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A Systematic Review Of Lamotrigine, Valproate Sodium, And Levetiracetam: Therapeutic Outcomes In Idiopathic Generalized Epilepsy

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ABSTRACT- Idiopathic Generalized Tonic Clonic Seizures are a common manifestation of epilepsy requiring effective long term management. Lamotrigene, valproate sodium and levetiracetam are commonly prescribed drugs.Lamotrigene is a broad spectrum antiepileptic drug, Evidence suggests that lamotigene effectively reduces seizure frequency while demonstrating a favorable safety profile, while well-tolerated and associated with fewer cognitive and psychiatric adverse effects, demonstrates comparatively lower efficacy in monotherapy for GTCS. Levetiracetam has demonstrated effectiveness comparable to traditional AEDs such as valproate and lamotrigine, with the advantage of minimal drug interactions and a lower risk of cognitive impairment. Levetiracetam, recognized for its favorable pharmacokinetic profile and minimal drug interactions, provides an alternative option, though neuropsychiatric side effects may impact patient adherence. Sodium valproate remains a highly effective first-line therapy due to its broad-spectrum activity, but concerns regarding teratogenicity and metabolic side effects limit its use in certain populations.The findings indicate that VPA remains one of the most effective treatment options for GTCS, particularly when used within an optimal dosage range. This review evaluates and compares the efficacy, tolerability, and these side effect profiles of three commonly prescribed antiepileptic drugs—lamotrigine (LTG), sodium valproate (SV), and levetiracetam (LEV)—in the treatment of adult patients with idiopathic GTCS.

INTRODUCTION-A long-term neurological condition with substantial morbidity is epilepsy. A significant subset of seizures are idiopathic generalized tonic-clonic seizures, which call for lifelong antiepileptic medication. The conventional first-line treatment has been sodium valproate; however, worries about its adverse effects, especially in women who are pregnant, have led to the exploration of substitutes including levetiracetam and lamotrigine. Bilateral, symmetrical convulsive motions and unconsciousness are hallmarks of generalized tonic-clonic seizures. Although valproate and other conventional first-line therapies are successful, there may be tolerability issues. An option with possible advantages in seizure management and neuroprotection is lamotrigine, a sodium channel blocker that also regulates the release of excitatory neurotransmitters. Generalized tonic-clonic seizures are the most severe and incapacitating of the seizure types that are a part of idiopathic generalized epilepsy (IGE). AEDs with shown effectiveness and tolerability are necessary for the long-term, effective therapy of IGTCS. Since it was licensed in 1999, LEV has been extensively researched for its ability to cure GTCS and its broad-spectrum antiepileptic qualities. GTCS is one of the syndromes that fall under the umbrella of idiopathic generalized epilepsy (IGE), which is defined by the occurrence of generalized

seizures. Because of its broad-spectrum effectiveness, sodium valproate is regarded as a first-line ASM for treating these seizures. However, issues with side effects and dosage optimization call for a thorough assessment of its therapeutic application.

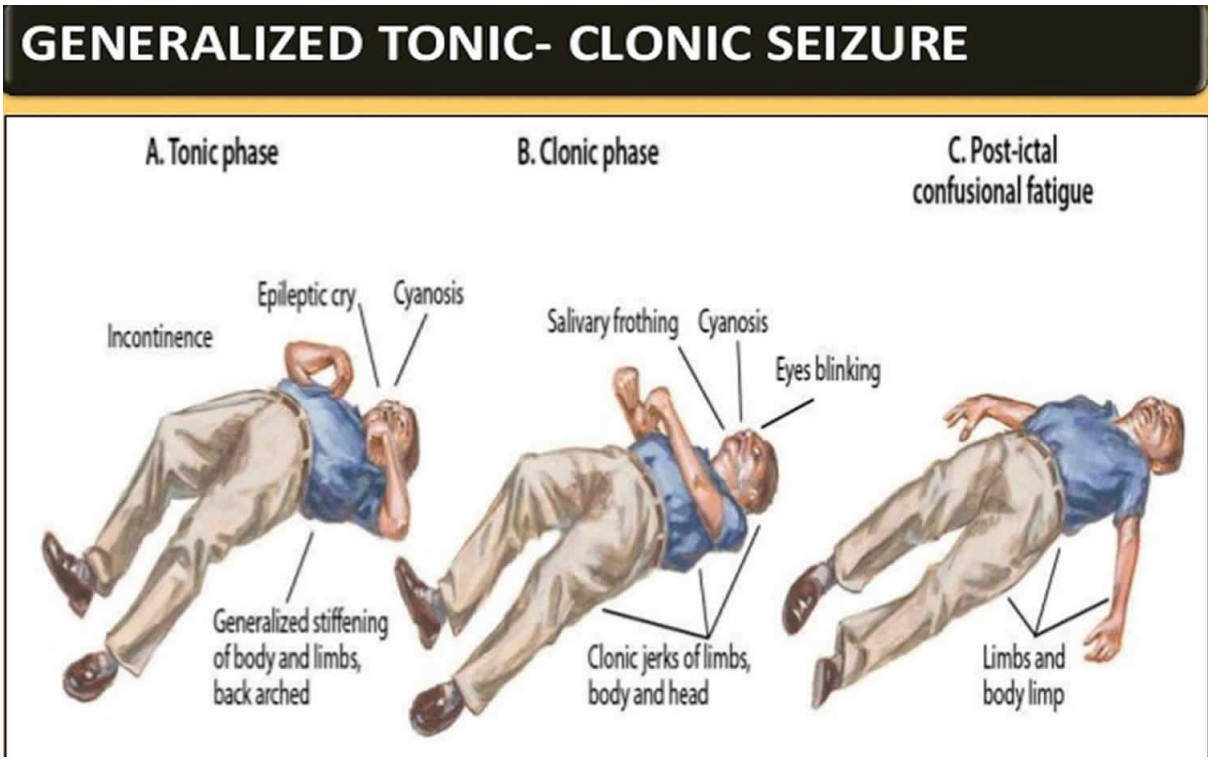

Figure-1

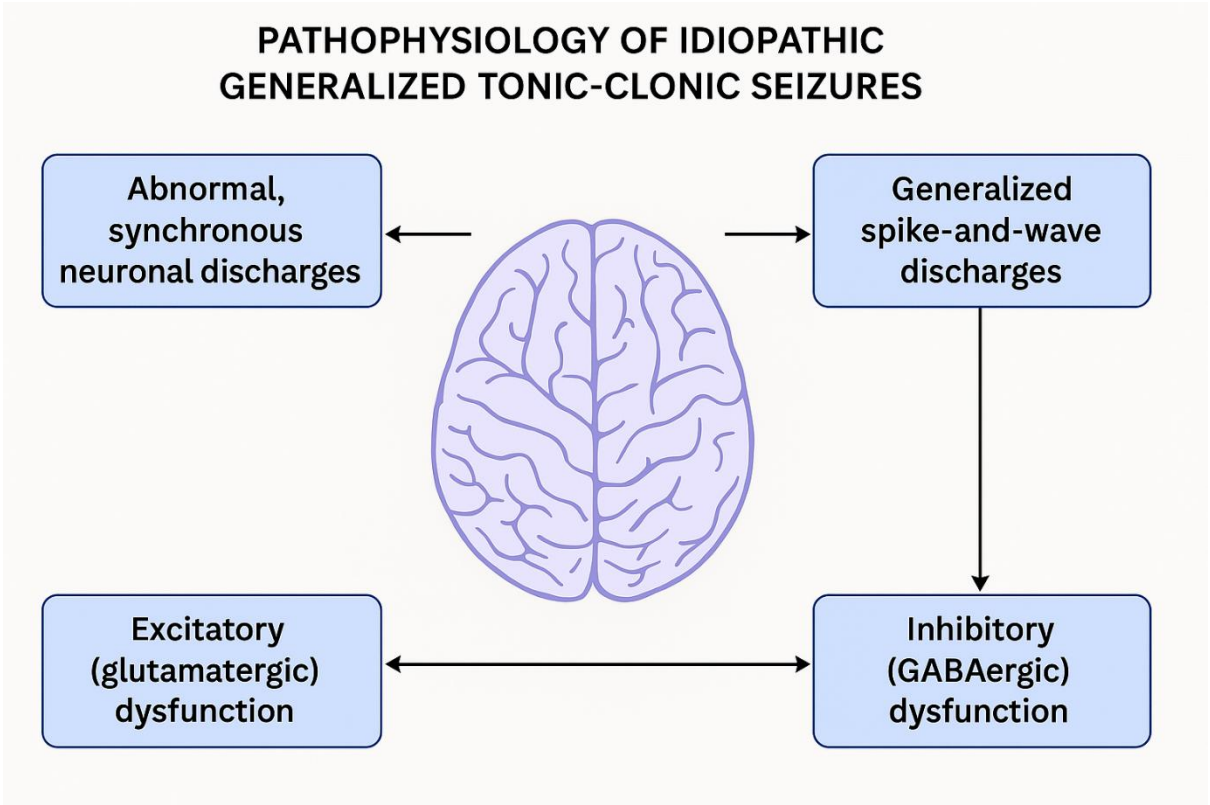

Figure-2

Figure- 2 Represent the Pathophysiology of the communication between brain cells is the fundamental cause of idiopathic generalized tonic-clonic seizures (IGTCS). Signals that stimulate and de-stimulate brain activity are delicately balanced in a healthy brain. This equilibrium is upset in individuals with IGTCS.

1. Excessive excitement Glutamate is a substance that normally aids brain cells in sending "go" signals. However, this mechanism may become hyperactive in IGTCS. This indicates that excessive and rapid firing of brain cells creates the conditions for a seizure.
2.Insufficient inhibition Conversely, another neurotransmitter known as GABA functions as a brake, slowing down as necessary. This brake system malfunctions in IGTCS, making it unable to stop the overexcited signals.
3.The brain's chain reaction: This imbalance—too much "go" and not enough "stop"—causes clusters of brain cells to begin firing in an unusually rhythmic manner. EEGs show these as "spike-and-wave discharges," which resemble an electrical storm sweeping through the brain.
To put it briefly, IGTCS occurs when the brain's communication systems are not in sync, which results in strong electrical activity spikes that trigger seizures. Because the inhibitory brakes aren't functioning and the excitatory gas pedal is locked, it's as if the brain's circuits become overloaded.

Comparison of Lamotrigine, Valproate Sodium, and Levetiracetam

Category	Lamotrigine	Valproate Sodium	Levetiracetam
Mechanism of Action	Blocks voltage-sensitive sodium channels, decreases glutamate release, stabilizes neuronal membranes, has weak receptor interactions (serotonin, dopamine, adrenergic, etc.), and may block Cav2.3 calcium currents.	Enhances GABAergic activity, inhibits sodium channels, activates ERK pathway, depletes inositol, inhibits PKC, disrupts fatty acid metabolism, and inhibits HDAC.	Binds to synaptic vesicle protein 2A (SV2A), modulates neurotransmitter release, weakly affects GABAergic neurotransmission, and blocks N-type calcium channels.
Absorption	Bioavailability: 98%. Peak plasma concentration: 1-1.5 hours (immediate-release), 4-11 hours (extended-release).	Bioavailability: ~90%. Tmax for extended-release tablets: 4-8 hours.	Bioavailability: ~100%. Tmax: ~1.3 hours. Food delays Tmax by ~1.5 hours.
Distribution	Protein binding: 55%. Volume of distribution: 0.9-1.3 L/kg.	Volume of distribution: 1 L/1.73m².	Volume of distribution: 0.5-0.7 L/kg.
Metabolism	Metabolized in liver and kidneys via glucuronidation, forming inactive metabolites.	Primarily metabolized via glucuronidation (30-50%) and mitochondrial β-oxidation (40%).	Minimally metabolized via enzymatic hydrolysis to form an inactive metabolite (L057, ~24%).
Elimination	Clearance: 0.4-1.1 mL/min/kg. Excreted through the kidneys.	Excreted primarily via hepatic metabolism (~90%), <3% excreted unchanged in urine.	66% excreted unchanged in urine; ~24% excreted as L057.
Half-Life	Adults: 25-33 hours; Elderly: 25-43 hours; Hepatic impairment: 26-148 hours; Renal failure: ~43 hours.	13-19 hours (adults); Neonates: 10-67 hours; Pediatric (<2 months): 7-13 hours.	6-8 hours (prolonged in elderly and renal impairment).
Uses	Monotherapy or adjunct therapy for seizures; bipolar disorder mood stabilization.	Monotherapy or adjunct therapy for absence seizures; bipolar disorder; migraine prophylaxis; off-label for status epilepticus.	Adjunct therapy for partial-onset, myoclonic, and generalized tonic-clonic seizures.
Common Side Effects	Vomiting, dizziness, headache, drowsiness, upset stomach.	Diarrhea, dizziness, drowsiness, hair loss, menstrual changes, tremor, weight changes.	Drowsiness, dizziness, headaches, irritability, nausea, blocked nose, itchy throat.
Serious Side Effects	Mood changes, suicidal thoughts, cardiac issues, muscle pain, vision problems.	Liver toxicity, pancreatitis, metabolic disorders, severe fatigue, jaundice.	Worsening seizures, kidney dysfunction, severe mental changes, abnormal behavior.

Category	Lamotrigine	Valproate Sodium	Levetiracetam
Warnings & Precautions	Risk of rash in children, dizziness, drowsiness; avoid alcohol; caution in hepatic/renal impairment.	Risk of severe liver damage (especially in children <2 years); contraindicated in certain metabolic disorders.	Do not stop abruptly; caution in kidney disease, mood disorders, pregnancy, and breastfeeding.
Interactions	Affected by enzyme-inducing drugs and valproic acid; reduces hormonal birth control effectiveness.	Interacts with seizure drugs, antibiotics, warfarin, antidepressants; affects lab tests.	No severe drug interactions; moderate interactions with lurasidone, orlistat, sevelamer.

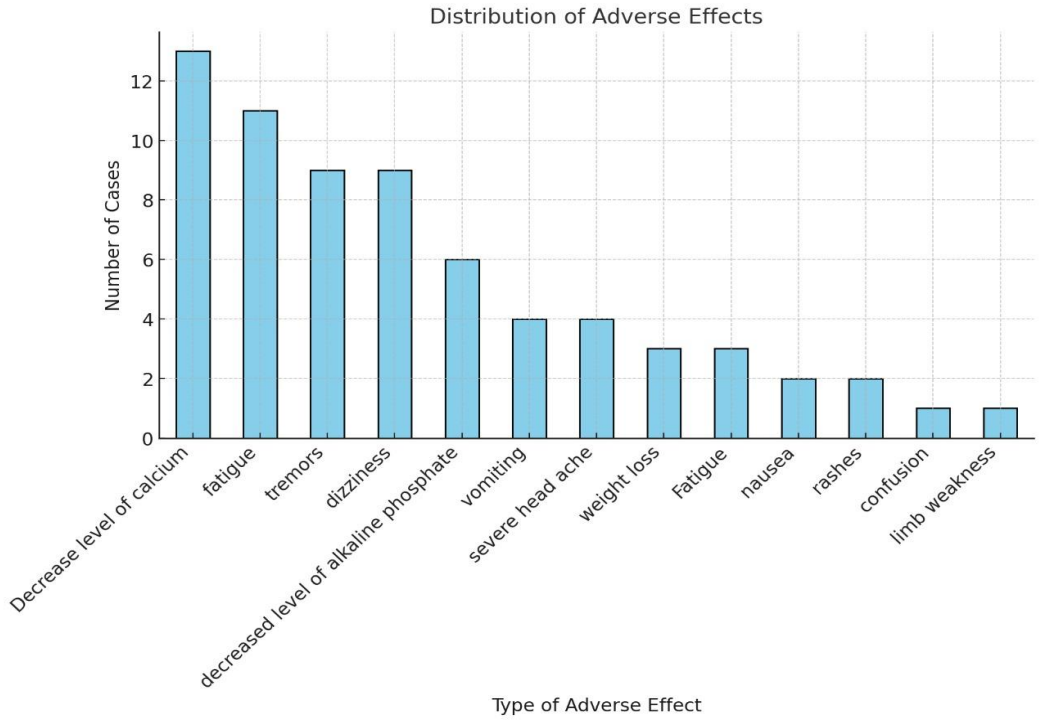

Figure-3

Figure-3 chart really shows why it's important to keep a close eye on both the body's metabolism and brain function in patients receiving treatment. Things like low calcium levels and symptoms such as fatigue, dizziness, and tremors are pretty common, and they can really affect how someone feels day to day. By spotting these issues early and managing them properly, we can help patients feel better and avoid more serious complications down the line.

Efficacy

Lamotrigine (LTG)-Less effective than valproate and levetiracetam in seizure control.Higher failure rate in managing generalized seizures, especially myoclonus.Often employed as an alternative if valproate is not appropriate.

Valproate Sodium (VPA): The most efficacious antiseizure drug (ASM) for generalized epilepsy, including Idiopathic Generalized Tonic-clonic seizures.Better in suppression of myoclonic and generalized tonic-clonic seizures.76.67% of patients on valproate remained seizure-free after 12 months in one study.In another study, valproate was found to be much superior to lamotrigine, but comparable with levetiracetam.

Levetiracetam (LEV)-Shows similar efficacy to valproate in controlling GTCS.More effective than lamotrigine in juvenile myoclonic epilepsy (JME) and generalized epilepsy.Preferred over valproate in women of childbearing age because of lower teratogenic risks

Tolerability

Lamotrigine-Better tolerated than valproate but more frequently fails to control generalized epilepsy .Rash and skin reactions, including severe Stevens-Johnson syndrome, are common problems.

Valproate sodium-Linked with dose-dependent side effects, such as weight gain, hair loss, tremor, endocrine disturbances, and metabolism .Contraindicated in pregnancy because of high teratogenic risks.Some patients are not able to tolerate its side effects.

Levetiracetam-Usually well tolerated with fewer drug interactions.Tiredness and occasional behavioral disturbances are the most common side effects.Used in preference for patients who develop unacceptable side effects with valproate.

Side Effects

Lamotrigine-Common: Rash, nausea, dizziness
Severe: Risk of Stevens-Johnson syndrome, higher seizure failure rate
Valproate-Common: Weight gain, hair loss, tremor, nausea
Severe: Liver toxicity, teratogenicity, cognitive impairment in children if taken during pregnancy
Levetiracetam-Common: Fatigue, dizziness, behavioral issues (aggression, irritability)
Severe: Rare psychiatric effects, mood disturbances

Clinical Implications and Practice and Future Research Recommendations

Based on the evidence, valproate is the first-line treatment for GTCS because of its greater efficacy. However, its most significant side effects, especially in childbearing women, render levetiracetam a more appropriate choice in this group. Levetiracetam is also an appropriate choice in intolerant patients to the metabolic side effects of valproate. Lamotrigine, though better tolerated, is less effective and can be used in situations where valproate and levetiracetam are contraindicated.An individualized regimen should be judiciously initiated, with due consideration of different comorbidities in a patient, lifestyle habits of an individual, and possible interactions between different drugs. Future research efforts should also involve head-to-head comparisons of these drugs in different patient subgroups to get additional information, and the attainment of long-term safety data, which is essential to control seizures to the best of one's abilities.

Conclusion- Among the three antiepileptic drugs—sodium valproate, lamotrigine, and levetiracetam—sodium valproate still stands out as the most reliable option for long-term seizure control in adults with idiopathic generalized tonic-clonic seizures. When taken in a sustained-release form, it helps maintain steady drug levels in the body due to its longer half-life, which in turn lowers the chances of seizures coming back. This makes it a strong choice for patients who need consistent, ongoing management of their condition.

However, levetiracetam and lamotrigine have been demonstrated to act more quickly, which makes them suitable options for patients who require seizure relief more quickly. Both have short-term, highly effective effects, despite their shorter duration. Levetiracetam is particularly appropriate for women who are pregnant or intend to become pregnant because it carries a significantly reduced risk of birth malformations than sodium valproate. They also generally have less adverse effects.

Ultimately, the needs of the individual should guide the selection of the appropriate medication. While some people might need something that provides better long-term control, others might benefit more from a fast-acting solution. It is important to consider factors such as lifestyle, other health conditions, and side effects. By taking these factors into account, medical professionals can create safe and efficient treatment programs for each patient with generalized tonic-clonic seizures.

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