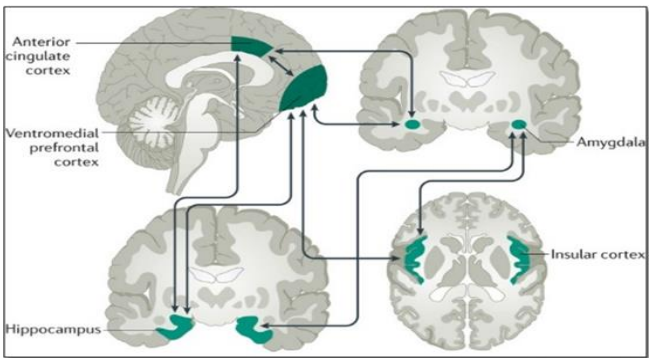

Fig 1 Pictorial Representation of the Parts of Brain that Influences the Anxiety [22]

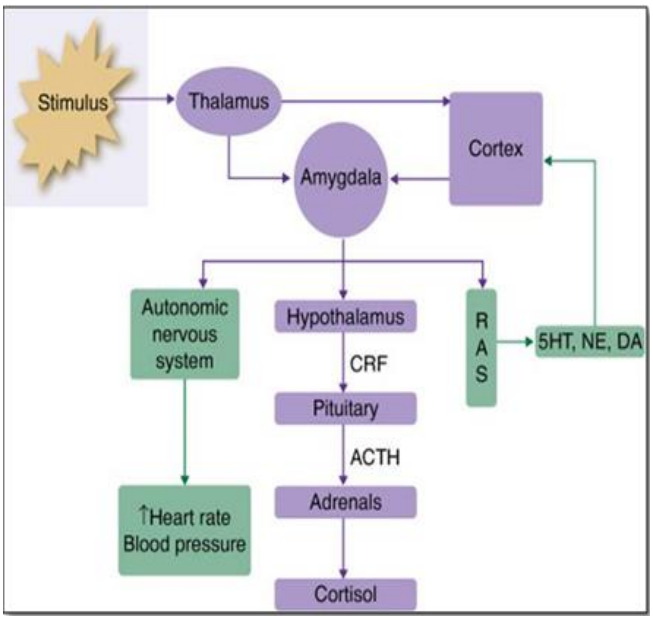

Fig 2 Pathophysiology of Anxiety [23]

➢ *Introduction*

Epilepsy, a chronic neurological illness, are seizures, which are recurrent paroxysmal clinical events. These seizures are brought on by an abnormal and hypersynchronous discharge of a group of brain neurons [24]. According to a World Health Organization research, epilepsy contributes almost seven million years of disability-adjusted life years to the worldwide sickness burden, making it a major cause of impairment [25]. Among the most common symptoms of epilepsy patients are staring, jerking, uncontrollably jerky movements, sudden falls, perplexity, aura, strange feelings and sensations, loss of consciousness, and concern [26].

➢ *Treatment*

Topiramate, lamotrigine, and valproic acid are the first-line medications for atonic, atypical myoclonic, and primary generalized tonic clonic seizures. These include valproic acid, oxcarbazepine, carbamazepine, and phenytoin for partial seizures. These include ethosuximide and valproic acid for absence seizures [27].

Numerous studies and research findings indicate that the combination of medications aids in the management of the illness. It has been observed that patients respond to the same medications at various dosages in different ways. This may indeed be the case, since several pathophysiological pathways can present in an individual at any given time. To have better results in this situation, varying therapy modalities would need to be used to varying degrees. The combination of lamotrigine and sodium valproate has been shown in numerous animal models to be effective in treating both partial-onset and generalized seizures. To treat a variety of seizures, lamotrigine and topiramate are another combination that is typically advised, as is valproate and ethosuximide to manage absence seizures[28].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR503

➢ *Recent Advances*

Table 3 Recently Marketed Drugs for Epilepsy

S.no	Drug	Treatment	Refs.
1	Vigabatrin	Infantile spasms and refractory complex partial seizures	29
2	Fenfluramine	Dravet syndrome and LGS	30
3	Cenobamate	Adult partial onset epilepsy	30
4	Cannabidiol	Dravet syndrome	31
5	Valium and nasal midazolam	Rescue therapy	30

Table 4 Novel Drugs in Clinical Trials [32]

S.no	Drug	Phase	Population
1	XEN1101	3	Focal and generalized epilepsy
2	BHV-7000	1	Drug-refractory focal and generalized epilepsy
3	ETX-123	Preclinical	Drug-refractory focal and generalized epilepsy
4	NBI-921352	2	Focal-onset seizures
5	Lacosamide	2/3	Neonates
6	OV329	1	Rare adult and pediatric epilepsies
7	Alprazolam	3	Long or clustering seizures
8	Ganaxolone	4	CDKL5 deficiency disorder (approved), TSC, LGS, refractory Status epilectus
9	NRTX-1001	½	Unilateral drug-refractory mesial temporal lobe epilepsy
10	Brivaracetam	2/3	Absence epilepsy
11	Radiprodil	2b	Pediatric patients with gain-of-function GRIN variants: seizure cohort, behavioral cohort
12	LP352	1b/2ia	DEEs
13	SPN-817	1ia	Adult patients with refractory focal impaired awareness epilepsy

- *Abbrevations:*
  TSC- tuberous sclerosis complex, LGS- Lennox–Gastaut syndrome, DEE- developmental and epileptic encephalopathy

Table 5 Novel Devices for Epilepsy [32]

S.no	Device	Phase	Population
1	EASEE	2	Drug-refractory epilepsy
2	Tdcs	3	Drug-refractory epilepsy
3	EmbarcePlus	FDA approved	Seizure detection
4	EpiCare@Home	CE mark approved	Seizure detection
5	REMI	Ongoing	Seizure detection
6	Epihunter	CE mark approved	Absence seizures

- *Abbrevations:*
  EASEE- Epicranial Application of Stimulation Electrodes for Epilepsy; REMI, Remote EEG Ambulatory Monitoring; tDCS, transcranial direct current stimulation.

➢ *Etiology*

There is a chance for both prompted an unprovoked seizures. Acute symptomatic seizures, also referred to as provoked seizures, can be caused by a variety of diseases. These ailments include tumors or other mass lesions, brain trauma, viral infections, poisonings, and vascular anomalies. Seizures can be brought on by a variety of factors, including problems with nearly any medical condition. The following is a list of some typical causes:

- Disturbances in electrolytes (hypo/hyper calcemia, hypo/hyper natremia)
- Adverse reactions to medications
- CNS infections
- Traumatic head injury
- Hypoxic brain injury
- Ischemic or hemorrhagic stroke
- Sleep deprivation
- Genetics [33]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR503

➢ *Pathophysiology*

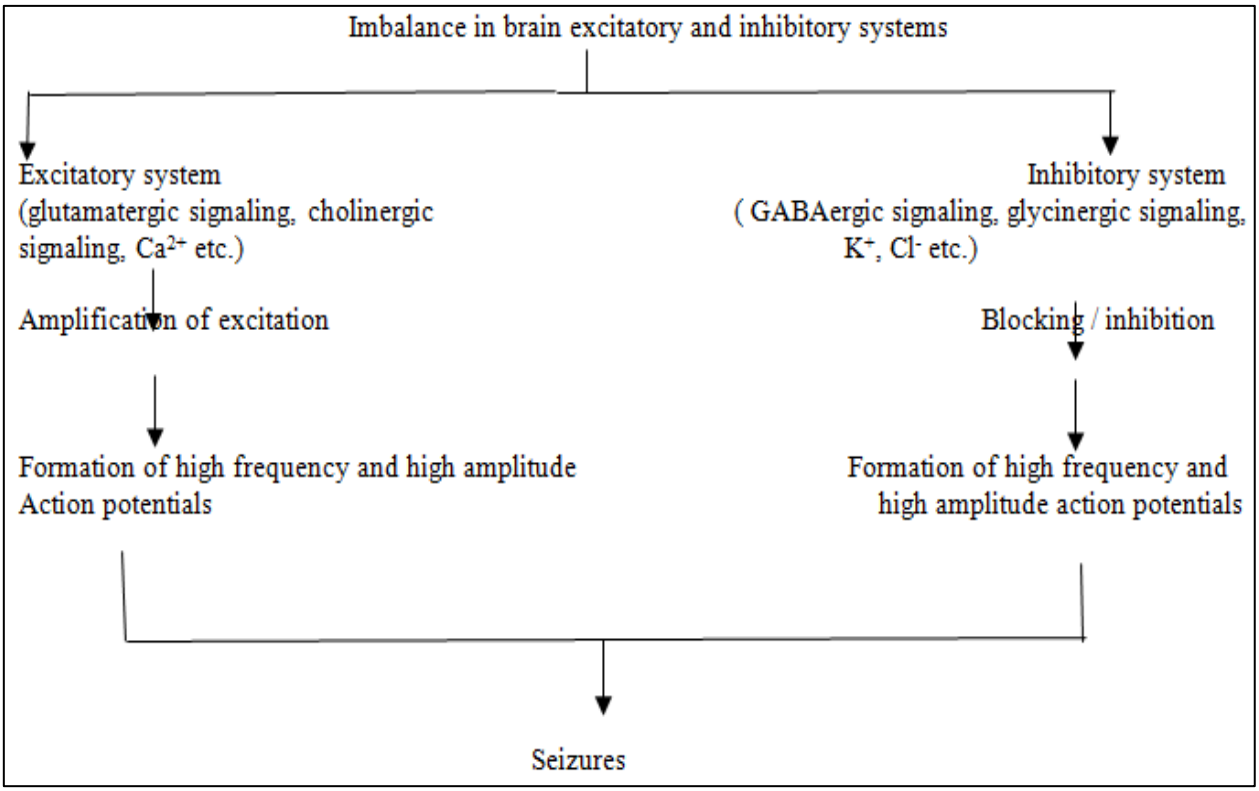

Fig 3 Flowchart of the Pathophysiology of Epilepsy [34]

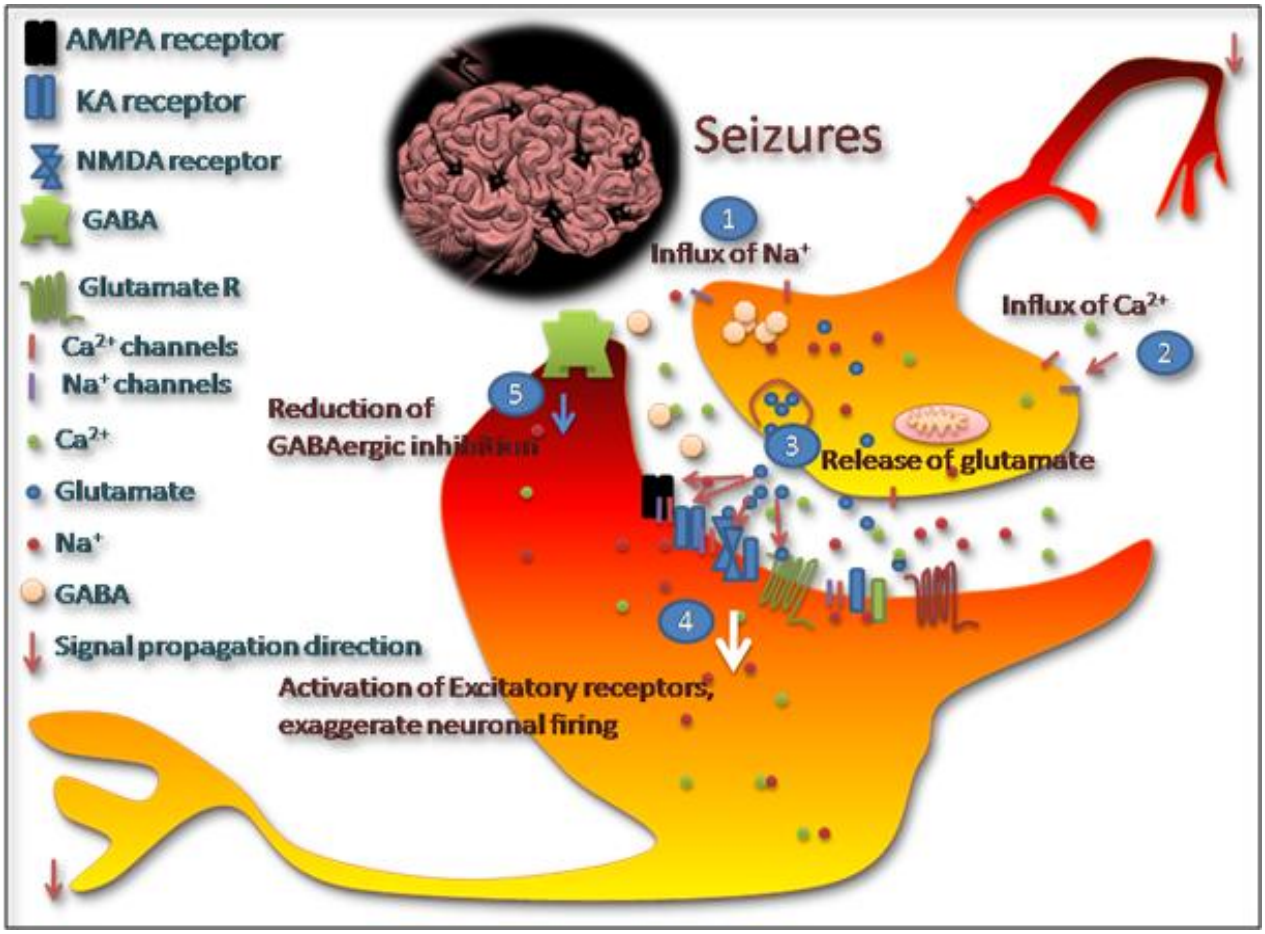

Fig 3 Pathophysiology of Epilepsy [35]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR503

IV. RELATIONSHIP BETWEEN ANXIETY AND EPILEPSY

GABA is predominantly associated with the neurochemical aspect of the neurobiological hypothesis because it is an inhibitory neurotransmitter. GABAergic inhibition failure in the central nervous system is frequently linked to anxiety disorders. For instance, patients with panic disorder exhibit decreased flumazenil binding to benzodiazepine receptors in certain brain areas, indicating down-regulation of these receptors. Interestingly, studies have shown that individuals with hippocampal sclerosis have similar reductions in flumazenil binding to benzodiazepine receptors in their temporal lobes. For those who have epilepsy, this recurrent metabolic imbalance may be a source of anxiety [36]. Epileptics frequently experience anxiety, particularly those who have temporal lobe epilepsy, which results in hyperexcitability in the hippocampus which is also responsible for the anxiety [37].

Preictal anxiety symptoms might manifest hours or days before a seizure. The phrase "ictal panic" describes anxiety symptoms that manifest during the ictal interval, which might be difficult to distinguish from a classic panic attack. Ictal panic or fear is the most prevalent type of simple partial seizures, accounting for 60% of all psychiatric auras and usually presenting as mental symptoms. Anxiety is the most prevalent emotional symptom in the 72 hours that follow a seizure or cluster of seizures. These often occur six to twenty-four hours following the onset of the seizure. It is common for postictal anxiety to coexist with other dysphoric symptoms, such as depression. Anxiety, panic episodes, agoraphobia, and compulsive symptoms are among the possible manifestations [38].

V. CONCLUSION

This review focuses on pathophysiology, etiology, treatment, and current developments related to anxiety and epilepsy. Anxiety and epilepsy coexist due to common neurobiological mechanisms and psychological factors, which significantly lowers the quality of life for the patient. It also discusses the intricate connection between epilepsy and anxiety. Improved knowledge of psychopathology is required for the creation of cognitive behavioral therapies. To enhance the patient's quality of life, prompt diagnosis and appropriate treatment are essential.

ACKNOWLEDGMENTS

The authors are grateful to the Principal Prof. M. Ganga Raju and Management of the Gokaraju Rangaraju College of Pharmacy, for the constant support and encouragement during the course of the work.

- *Conflict of Interest*

Authors doesnot have conflict of interest in the publication of this manuscript.

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