

The Antiepileptic Lamotrigine Use in Psychiatric Disorders

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Abstract

This article summarizes lamotrigine mechanism of action, adverse effects, interaction with other medications and dosing regimen. It also reviews lamotrigine use in its approved indications for bipolar disorder and some of its off-label use in the treatment of schizoaffective disorder, obsessive compulsive disorder, posttraumatic stress disorder, borderline personality disorder, derealization and depersonalization disorder and eating disorders.

Keywords: Antiepileptics; Lamotrigine; Bipolar Disorder; Pharmacological Treatment; Psychiatric Disorders

Historical Background

Lamotrigine (LMG) was first approved in the United States in 1994 as an adjunct therapy for partial seizures and subsequently gained additional approval in June 2003 for the management of bipolar disorder [1-3]. It belongs to the so-called third or new generation of antiepileptics. The first author who produced scientific data on the efficacy of LMG in bipolar disorder was Richard H. Weisler from the University of North Carolina Chapel Hill School of Medicine at Chapel Hill, North Carolina, USA. The development of LMG as a mood stabilizer provided an example of the important values of prescience, patience and persistence in bringing a novel idea into a full clinical fruition [3].

Mechanism of action

Pharmacodynamics

The cellular mechanism of action of LMG is not completely understood, and it may have multiple effects. It is a (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-phenyltriazine derivative), that inhibits voltage-activated sodium channels and, possibly, calcium channels [4,5]. As a result it stabilizes pre-synaptic neuronal membranes by blocking voltage-dependent sodium and calcium channels, and reduces the release of excitatory amino acids, such as glutamate and aspartate [6]. The action mechanisms underlying its mood-stabilizing effects are not completely known and it is suggested that its modulating effects on various ion channels, could result in attenuating neuronal activities that are possibly associated with bipolar disorder [7,8].

Pharmacokinetics

Studies show that LMG is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours (T_{max}) post dosing [8]. When administered with food, the rate of absorption is slightly reduced, but the effect remains unchanged. It primarily undergoes hepatic metabolism through glucuronidation, producing inactive metabolites that mainly consist

of lamotrigine 2N-glucuronide, and to a lesser extent the 5N-glucuronide, N-oxide and N-methyl metabolites, all of which are renally excreted [9]. Approximately 55% of LMG is bound to plasma proteins and its half-life ($t_{1/2}$) is 24 hours [10]. Its concentrations in the cerebrospinal fluid (CSF) are similar to free non-protein-bound concentrations and the CSF:plasma concentration ratio is 0.43 [11]. Clearance is substantially decreased in the presence of hepatic or renal impairment, although age, gender and smoking do not appear to have significant impact on its pharmacokinetics. Clearance is also estimated to be about 25% lower in the non-Caucasian populations [8].

Adverse effects

Monotherapy with LMG is most frequently associated with dizziness, diplopia, ataxia, blurred vision and somnolence [12]. Skin rash is the most frequent cause of therapy withdrawal with occurring in 4% in clinical trials and it is typically maculopapular or erythematous and displays characteristics of a delayed type hypersensitivity reaction, appearing within the first month of therapy and resolving rapidly upon treatment withdrawal [13]. In 0.3% of cases it may progress to potentially fatal forms such as erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [12,13]. The latter finding mandates that LMG be stopped at the first sign of rash and not restarted. The risk of developing a life-threatening rash such as SJS, TEN, or angioedema is rare and is approximately 0.08% to 0.13% (per 1,000) in adult patients [12,13]. There are as yet no factors identified that are known to predict the risk of occurrence of SJS, or TEN associated with LMG with some suggestions, yet to be proven include the possibility of increased risk by (1) the co-administration of LMG with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose, or (3) exceeding the recommended dose escalation. However, cases have been reported in the absence of these factors [14]. Mechanisms for LMG-induced SJS or TEN are less well understood with some evidence suggesting it to be a consequence of chemotoxic and immunologically mediated injury [14]. Nearly all cases of life-threatening rashes associated with LMG have occurred within 2 to 8 weeks of treatment initiation. Some isolated cases have been reported after prolonged treatment (e.g. 6 months) [15,16]. Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash. The rate of hospitalization and LMG discontinuation due to reported SJS or TEN, is considered relatively low at approximately 0.1% [17]. Although rash is a potentially life-threatening reaction, the risk of serious rash due to LMG should be weighed against more common risks associated with untreated or undertreated presenting severe symptoms [18].

In September 2006, the USA Food and Drug Administration (FDA) issued a warning stating that taking LMG during the first trimester of pregnancy may increase the risk for cleft lip and palate malformation in newborns [19]. Since then, review studies have found that overall rates of congenital malformations in infants exposed to LMG in utero are relatively low (1 - 4%), compared to the typical 3% rate in the untreated population [20]. It is not recommended to breast feed during treatment with LMG since it is expressed in breast milk [21]. Aseptic meningitis was reported in the FDA Adverse Event Reporting System in 40 patients taking LMG, according to a 2012 report [22]. On January 31, 2008, the FDA issued an alert regarding increased risk of suicidal thoughts and behavior related to use of antiepileptic drugs (AEDs), then on July 10, 2008, an FDA scientific advisory committee advised that although, there was a significant positive association between AEDs and suicidality the vote was against placing a black box warning on AEDs for suicidality [23].

Medications interaction

Carbamazepine inducing enzymes lower LMG plasma levels [24], while depakote (valproate) could double LMG plasma levels [25]. The depressant effects of alcohol or other central nervous system depressants, including anti-histaminics, sedatives, hypnotics, narcotics, barbiturates, muscle relaxants, and anesthetics, including some dental anesthetics may increase with LMG use [26]. Hormone replacement therapy and hormonal contraceptives increase LMG clearance and are associated with decreased LMG blood levels [26-29]. Contraceptives such as ethinylestradiol and levonorgestrel can lower the plasma level of LMG by as much as 50% [28]. The likely mechanism of increased metabolism of LMG by contraceptive has been attributed to the induction of the uridine diphosphate glucuronosyltransferase system. Older age, male gender and the co-administration with carbamazepine, fluoxetine, lithium, phenytoin, phenobarbital, or topiramate are associated with decreasing LMG level [30]. In addition dosing recommendations indicate that LMG doses should be halved in individuals taking enzyme inhibitors and doubled in those on enzyme inducers [31].

Dosing regimen

Available forms of LMG include 25, 100, 150 and 200 mg tablets and 2, 5 and 25 mg chewable/dispersible tablets. Patients receiving concurrent therapy with enzyme inducing drugs and valproate should receive 25 mg every other day for 14 days followed by 25 mg once daily for 14 days followed by dose escalation in 25 to 50 mg/day increments every one to two weeks to the maintenance dose [32]. When LMG is administered with another medication that can induce its glucuronidation the initial starting dose of LMG should be 50 mg once daily [33] an initial dose is 25 mg twice daily, increasing to 50 mg twice daily after two weeks and titrating upward by 100-mg-per-day increments every one to two weeks as needed to a usual maintenance dose of 300 to 500 mg per day. There are no specific dosing recommendations for patients with severe renal impairment with or without hemodialysis support [34,35]. In patients with moderate or severe hepatic impairment, initial, incremental, and maintenance doses should be reduced by 50% and 75%, respectively [34]. When LMG is used as a mood stabilizer or as an antidepressant for the treatment of depression, the optimum dose usually ranges between 100 to 200 mg per day. An extended-release formulation of LMG, which can be given once as opposed to twice daily, provides more stable serum concentrations than the immediate-release formulation. Recent bioequivalence studies evaluating 50-mg doses of LMG recommended that such doses may minimize the risk of severe rash or SJS [36].

Even though LMG has been reported to be well tolerated in cases of accidental overdose, there is a risk of toxic effects which can be life threatening in deliberate overdose suicidal attempts. This needs to be borne in mind when prescribing to patients at an increased risk of deliberate drug overdose [37].

Lamotrigine use in psychiatric disorders**Bipolar disorder**

This psychiatric disorder can be described as a mental illness that is manifested by marked and extreme mood changes, thoughts, energy and behaviors which usually alternate between the poles of mania and depression, used to be known as "Manic Depression" [38]. Mood changes or swings vary in their severity from feelings of deep despair to extreme and heightened level of in energy. These are usually characterized as experiencing the "highs" and "lows" of the illness [38]. The mood swings usually begins in late adolescence and typically presenting as depression during the teen years. It could also occur in early childhood or even as late as in the 40 and 50s [39]. Bipolar disorder include 2 subtypes bipolar I and bipolar II [40]. Patients with bipolar I disorder experience manic episodes, and nearly always major depressive episodes while in bipolar II disorder patients experience a less severe form of mania referred to as hypomania and major depressive episodes [40]. In bipolar disorder with mixed features, there are symptoms of depression, in addition to increased activity and excitation. Sometimes the increased activity is expressed as hypomanic symptoms of inner tension, racing thoughts, dramatic expression of suffering, and unproductive agitation [39]. In rapid cyclic bipolar disorder, there are frequent, distinct four or more episodes of mania or depression in one year. It can occur at any point in the course of bipolar disorder and can remit and reemerge over many years depending on how well the illness is treated [39,40]. Cyclothymic disorder also referred to as cyclothymia is a diagnosis assigned to patients who experience mood cycling over a two years period, but have not met the diagnostic criteria for Bipolar I, Bipolar II, or Depressive disorder [40]. There are ongoing debates among clinicians and researchers if cyclothymic disorder is a discrete disease process, a temperamental variation, or a premorbid syndrome for Bipolar I or II disorders [41]. The FDA approved LMG for the prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes and it is also indicated for the maintenance treatment of bipolar I disorder to delay the time of occurrence of a depressed mood episodes [7]. Although LMG has been used off-label by some clinicians for prevention of depression in the treatment of bipolar II disorder, the evidence for its effectiveness in that context is limited [42]. The usefulness of LMG in the acute treatment of manic or depressive episodes, rapid cycling bipolar disorder and cyclothymic disorder remain anecdotal and not well replicated [43-45].

Schizoaffective disorder

In this mental disorder there is a combination of symptoms of schizophrenia, such as hallucinations or delusions, and mood disorder symptoms, such as depression or mania [39]. There are two types of schizoaffective disorder, the bipolar type, which includes episodes of mania and sometimes major depression and the depressive type, which includes only major depressive episodes [40]. Schizoaffective disorder has a wide range of signs and symptoms that make it challenging to diagnose and there are ongoing debates about whether

schizoaffective disorder should be considered a separate diagnosis or a subtype of either schizophrenia or bipolar disorder. The most common regimen for the treatment of schizoaffective disorder is the use of an antipsychotic only followed closely by the combination of an antipsychotic and a mood stabilizer. Other treatment regimens would either combine antipsychotic with antidepressant or an antipsychotic with a mood stabilizer and an antidepressant [46]. In some anecdotal reports, LMG has been used as a sole agent for the treatment of schizoaffective disorder [47,48].

Unipolar depression

This Category of depression has been interchangeably used with the term Major Depression and usually described as any mood disorder which has been manifested by at least one major depressive episode or an extended time frame of depressive indicators with no past occurrences of manic or hypomanic indicators or combined episodes. A major depressive episode typically lasts 2 weeks in duration and is characterized by many symptoms including persistent depressed mood, poor or increased appetite, weight gain or loss, insomnia or conversely excessive sleep, a general lack of energy with feelings of helplessness, hopelessness, loss of self-worth and suicidal thoughts. Major depression has a recurrent clinical course and requires ongoing treatment and follow-ups to stabilize it and prevent deterioration of psychological, social, occupational and interpersonal functioning.

Some clinicians use LMG to treat patients with unipolar depressive disorder who have not responded adequately to other conventional treatment intervention with antidepressants. Although this off-label use of LMG is not infrequent some studies are urging clinicians not to prescribe LMG for unipolar or major depression treatment [49-51]. Other studies have shown LMG to be superior to placebo in improving unipolar and bipolar depressive symptoms, without causing more frequent adverse effects and treatment discontinuations [52].

Borderline personality disorder (BPD)

This is a personality disorder that is usually manifested by unstable relationships with intense mood swings, and extreme inappropriate or extreme emotional reactions, persistent fear of abandonment and rejection, feelings of isolation, boredom and emptiness in addition to impulsive, risky, and dangerous behaviors, including reckless driving, drug or alcohol use and unsafe sexual relationships [40]. Patients with BPD often engage in self-destructive behaviors, including suicide attempts, self-cutting and other self-injurious acts [53]. Patients with BPD also exhibit difficulties with academic and occupational achievements and in maintaining healthy personal relationships. Although there is no medications that are currently FDA approved for treatment of BPD, patients have been treated with various medication combination including antipsychotics, mood stabilizers, antidepressants, antianxiety medications, and anticonvulsants including LMG [54]. The addition of LMG to the usual care of patients with BPD was not found to be clinically effective as a long term intervention and future research into treatment should rather focus on improving the evidence base for the long term clinical effectiveness of non-pharmacological treatment interventions [55].

Obsessive-compulsive disorder (OCD)

OCD is a condition characterized by recurrent obsessions or compulsions, or both, that cause impairment, distress and interference with life functioning. Obsessions are mostly related to concerns about contamination, sexual, somatic and religious preoccupations. Compulsions include washing, checking, repeating, ordering and counting. Resistance to various pharmacological interventions has been one of the major challenges in the management of OCD and such resistance adds to the disabling effects of that illness. There have been different clinical strategies used by clinicians to counter this resistance. The augmentation treatment with LMG has been well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant OCD [56,57].

Post-traumatic stress disorder (PTSD)

This trauma and stressors related disorder usually develops following a traumatic event that involved physical harm or the threat of physical harm that been experienced or witnessed. It is characterized by recurrent and intrusive distressing recollections of the traumatic

event, recurrence of nightmares, a sense of reliving the experience with intense psychological or physiological distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, or inability to recall important aspects of the trauma, loss of interest, estrangement from others, and additional symptoms of sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response [40,58]. In some patients dissociative flashback episodes could also occur [40]. Patients with PTSD are usually treated with the antidepressant selective serotonin reuptake inhibitors (SSRIs) class of medications but many PTSD patients do not respond to the SSRIs, thus prompting clinicians to use other pharmacological agents such as mood stabilizers and anticonvulsants including LMG [59]. The adjunct use of LMG in combination with antidepressants could be an alternative in treating refractory and treatment resistant PTSD patients [60,61].

Depersonalization and derealization disorder (DDD)

This disorder is characterized by persistent or recurrent depersonalization and/or derealization that causes clinically significant distress, while maintaining intact reality testing [62]. It has a prevalence of approximately 2% and is associated with significant morbidity, but is often undetected or misdiagnosed, leading to delays in treatment. In depersonalization there is a persistent or recurrent feeling of detachment or estrangement from one's self. Patients who experience depersonalization may report the sense of being an outside observer of their mental processes or their body. They often report feeling a loss of control over their thoughts, perceptions, and actions. Some describes feelings of being an automaton or as if they are in a dream or as if they are watching themselves in a movie. In derealization there is a general sense of detachment or unreality regarding the world in which individuals or objects are experienced as unreal, dream-like, foggy, lifeless, or visually distorted [63]. One of the few pharmacological treatments that has shown some efficacy in DDD treatment is the combination of SSRIs with LMG [64] and this combined pharmacological effect suggests the involvement of both serotonergic and glutamatergic mechanisms in DDD [64,65].

Eating disorders

Some of the severely dysregulated eating disorder patients often have little or no response to monotherapy with SSRI antidepressant, and in some cases, may become more agitated with this treatment [66]. Medications with mood-stabilizing properties may be a viable alternative to consider such as LMG [67]. When used in the treatment of eating disorder LMG was associated with a numerically greater amount of weight loss (1.17 vs. 0.15 kg) and significant reductions in fasting levels of glucose, insulin and triglycerides. It was also well tolerated and associated with no serious adverse events [67].

Conclusion

Although the antiepileptic LMG is only FDA approved for the treatment of certain seizure disorders and for delaying the onset of depressive episodes in bipolar I disorder, several off-label psychiatric uses have been recorded in clinical practice. This article summarized LMG mechanism of action, adverse effects, interaction with other medications and dosing regimen. It also reviewed LMG uses in the treatment of other types of mood disorders including bipolar II disorder, unipolar depression, BPD, OCD, PTSD, DDD and eating disorders. Prior to the implementing of wide general use of LMG in treating these psychiatric disorders more evidence need to be gathered and confirmed through the conduction of randomized, placebo controlled and double blinded studies in a large size population of patients.

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Conflicts of Interests

No conflicts of interests. The materials described in this manuscript are those of the authors and do not reflect the views of the Department of Veterans Affairs or the VA Northern California Health Care System or the Department of Psychiatry and Behavioral Sciences, UC Davis, School of Medicine, Sacramento, California, or the Substance Abuse Treatment Facility and State Prison in Corcoran, California.

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