International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

A Comphrehensive Review on Lamotrigine

[1]Mr. Sumedh Paralkar, [2]Dr. Yogesh Thorat, [3]Dr. BalkirshnaTiwari, [4]Ms. Sweta Kota, [5] Ms. SnehaKota

[1]*Assistant Professor,Amepurva Fourm's Nirant Institute of Pharmacy, Solapur, Maharashtra, India*
[3] *Vice-Principal,Amepurva Fourm's Nirant Institute of Pharmacy, Solapur, Maharashtra, India*
[4, 5] *Student, AmepurvaFourm's Nirant Institute of Pharmacy, Solapur, Maharashtra, India*
[2] *Associate Professor, DSTS Mandal's College of Pharmacy, Solapur*

Submitted: 10-04-2024 Accepted: 20-04-2024

ABSTRACT:
Lamotrigine,is a phenyltriazine derivative and a well-known anticonvulsant medication that has demonstrated effectiveness in preventing mood episodes in adult bipolar I disorder patients. The medication's mechanism of action in bipolar disorder patients may be associated with presynaptic neurons' suppression of calcium and sodium channels, which stabilizes the neuronal membrane.

In two extensive, randomised, double-blind trials spanning eighteen months, lamotrigine medication greatly abated the time to intervention with additional pharmacotherapy or electroconvulsive therapy for any new mood episode (mania, hypomania, depression, and mixed episodes), relative to placebo. Lamotrigine also had a considerably longer time to depression intervention compared to a placebo. Patients who had experienced recent manic/hypomanic episodes as well as depressive episodes showed these effects of lamotrigine. Pooled data only demonstrated that lamotrigine was effective in postponing manic/hypomanic episodes; nevertheless, lithium outperformed lamotrigine in this regard.Lamotrigine is superior to placebo in two out of four short-term, double-blind trials when treating patients with treatment-refractory bipolar disorder or bipolar depression. There is no evidence that lamotrigine is effective in treating acute manic episodes.To reduce the risk of severe rash, lamotrigine dosage is titrated over a 6-week period to 200 mg/day. When used in conjunction with carbamazepine or valproate semisodium, modifications to the starting and goal dosages are necessary.[1]

INTRODUCTION:

Lamotrigine development was predicted to have been developed for a fraction of the price of vigabatrin. Operated a little sooner, but it was beset by issues with possible demyelination in animal models. Lamotrigine was synthesized as one of a series of folic acid antagonists, and its mechanism of action was originally believed to be connected to the theory that folate was a proconvulsant. Lamotrigine, however, primarily functions by blocking the release of excitatory amino acids, which stabilizes neuronal membranes by means of voltage-sensitive sodium channels.one of the Welcome scientists who worked on the drug's development, AW Peck, reported on the clinical pharmacology of Lamotrigine.

Lamotrigine pharmacokinetics and pharmacodynamics were investigated in participants who were in good health. Anlamotrigine dose of 240 mg resulted in peak plasma concentrations of in an open dose-escalating trial about 3 lg/mg without causing any noteworthy side effects. Further pharmacokinetic investigations demonstrated total oral absorption, first-order kinetics with an approximate half-life of a day, and a primary excretion pathway shown as a glucuronide in the urineEarly epilepsy patient studies showed that patients who received enzyme-inducing AEDs had faster metabolisms, while those who received VPAs had slower metabolisms. According to these investigations, lamotrigine possesses desirable pharmacokinetic characteristics that are able and reliable. Absence of pharmacological and dynamic effects indicates a high therapeutic index.Since Lamotrigineglucuronidation route shares an enzyme system with phenytoin, lamotrigine dosages should be increased when combined with phenytoin, but decreased when VPA is present.[2]

One prescribed medication is lamotrigine. Orally disintegrating pills (which dissolve on the tongue), chewable tablets, immediate-release oral tablets, and extended-release oral tablets are the four types available for oral administration. Lamictal, Lamictal XR (extended-release),

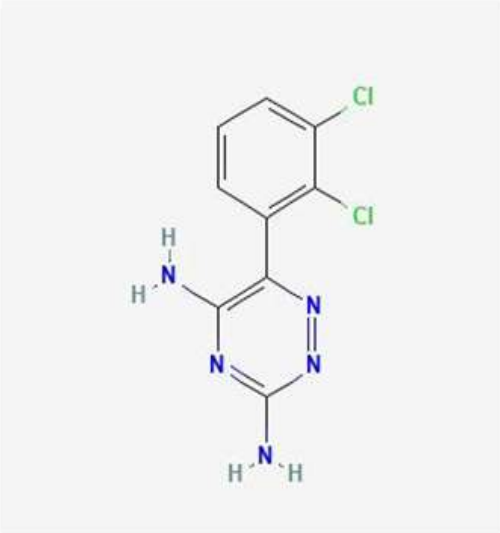
International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

Lamictal CD (chewable), and Lamictal ODT (dissolves on the tongue) are brand names for lamotrigine. Generic versions of it are also offered. Brand-name medications typically cost more than generic alternatives. In certain instances, they could not be offered in dosage or form that the name-brand medications do.combination therapies may include lamotrigine. You might thus need to take it in addition to other treatments[3]

Let's start with the medicine itself. This medicine is a mood stabilizer for bipolar illness in adults and children aged 10 and older. It works by enhancing the activity of particular neurotransmitters in the brain, thereby stabilizing your mood. Because it is a mood stabilizer, it is not an antidepressant or anti-anxiety medication, but people have been known to use it off-label for these purposes. When treating bipolar disorder, doctors typically prescribe one of these medications in conjunction with another type of medication known as an antipsychotic, which is usually taken at night to aid sleep because it can cause insomnia.These sorts of combo meds can have serious side effects, thus they are only administered when absolutely requir[4]

CHEMICAL FORMULA OF LAMOTRIGINE: C9H7Cl2N5 [5]

STRUCTURE OF LAMOTRIGINE:[5]



LAMOTRIGINE'S HIGHLIGHTS:

1. Both generic and brand-name versions of lamotrigine oral tablets are accessible. Lamictal XR, Lamictal CD, Lamictal ODT, and Lamictal are the brand names.
2. There are four different ways to take lamotrigine: chewable, extended-release, immediate-release, and oral disintegrating (which dissolves on the tongue) pills.
3. Oral lamotrigine tablets are prescribed medications for the treatment of specific forms of epileptic seizures. Bipolar disorder is also treated with it.[3]

LAMOTRIGINE SIDE EFFECTS: Lamotrigine oral tablets could make you feel sleepy. Make sure you understand how this drug affects you before operating heavy machinery, driving, or engaging in any other risky activities.
There are other side effects that lamotrigine may have

More common side effects

- Vertigo drowsiness
- Migraine
- Distorted vision,
- Double vision
- Feeling sick and Throwing up
- Stomach discomfort
- Diarrhea balance and Coordination issues
- Difficulty sleeping
- Back pain
- Dry mouth,
- Painful throat
- Fever,
- Trembling, and
- Anxiety

These side effects could disappear in a few days or a few weeks if they are minor. Consult your physician or pharmacist if they become worse or don't go away.[3]

Serious side effects

In the event that you experience severe side effects, contact your doctor straight away. If you believe you are experiencing a medical emergency or your symptoms feel life-threatening, call 911. The following are examples of serious side effects and symptoms:
Dangerous skin rashes known as toxic epidermal necrolysis and Stevens-Johnson Syndrome.symptomsinclude :

- Blistering or peeling of the skin,
- Hives,
- Rash,
- Painful ulcers in the mouth or around theeyes are other symptoms.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

Another name for multi-organ hypersensitivity is drug response with eosinophilia and systemic symptoms (DRESS). Possible symptoms include:

- Fever
- Rash
- Enlarged lymph nodes
- Extreme physical soreness and
- Recurrent infections
- Face, Eyes, Lips, or Tongue swelling;
- Unusual bleeding or bruises;
- Weakness or exhaustion
- Discoloration of your skin or the white area around your eyes

Behavioral or emotional shifts. Among the symptoms are :

- Attempts to injure or kill oneself, or ideas of doing so
- New or worsening sadness or anxiety
- Restlessness
- Episodes of terror
- Difficulty falling asleep
- Fury violent or aggressive conduct
- Angry behavior that is new or
- Worsening harmful tendencies or
- Impulses
- Sharp rise in conversation and activity

Meningitis that is aseptic (inflammation of the membrane covering the brain and spinal cord). Among the symptoms are :

- Nausea,
- Vomiting,
- Headache, and
- Fever
- Stiff neck rash,
- Greater sensitivity to light than usual, and
- Muscle aches
- Chills
- Confused
- Tiredness

A potentially fatal immune system reaction known as hemophagocytic lymphohistiocytosis (HLH). Among the symptoms are:

- High fever, Usually more than 101°F
- Swelling of the lymph nodes
- Abnormal cardiac rhythm
- A fast, sluggish, or Hammering heartbeat are examples of symptoms.
- Breathing Difficulti[3]

INTERACTION OF LAMOTRIGINE:

Herbs, vitamins, and other drugs you may be taking may interact with lamotrigine oral tablet. A compound that modifies the activity of a drug is called an interaction. This can be hazardous or impair the medication's effectiveness.The cautious management of all your drugs by your doctor will help prevent interactions. Make careful to disclose to your physician any and all vitamins, herbs, and drugs you take. Speak with your pharmacist or doctor to learn how this medication might interact with anything else you take.

The following list contains some examples of medications that may interact with

1] Medications to prevent seizures

Your body's lamotrigine level may drop if you use some other antiseizure medications along with lamotrigine. This may have an impact on lamotrigine's effectiveness. Some medications include, for example:

Conversely, **valproate** can increase your body's lamotrigine levels. Examples of these medications are

- Carbamazepine,
- Phenobarbital,
- Primidone, and
- Phenytoin.

Increased adverse effects could be harmful as a result of this.

2] Medication for heart arrhythmias

Heart arrhythmias are treated with **Dofetilide**. Dofetilide levels in your body may rise when used in conjunction with lamotrigine. This could result in deadly arrhythmias.

3] Medications for HIV

The amount of lamotrigine in your body can decrease if you take it with certain HIV treatment medications. This may impact lamotrigine's effectiveness. These medications include, for instance:

Atazanavir/Ritonavir
Lopinavir

4] Contraceptives used orally

It is possible for the level of lamotrigine in your body to decrease when taking combination oral contraceptives (those that contain both progesterone and estrogen). How well lamotrigine works may be impacted by this.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

5] Medication for tuberculosis

The medication **Rifampin** is used to treat TB. It can reduce the amount of lamotrigine in your body when used with lamotrigine. This may impact lamotrigine's effectiveness.[3]

ALERTS ON LAMOTRIGINE:

There are multiple warnings for this medicine.

- **Immune system reaction that could be fatal**

Rarely, this medication may result in hemophagocytic lymphohistiocytosis (HLH), a serious immune system reaction. In the absence of quick medical attention, this reaction can be fatal and causes extreme inflammation throughout the body. Fever, rash, and enlarged liver, spleen, and lymph nodes are typical symptoms. Reduced liver function, lowered blood cell counts, and issues with blood clotting are also among them.

- **Organ damage alert**

This medication has the potential to seriously harm some body parts. These consist of your blood cells and liver.

- **Warning against suicide**

You may consider hurting yourself while using this medicine. Speak with your doctor if you notice any abrupt changes in your mood, habits, thoughts, or feelings

- **Warning signs of heart illness**

You should not use lamotrigine if you have experienced heart failure, a rapid heartbeat, or other cardiac issues. You could experience an irregular heartbeat with this medication, which could result in an abrupt death. Chest pain, dizziness, breathlessness, and an irregular, rapid, or hammering heartbeat are some of the symptoms. If any of these symptoms apply to you, give your doctor a call.

- **Warning about allergies**

This medication may result in a serious allergic reaction. Among the symptoms are

- Rash
- Breathing difficulties
- Swelling of the face, throat, and tongue
- Hives
- Itching
- Severe mouth sores

Ifyou have ever experienced an allergic response to this medication, never take it again. Retaking it can prove to be lethal (cause death).[3]

ALERTS FOR INDIVIDUALS WITH SPECIFIC MEDICAL CONDITIONS :

- **Regardingthose suffering from liver disease:**

Your liver breaks down this medication. A medication may remain in your body for longer if your liver isn't functioning properly. You could have more adverse effects as a result of this. Your doctor might reduce how much of this medication you take.

- **Regarding individuals with renal disease**:

Your kidneys eliminate this medication from your body. More of the medication may linger in your body longer if your kidneys aren't functioning properly. You could have more adverse effects as a result of this. Your doctor might reduce how much of this medication you take. Your doctor might stop you from using this medication altogether if your renal issues are really serious.

- **Regarding individuals with heart disease :**

medication has the potential to cause sudden death and fast heartbeat in those who have heart problems. You should not use this medication if you have a history of second or third-degree heart block, heart failure, an irregular pulse, or any other cardiac issues.[3]

ALERTS ON OTHER GROUPS :

- **Regardingexpectantmothers**:

Pregnancy-related drugs are under category C. This implies two things:

i. Research on animals has demonstrated that when a mother uses a drug, the fetus suffers negative consequences.
ii. It's unclear how the medication might impact the fetus because not enough research has been done on humans.

If you are expecting a child or are currently pregnant, consult your physician. Only in cases where the possible benefit outweighs the possible risk should this medication be taken.

Contact your doctor immediately if you become pregnant while taking this medication.

- **For nursing mothers**:

This medication is found in breast milk and can have major negative effects on a nursing kid. Inform your physician if you are nursing your child. Find out what your child should eat to avoid food allergies while using this medicine.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

Keep a watchful eye on your child if you are nursing while taking this medication. Keep an eye out for signs such as difficulty breathing, short bursts of nodding off, excessive tiredness, or difficulty sucking. If any of these symptoms appear, give your child's doctor a call straight immediately.

- **Regardingchildren**:

It is unknown if this medication's immediate-release formulation is secure and efficient in treating seizures in kids under the age of two. Furthermore, it's unclear if children under the age of 13 may safely and effectively use this medication's extended-release formulation.

Furthermore, it is unknown if treating bipolar disorder in children under the age of 18 with this medication's immediate-release formulation is both safe and successful.[3]

ROUTE OF ADMINISTRATION OF LAMOTRIGINE :

This may not include all conceivable dosages and medication forms. The following will determine Dose of drug, form, and frequency of use:

- Age
- Illness
- Level of seriousness
- Any additional medical issues
- Previous response to the drug.[3]

ADR REPORTS ON LAMOTRIGINE :

There are**69724** reports with Lamotrigine[31]

- Reported potential side effects
- Blood and Lymphatic system disorders (2% , 3236 ADRs)
- Cardiac disorders (1% , 2019 ADRs)
- Congenital , Familial and Genetic disorders (1% , 1597 ADRs)
- Ear and Labyrinth disorders (1% , 944 ADRs)
- Endocrine disorders (0% , 267 ADRs)
- Eye disorders (3% , 3624 ADRs)
- Gastrointestinal disorders (6% , 8233 ADRs)
- General disorders and Administration site conditions (14% , 19109 ADRs)
- Hepatobiliary disorders (1% , 1613 ADRs)
- Immune System disorders (1% , 2089 ADRs)
- Infections and Infestations (2% , 2905 ADRs)
- Injury , Poisoning and Procedural complications (8% , 11614 ADRs)
- Investigations (4% , 6251 ADRs)
- Metabolism and Nutrition disorders (1% , 2003 ADRs)
- Musculoskeletal and Connective tissue disorders (2% , 3355 ADRs)
- Neoplasm benign , Malignant and Unspecified (incl cysts and polyps) (0 % , 403ADRs)
- Nervous system disorders (14% , 19060 ADRs)
- Pregnancy , Puerperium and Perinatal conditions (1% , 1494 ADRs)
- Product issues (2% , 2404 ADRs)
- Psychiatric disorders (9% , 12626 ADRs
- Renal and Urinary disorders (1% , 1359 ADRs)
- Reproductive system and Breast disorders (1% , 1196 ADRs)
- Respiratory , Thoracic and Mediastinal disorders (3% , 4212 ADRs)
- Skin and Subcutaneous tissue disorders (17% , 24232 ADRs)
- Social circumstances (1 % , 753 ADRs)
- Surgical and medical procedures (1% , 1283 ADRs)
- Vascular disorders (1% , 1500 ADRs)

GEOGRAPHICAL DISTRIBUTION[31]

Continent	Count	Percentage
Africa	699	1
Americas	39324	56
Asia	8542	12
Europe	19828	28
Oceania	1331	2

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

PATIENT SEX DISTRIBUTION [31]

Sex	Count	Percentage
Female	42571	61
Male	20553	29
Unknown	6600	9

AGE GROUP DISTRIBUTION [31]

AgeGroup	Count	Percentage
0 – 27 days	530	1
28 days to 23 months	345	0
2 – 11 years	3359	5
12 – 17 years	3872	6
18 – 44 years	22527	32
45 – 64 years	12437	18
65 – 74 years	3049	4
≥ 75 years	2106	3
Unknown	21499	31

ADR REPORTS PER YEARS[31]

Year	Count	Percentage
2024	796	1
2023	3165	5
2022	3124	4
2021	2985	4
2020	3952	6
2019	4943	7
2018	3750	5
2017	3397	5
2016	3387	5
2015	4900	7
2014	4722	7
2013	1862	3
2012	2414	3
2011	3753	5
2010	3196	5
2009	3362	5
Year	**Count**	**Percentage**
2008	5846	8
2007	151	0
2006	1024	1
2005	3205	5
2004	624	1
2003	599	1
2002	313	0
2001	461	1
2000	860	1
1999	442	1
1998	293	0
1997	529	1

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

1996	538	1
1995	381	1
1994	678	1
1993	62	0
1992	10	0

Current data set date is 01/4/ 2024. The data set is normally updated on Sundays at 17 : 00 CET (± 1 hour) [32]

MECHANISM OF ACTION OF LAMOTRIGINE (LAMICTAL):

The specific mechanism of action of lamotrigine is unknown, however it may exert cellular actions that contribute to its efficacy in a variety of diseases. Although chemically unrelated, lamotrigine's activities are similar to those of phenytoin and carbamazepine: it inhibits voltage-sensitive sodium channels, stabilizes neuronal membranes, and modulates the release of presynaptic excitatory neurotransmitter.[33,34 , 38]

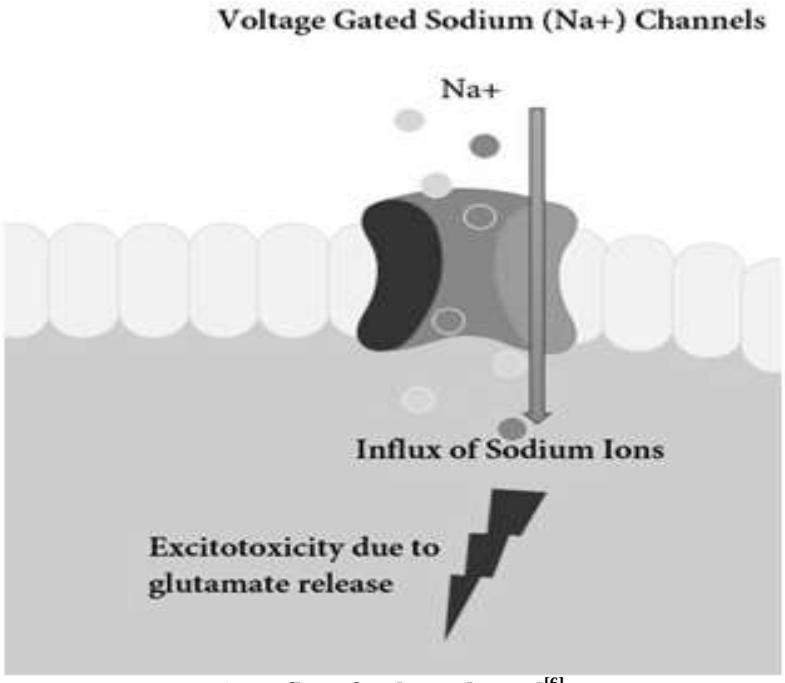


Fig :Influx of sodium channel[6]

Lamotrigine most likely inhibits sodium currents by selectively binding to the inactive sodium channel, preventing the release of glutamate, an excitatory amino acid. Lamotrigine's mechanism of action in lowering anticonvulsant activity is most likely the same in the treatment of bipolar disorders. Studies on lamotrigine have discovered its binding to sodium channels in a form comparable to local anesthetics, which could explain the shown clinical efficacy of lamotrigine in various neuropathic pain conditions.[37]

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

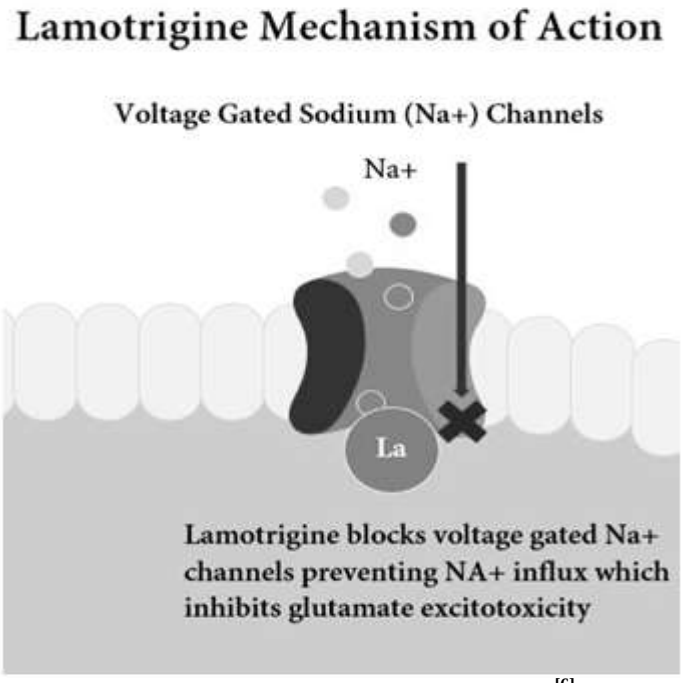


Fig : Inhibiting Glutamate Excitotoxicity[6]

Lamotrigine has binding characteristics to a variety of receptors. In lab binding experiments, it has a mild inhibitory impact on the serotonin 5-HT3 receptor. Lamotrigine binds weakly to Adenosine A1/A2 receptors, α1/α2/β adrenergic receptors, dopamine D1/D2 receptors, GABA A/B receptors, histamine H1 receptors, κ-opioid receptor (KOR), mACh receptors, and serotonin 5-HT2 receptors (IC50>100 μM). Sigma opioidreceptors had weak inhibitory effects.An in vivo study found that lamotrigine suppresses Cav2.3 (R-type) calcium currents, which could contribute to its anticonvulsant

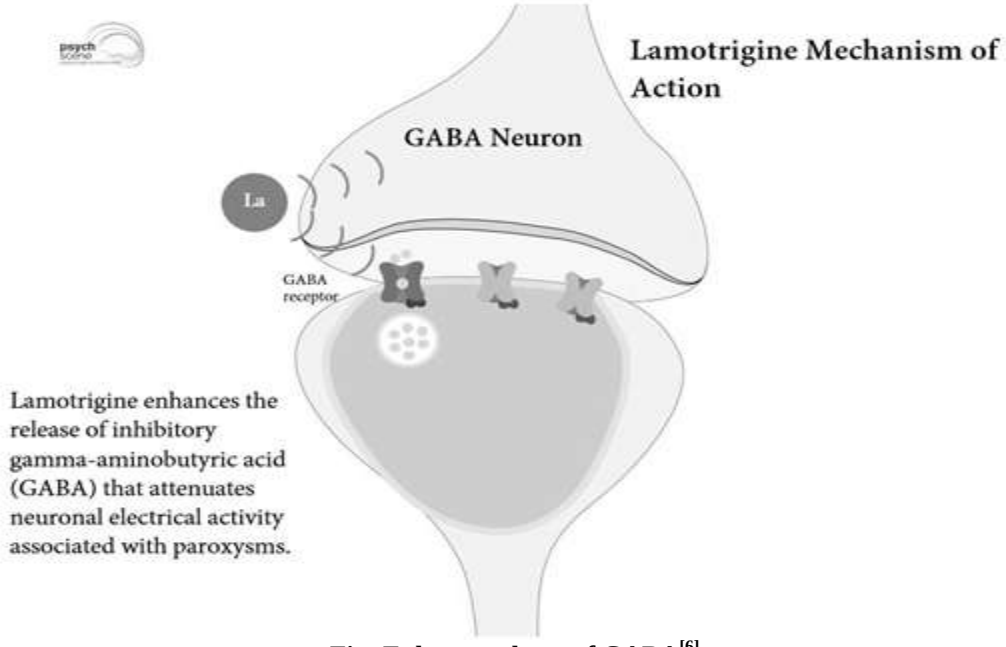


Fig :Enhance release of GABA[6]

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1561-1571 www.ijprajournal.com ISSN: 2249-7781

PHARMACOKINETICS OF LAMOTRIGINE (LAMICTAL):

- **Absorption**

Lamotrigine is rapidly and thoroughly absorbed, with low first-pass metabolic effects, and its bioavailability is estimated at 98%. Cmax occurs 1.4 to 4.8 hours after injection, depending on the dose, concomitant medications, and epileptic state. The rate and amount of lamictal absorption are thought to be the same for compressed tablets swallowed with water and chewable dispersible tablets taken with or without water.[38, 39]

- **Distribution**

The mean apparent volume of distribution (Vd/F) of lamotrigine after oral administration ranges from 0.9 to 1.3 L/kg and is dosage independent. Lamotrigine accumulated in the kidney of the male rat and is expected to function similarly in humans. Lamotrigine also binds to melanin-rich tissues, including the eyes and pigmented skin.[38, 39]

- **ProteinBinding**

The plasma protein binding of lamotrigine is estimated to be 55%. Due to its weaker protein binding, this medication is unlikely to have clinically relevant interactions with other drugs via competition for protein binding sites.[38,39]

- **Metabolism**

Lamotrigine is mostly glucuronidated, resulting in 2-N-glucuronide conjugate, a pharmacologically inactive metabolite. During clinical studies, the total radioactivity observed following a 240mg radiolabeled dosage of lamotrigine was as follows: lamotrigine as unmodified medication (10%), a 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and various other minor metabolites (4%).[36 , 38]

- **The elimination route**

Lamotrigine is eliminated in both the urine and the stool.Following oral administration of 240 mg radiolabelled lamotrigine, approximately 94% of the total medication and its metabolites are retrieved in the urine, with the remaining 2% recovered in feces. One pharmacokinetic investigation discovered 43 to 87% of a lamotrigine dosage in urine, primarily as glucoronate metabolites.2-N-glucuronide is primarily eliminated through the urine.[35, 36 ,,38]

- **Half-life**

The typical elimination half-life of lamotrigine is 14-59 hours. The value is determined by the dose delivered, any concurrent pharmacological therapy, and the disease status. In healthy participants, one pharmacokinetic investigation indicated a half-life ranging from 22.8 to 37.4 hours. It also said that enzyme-inducing antiepileptic medicines including pheobarbital, phenytoin, and carbamazepine shorten the half-life of lamotrigine. Valproic acid, on the other hand, prolongs the half-life of lamotrigine (48–59 hours).[35,39]

- **Clearance**

The mean apparent plasma clearance (Cl/F) varies between 0.18 and 1.21 mL/min/kg. The numbers vary depending on the dose regimen, concomitant antiepileptic medicines, and individual illness condition.In one study, healthy individuals on lamictal monotherapy had a clearance of around 0.44 mL/min/kg following a single dose.[38]

- **Toxicity**

The oral LD50 for mouse and rat is 205 mg/kg and 245 mg/kg, respectively. There have been fatal occurrences of lamotrigine overdose involving up to 15g. Ataxia, nystagmus, increased seizures, decreased state of consciousness, coma, and intraventricular conduction delay have all been reported as signs of lamotrigine overdose. Although there is no known antidote for lamotrigine, hospitalization and general supportive measures should be used in the event of a suspected lamotrigine overdose. Gastric lavage and emesis may be necessary in conjunction with airway protection. It is unknown at this time if hemodialysis is an effective method of eliminating lamotrigine from the systemic circulation.[38,39]

REFERENCE:

[1]. David R. Goldsmith / A Review of Lamotrigine: A Review of its use in Bipolar Disorder/ Springer link/ volume 63, pages 2009-2010 (2003)
[2]. Frank J. E. Vajda/ Lamotrigine in epilepsy, pregnancy and psychiatry - a drug for all seasons? / Journal of Clinical Neuroscience 20 (2013) 13-16
[3]. https://www.healthline.com/health/drugs/lamotrigine-oral-tablet#side-effects

[4]. https://mantracare.org/therapy/medication/lamictal/
[5]. https://go.drugbank.com/drugs/DB00555
[6]. https://psychscenehub.com/psychinsights/lamotrigine-mechanism-of-action-efficacy-side-effects-and-clinical-pearls-2/
[7]. https://en.m.wikipedia.org/wiki/Lamotrigine Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
[8]. Meador KJ,et al. /Antiepileptic drug use in women of childbearing age. /Epilepsy Behav Juill./2009;15(3):339–43.
[9]. Audrey peron/ Neurodevelopmental outcomes after prenatal exposure to lamotrigine Monotherapy in women with epilepsy : a systemic review and meta-analysis/BMC Pregnancy and Childbirth /(2024) 24: 103
[10]. Gurudeep Chatwal, G.R. Anand,/ Instrumental Methods of Chemical Analysis,/ ed-5th, Himalaya Publishing House, New Delhi.,/ PP.2.624-2.629, 2007.
[11]. Skoog D.A. Holler/Principles of Instrumental Analysis, / ed-5th, Thomson BrooksCole Asia Pvt. Ltd., Singapore, /PP.4-7, 2004.
[12]. Sweetman S C Martindale,/ The Complete Drug Reference./ 34th Ed. London, Pharmaceutical Press, /2005
[13]. Ankit Patel, / "RP-HPLC Method Development and Validation of Lamotrigine in Tablet Dosage Form", /International Journal of Advanced Research in Pharmaceutical & Bio Sciences, / 2012; Vol.2 (2):95-102.
[14]. Ayyagari Rama Murthy /Development and Validation of Lamotrigine by High Performance Liquid Chromatography,/ International Journal for Pharmaceutical Research Scholars (IJPRS), /V-3, I-3, 2014 ISSN No: 2277-7873
[15]. Siyao Jin, / Development and validation of an improved HPLC-UV method for simultaneous determination of lamotrigine and oxcarbazepine and its active metabolite 10,11-dihydro-10-hydroxycarbazepine in human blood plasma and comparison with an UHPLCMS/MS method, /Journal of Analytical Science and Technology,/ (2019) 10:36.
[16]. H.D. Revanasiddappa, /Development and Validation of Indirect Spectrophotometric Methods for Lamotrigine in Pure and The Tablet Dosage Forms, /Analele Universităţii Din Bucureşti–Chimie (Serie Nouă),/ Vol 20 No. 1, Page. 49 –55
[17]. Fadhil M. Najib,/Four Spectrophotometric Methods for Simultaneous Determination of Carbamazepine and Lamotrigine in Binary Mixtures and Urine Samples,/ The Malaysian Journal of Analytical Sciences, /Vol 18 No 3 (2014): 491 – 506
[18]. Vijay R. Rama, /Development and validation of a stability indicating HPLC assay method for determination of Lamotrigine in tablet formulation, /Pelagia Research Library der Chemica Sinica,/ 2011, 2 (2): 58-65
[19]. T. Vijaya Bhaskara Reddy, /Stability Indicating Reversed Phase UPLC Method For The Assay of Lamotrigine In Tablet Dosage Forms,/ Journal Of Global Trends In Pharmaceutical Sciences /Volume-4, Issue-4, Pp-1346-1355, October-December 2013
[20]. Nadia Fayek YOUSSEF* / Development and Validation of Spectrophotometric, TLC and HPLC Methods for the Determination of Lamotrigine in Presence of Its Impurity, /National Organization for Drug Control and Research "NODCAR", /Chem. Pharm. Bull. 55(4) 541-545 (2007)
[21]. Rutuja S Nalkar / A review on Analytical Method for Determination of lamotrigine in Bulk and Pharmaceutical Dosage Form / Research Journal of Science and Technology /Volume 13,Issue -3 (2021) 2349-2988
[22]. https://pubmed.ncbi.nlm.nih.gov/28862044/
[23]. https://www.researchgate.net/publication/365806276_Solubility_of_Lamotrigine_in_Polyethylene_Glycol_400_2-Propanol_Mixtures_at_Different_Temperatures
[24]. https://www.researchgate.net/publication/376341303_A_single_dose_of_lamotrigine_induces_a_positive_memory_bias_in_healthy_volunteers
[25]. https://www.researchgate.net/publication/366670973_Formulation_and_characterization_of_lamotrigine_nasal_insert_targeted_brain_for_enhanced_epilepsy_treatment
[26]. https://www.researchgate.net/publication/355676774_Solubility_study_of_lamotrigin

e_in_the_aqueous_mixture_of_choline_chloride_based_deep_eutectic_solvent_at_different_temperatures
[27]. https://www.researchgate.net/publication/335373731_Lamotrigine_Induces_Tremor_among_Epilepsy_Patients_Probably_via_Cerebellar_Pathways
[28]. https://www.researchgate.net/publication/329501891_Lamotrigine_as_a_mood_stabilizer_insights_from_the_pre-clinical_evidence
[29]. https://www.researchgate.net/publication/299134579_Efficacy_and_Safety_of_Lamotrigine_as_Add-On_Treatment_to_Lithium_in_Bipolar_Depression_A_Multicenter_Double-Blind_Placebo-Controlled_Trial
[30]. Sung Gyu/Liver dysfunction induced by systemic hypersensitivity reaction to lamotrigine: case report/Clinical and Molecular Hepatology /2015;21:180-182
[31]. Vigiaccess
[32]. Dibue-Adjei et. al /Cav2.3 (R-Type) Calcium Channels are Critical for Mediating Anticonvulsive and Neuroprotective Properties of Lamotrigine In Vivo./ Cell Physiol Biochem./ 2017;44(3):935-947.
[33]. Goa KL, /Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilepsy. Drugs. /1993 Jul;46(1):152-76.
[34]. Prabhavalkar KS et. al / Management of bipolar depression with lamotrigine: an antiepileptic mood stabilizer./ Front Pharmacol./ 2015 Oct 23;6:242.
[35]. Rambeck B,et.al/ Lamotrigine clinical pharmacokinetics./ Clin Pharmacokinet. /1993 Dec;25(6):433-43
[36]. Milosheska D, et. al / Pharmacokinetics of lamotrigine and its metabolite N-2-glucuronide: Influence of polymorphism of UDP-glucuronosyltransferases and drug transporters. /Br J Clin Pharmacol./ 2016 Aug;82(2):399-411.
[37]. 44. (2012). In Rang and Dale's Pharmacology (7th ed., pp. 544, 549). Edinburgh: Elsevier/Churchill Livingstone. [ISBN:978-0-7020-3471-8]
[38]. Lamictal FDA Label
[39]. FDA Approved Products: Lamictal (lamotrigine) chewable dispersible tablets
[40]. Jeffrey M. Mufson, M.D/Lamotrigine: Pharmacology, clinical utility, and New safety concern / The American Journal of Psychiatry Residents Journal /December 2018
[41]. SajeedaS/Lamotrigine—A Review of Analytical Methods Developed for Pharmaceutical Formulations and Biological Matrices/Critical Reviews in Analytical Chemistry /Volume 52, 2022 - Issue 7 /Pages 1451-1460