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REVIEW

Lamotrigine: Once Daily Add-on Therapy for Epilepsy in Adults Experiencing Partial Onset Seizures

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Abstract: Lamotrigine (LTG) is a newer antiepileptic medication that has multiple indications for epilepsy including add-on therapy for partial onset epilepsy in adults.

The primary antiseizure mechanism of action is blockage of voltage-sensitive sodium channels which stabilizes neuronal membranes and inhibits excitatory presynaptic neurotransmitter release. It has linear pharmacokinetics with rapid absorption with a $t_{max} < 3$ hours and no first pass metabolism. Bioavailability is nearly 100% with approximately 55% protein binding. Glucuronidation is the mechanism of elimination with a half life of approximately 24 hours. Co administration with an enzyme inducer shortens the half life to approximately 15 hours while enzyme inhibitors such as valproic acid lengthen the half life to over 60 hours. Immediate release preparations can be given once a day alone or with enzyme inhibitors and the recently available extended release preparation can be given once a day even with enzyme inducers. Pregnancy and oral contraceptive pills significantly alter the metabolism of LTG.

Efficacy has been demonstrated in multiple clinical trials with a satisfactory safety profile. The most commonly reported CNS related adverse events include dizziness, diplopia, ataxia, headache and somnolence. The most commonly reported non-CNS related adverse event is rash, which is typically benign and self limited with only rare occurrence of Stevens-Johnson syndrome.

LTG is a particularly good choice of antiepileptic medication in persons with comorbid mood disorders as it also has an indication for treatment of bipolar disorder and in the elderly population due to its tolerability, lack of interaction with anticoagulants and antiplatelet agents and linear pharmacokinetics.

Keywords: lamotrigine, partial onset epilepsy, once daily treatment, anticonvulsant

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Introduction

The prevalence of active epilepsy is estimated at roughly 3 million in the United States with about 200,000 new cases of epilepsy diagnosed each year and 300,000 having a first convulsion each year.[1] The trend over the past several years has changed with a decreased incidence in children and an increased incidence in the elderly with 3% of the population over age 75 diagnosed with epilepsy and 10% having experienced some type of seizure.[1] A large epidemiologic study conducted in Rochester, Minnesota estimated that partial seizures occurred in 57% of all incident cases.[2]

Lamotrigine [3,5-diamino-6-(2,3-dicholorophenyl)-1,2,4-triazine, BW430C] is a newer generation antiepileptic medication that is structurally unrelated to other major antiepileptic medications. It was developed as an antiepileptic medication based on its effectiveness in the maximal electroshock (MES) model, the visually and electrically evoked afterdischarge (WEAD and EEAD) models, as well as the pentylenetetrazol (PTZ) model in mice in the early 1980s.[3,4] Lamotrigine (LTG) has been in clinical use since the early 1990s for use as adjunctive treatment for partial onset epilepsy in adults and was FDA approved for this indication in 1994. It has since been approved for adjunctive treatment of primary generalized tonic clonic seizures and the generalized seizures of Lennox Gastaut Syndrome in patients over 2 years of age as well as conversion to monotherapy in patients with partial seizures receiving treatment with either carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), or valproate (VPA), however, the purpose of this review is to provide data on LTG as once daily add-on therapy for partial onset epilepsy in adults. Lamotrigine is currently available as immediate release (IR) tablets, immediate release dispersion tablets, immediate release disintegrating tablets and most recently available as extended release (XR) tablets using GlaxoSmithKline's DiffCORE technology.[5]

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Mechanism of action

The proposed mechanism of antiseizure action of LTG is blockage of voltage-sensitive sodium channels which thereby stabilizes neuronal membranes and inhibits excitatory presynaptic neurotransmitter release, principally glutamate and aspartate.[6,7] However, it has demonstrated a broad spectrum of activity and may also exert calcium antagonistic properties as shown in the zero- Mg^{2+} model thought to cause epileptiform discharges due to increased transmembranous calcium ion fluxes.[8,9] Other effects of LTG include limitation of excitation by strengthening of the fast potassium outward current,[9,10] exhibition of action at the hyperpolarization-acivated cation inward current (I_h) present in dendrites,[11] and exertion of a blocking action on the muscle nicotinic receptor channels.[12]

Pharmacokinetics and metabolisms

The pharmacokinetics of LTG are described as a one-compartment open model with first order absorption and elimination. There is a linear relationship between dose administered and maximal plasma concentration and area under the curve (AUC). Rapid absorption is seen with a $t_{max} < 3$ hours after single and multiple doses with no extensive inter-individual variability in absorption and no saturation of absorption in the therapeutic dose range studied.[13] The absorption is not affected by food and there is no first-pass metabolism.[14,15]

Lamotrigine is lipophilic with penetration into the brain[16] and a bioavailability of nearly 100% following oral dosing.[15] However, body weight correlates negatively with serum concentration and should therefore be taken into account when dosing LTG.[17] It demonstrates approximately 55% plasma protein binding[13] with no evident relationship between the protein binding and tissue distribution.[16]

Glucuronidation is the mechanism of elimination through the formation of ***N***-glucuronic acid conjugates, 70% of which are recovered in the urine, with little to no autoinduction.[13,14] Renal excretion is a minor elimination pathway with only 10% of dose excreted unchanged in the urine.[15] The elimination half life of LTG is approximately 24 hours. However, co administration with enzyme inducers such as PHT, CBZ, PB and primidone reduces this half life to approximately 15 hours while the enzyme inhibitor VPA lengthens the half life to over 60 hours.[13,18] The administration of both an inducer and inhibitor results in a half life similar to LTG alone.[18] Therefore, the immediate release preparation of lamotrigine can be used once daily either alone or in the presence of an enzyme inhibitor

but must be dosed twice daily if used with an enzyme inducing drug. The extended release preparation can be given once daily even with enzyme inducers as the XR tablets contain a modified release eroding matrix formulation (DiffCORE) which controls the dissolution rate over 12–15 hours.[5] An open label conversion study in 44 patients demonstrated that patients could be switched directly from LTG IR to LTG XR based on the same total daily dose regardless of the concomitant antiepileptic medication (AED) while maintaining comparable steady state trough concentrations with fewer fluctuations in LTG concentration over a 24 hour period with the XR preparation than with the twice daily IR preparation (See Fig. 1).[19]

Drug-drug interactions

In contrast to many other AED, LTG does not significantly interact with oral contraceptive pills, however, since estrogenic substrates are also metabolized by glucuronidation, oral contraceptive pills significantly and rapidly (within 1 week) decrease the concentration of LTG by up to 50%.[20] Similarly, the clearance of LTG is altered during pregnancy. Both the total and free LTG clearance increase in all trimesters of pregnancy, with the greatest increase occurring during the third trimester and considerable inter-individual variability.[21,22] In a prospective, observational study of 53 pregnancies, most increases in seizures occurred during the second trimester and were associated with a decrease to 65% of the individual's target LTG concentration.[22] Any other known inducers or inhibitors of glucuronidation may also interact with LTG.

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) for LTG has been controversial with no clear relationship between concentration and either efficacy or toxicity has been demonstrated.[18,23] However, this has been viewed as an inadequate method as it compares both well

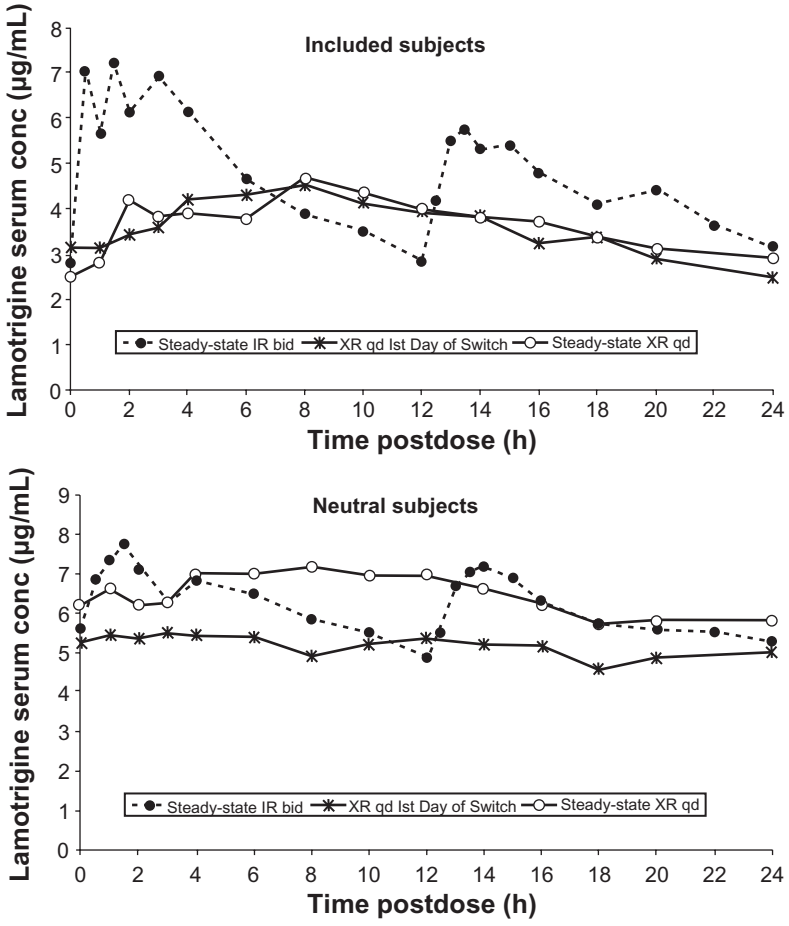

Figure 1. Median serum LTG concentration-time profiles for steady state LTG IR twice daily to LTG XR for induced and neutral subjects. Modified from Thompson, et al. *Epilepsia*. 2008.[19]

controlled and drug-resistant patients. Some feel that TDM does have a place in management of epilepsy patients on LTG to determine individual reference ranges,[24,25] and TDM is now indicated in pregnancy given the resulting significant change in the LTG clearance.[26,27] Regardless of serum drug levels, the "start low and go slow" titration allows adjustment of dosage for clinical efficacy and minimizes the risk of toxicity.

Clinical Studies

Efficacy

The initial "exploratory" studies of the tolerability and pharmacokinetics of LTG were performed in the mid 1980s[28,29] and were followed by a double blind, placebo-controlled crossover trial of LTG as add-on therapy for intractable epilepsy in 30 patients from 3 outpatient clinics showing a modest but statistically significant reduction in total and partial seizures in patients taking LTG versus placebo.[30] Small studies in France[31] and England[32] had similar results.

A larger, randomized, double blind, placebo controlled, crossover trial in 98 patients at 7 clinical centers to determine safety and efficacy of LTG for add-on therapy in refractory partial epilepsy was then undertaken.[33] Each treatment period lasted 14 weeks. The study population was 53% female and 90% white with a mean age of 35 years. More than half of the patients were receiving 2 or more concomitant AEDs with CBZ being the most frequently prescribed. During the LTG maintenance period with a maximum LTG study dose of 400 mg per day, median seizure frequency was reduced by 25% ($p < 0.001$). Across all centers, 44% of LTG patients had >25% reduction in seizure frequency compared with placebo with 20% of patients having >50% decrease in seizure frequency. The number of seizure days was reduced by 18% ($p < 0.01$) in those taking LTG compared to placebo. Most adverse experiences were mild to moderate and did not require discontinuation of the study medication. Only a few adverse experiences occurred at significantly higher rates with LTG than with placebo. These included ataxia, dizziness, diplopia, somnolence, rash, and blurred vision. Rash was the most commonly reported non-CNS related adverse experience occurring in 6% of patient during placebo treatment and 15% during LTG treatment. During LTG treatment, 5% of patients had adverse experiences requiring discontinuation of study participation prematurely compared with 1% during placebo treatment. Three LTG patients and one placebo patient were withdrawn after exhibiting a rash, and two LTG patients were withdrawn after experiencing mild to moderate CNS-related symptoms of dizziness, ataxia, nausea, headache and somnolence.

A dose response study to evaluate efficacy and safety of 300 and 500 mg per day of LTG as add-on therapy for partial onset epilepsy was done in a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of 216 patients.[34] During 6 months of treatment, the mean seizure frequency decreased by 20% with 300 mg of LTG daily and by 36% with 500 mg daily. Seizure frequency decreased by >50% in one third of the 500 mg group and by one fifth in the 300 mg group with a statistically significant reduction in seizure frequency and seizure days for the 500 mg group.

The SANAD (Standard and New Antiepilepsy Drugs) Study group examined the effectiveness of CBZ, gabapentin (GBP), LTG, oxcarbazepine (OXC) and topiramate (TPM) for treatment of partial epilepsy in an un-blinded randomized controlled trial of 1721 patients in the UK for whom CBZ was deemed to be the standard treatment.[35] From December 1999 through August 2004, patients with newly diagnosed epilepsy, those who had failed treatment with previous monotherapy and those who had entered a period of remission from seizures but had relapsed after withdrawal of treatment were included in the trial. The two primary outcome measures were time from randomization to treatment failure and the time from randomization to the achievement of a 1 year period of seizure remission. Secondary outcomes included time from randomization to a first seizure, time to achieve 2-year remission, and incidence of clinically important adverse events and side-effects. 1721 patients were randomized to CBZ (378), GBP (377), LTG (378), OXC (210) and TPM (378) with 5406 patient years of follow up. Across the entire duration of the trial, LTG was better than all other drugs for pair-wise comparisons for time to treatment failure for any reason (inadequate seizure control or unacceptable adverse events) (See Fig. 2). LTG and GBP were least likely to result in treatment failure for unacceptable adverse events, however, GBP was

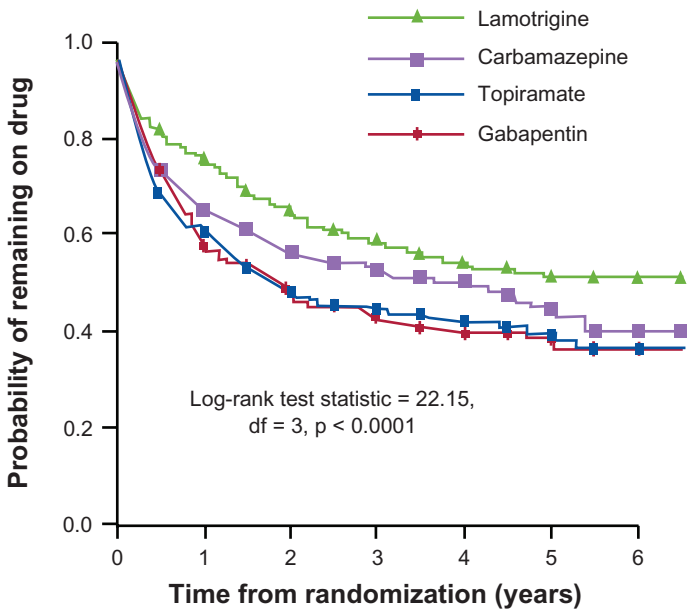

Figure 2. Time to treatment failure in the SANAD study of effectiveness of CBZ, GBP, LTG or TPM for treatment of partial onset epilepsy. Modified from Marson, et al. *Lancet*. 2007.[35]

most likely to be associated with treatment failure for inadequate seizure control. CBZ was the least likely to be associated with treatment failure due to inadequate seizure control, but there was no significant difference between CBZ and LTG. When comparing treatment failures, LTG was 10%–11% better for treatment withdrawal for adverse events (statistically different at all time points between 1 and 6 years) compared to CBZ and similar to CBZ for incidence of treatment failure due to inadequate seizure control. Economic analysis supported LTG over CBZ in terms of both cost per seizure avoided and cost per quality adjusted life year (QALY).

In a small study of 16 patients over 15 to 38 months the long term efficacy and safety of LTG was assessed as add-on therapy in refractory epilepsy. This study confirmed moderate efficacy and low toxicity.[36]

Safety and tolerability

In general, LTG has a satisfactory safety profile with mild CNS effects and mild skin rash being the most commonly reported adverse events in all of the initial trials.[28–33,37] A common observation was that dizziness and diplopia were more common when LTG was added to CBZ therapy.[38]

A double blind, parallel-treatment study comparing the safety of LTG versus placebo for 24 weeks as add-on therapy in 446 refractory patients[39] revealed treatment related adverse experiences (AE) in >10% of LTG patients which were statistically increased compared to placebo included blurred vision, ataxia, diplopia, dizziness and somnolence. Eight percent of both LTG and placebo patients discontinued their treatment due to AEs with the most common AEs at discontinuation being dizziness (3%), blurred vision (1%), headache (1%) and rash (1%) in LTG patients and ataxia (2%) among placebo patients.

An open-label, 6 year continuation study reported on the long term tolerability of LTG in 527 adult patients, 381 of whom received LTG for at least 2 years, and 248 of whom received LTG for at least 5 years.[40] Patients who had participated in one of the initial clinical studies of LTG as adjunctive therapy for partial seizures were enrolled and continued to take LTG at the same dose they received in the initial study, but their dose could be adjusted to a maximum of 1000 mg/day depending on their clinical response. Adverse events regardless of cause occurring in at least 20% of patients continuing LTG (n = 452) included dizziness (53.5%), diplopia (35.8%), ataxia (25%), headache (33.9%), and somnolence (20.6). Rash, regardless of type, seriousness or suspected cause, was reported by 11 patients (14.7%) with initial LTG exposure compared to 47 patients (10.4%) continuing LTG treatment. Rash was reported as a serious adverse event in only 0.4% of patients, none of whom required hospitalization or developed Stevens-Johnson syndrome.

The primary safety concerns with LTG therapy have been its association with rash, especially Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and anticonvulsant hypersensitivity syndrome (AHS), all of which are difficult to track due to inconsistencies in diagnosis. Both SJS and TEN are characterized by erythema with blisters and erosions of the skin as well as hemorrhagic erosions of mucous membranes.[41] The strongest predictor of rash to LTG is a history of rash with another AED.[42] Benign and self limited morbilliform rash and urticaria are the most common forms of cutaneous reactions reported with LTG. Based on pooled clinical trial experience in approximately 4000 patients, rash leading to hospitalization was reported in 11 patients with incidence of 0.3%. Four of these were reportedly SJS, giving an incidence of 0.1%.[37] The majority of rashes

occur within the first 8–10 weeks of treatment[37,41,43,44] (See Fig. 3) with the highest incidence occurring in those receiving both LTG and VPA.[37,44] There is a suggestion that the incidence of rash decreased after modification of the recommended dose escalation regimen.[41]

Anticonvulsant hypersensitivity syndrome (AHS) is characterized by the onset of fever usually 2 to 6 weeks after initiation of therapy followed by a skin eruption or lymphadenopathy and internal organ involvement, most prominently hepatitis, eosinophilia, blood dyscrasias and nephritis.[45] The syndrome's variable presentation including diverse clinical features and laboratory abnormalities has resulted in inaccurate reporting. Twenty six cases fitting the definition of AHS were reported from a review of the literature and 257 cases from the World Health Organization database.[46] Only 35% of the cases were published, but in all cases LTG was used concomitantly with other AEDs, 42% with an aromatic anticonvulsant, and 58% with VPA. It is important to note that none of the serious reactions including TEN and AHS associated with multiorgan failure occurred during clinical trials and are only reported with LTG in post marketing reports. SJS has been reported in only 0.1% of clinical trial patients.[37]

Safety in pregnancy

Women with epilepsy are of particular concern as there have been reports of increased risk of fetal malformations with use of both the older AEDs[47] and newer AEDs.[48] Pregnancy registries are currently used as a method of post marketing surveillance to determine the frequency of major congenital malformations (MCMs). The UK Epilepsy and Pregnancy Register prospectively examined the risk of MCMs from in-utero exposure to AEDs in 3607 cases. Of all live births, the rate of MCMs was only 4.2% for all AEDs. There were fewer MCMs in pregnancies exposed only to LTG compared to VPA but there was a positive dose response for MCMs with LTG ($p = 0.005$). MCMs occurred more often with polytherapy (6%) than for monotherapy (3.7%) with an adjusted odds ratio of 1.83 ($p = 0.002$). Polytherapy combinations containing VPA carried higher risk of MCMs than those combinations not containing VPA with the combination of VPA and LTG ($n = 141$) having a MCM rate of 9.6%.[49]

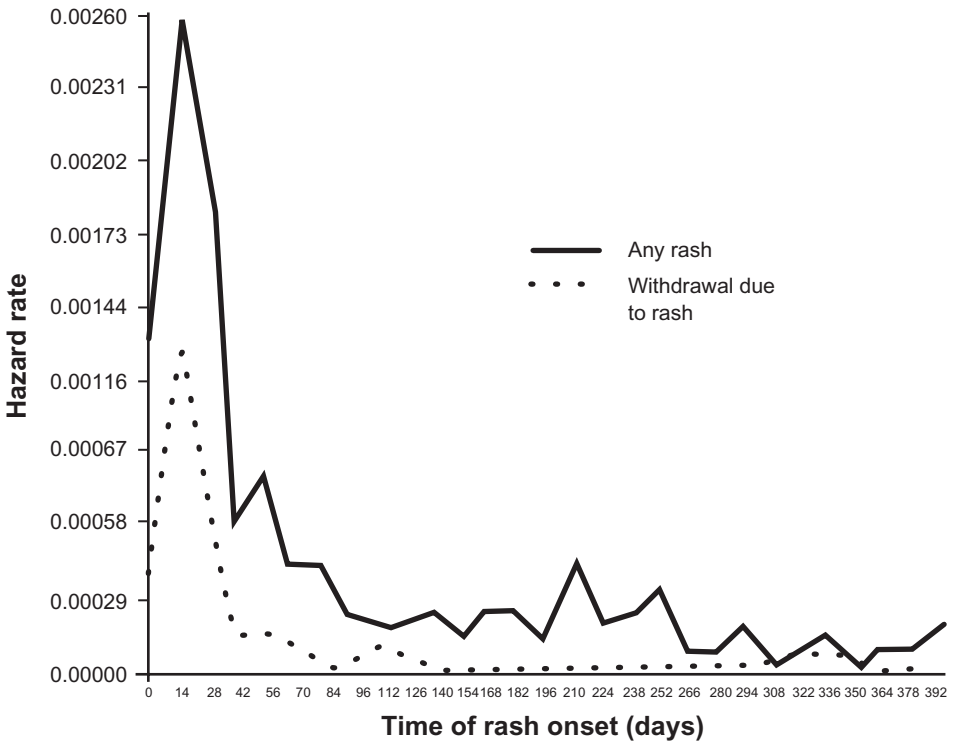

Figure 3. Hazard plot for the time of rash development or discontinuation due to rash after the initiation of LTG in clinical trials. Modified from Guberman, et al. *Epilepsia*. 1999.[43]

The International Lamotrigine Pregnancy Registry found that risk of all MCMs among offspring exposed to LTG monotherapy was 2.9%, which is similar to that of the general population.[50] Those women taking LTG in combination with VPA (n = 88) reported 11 MCMs (12.5%) as compared with women on LTG polytherapy without VPA (n = 182) who reported only 5 MCMs (2.7%). No distinctive pattern of MCMs was apparent with exposure to LTG but the sample size of 725 was too small to detect any but very large increases in specific MCMs. However the North American AED Pregnancy Registry reported on 684 infants exposed to LTG in North American and found a 10.4-fold increase in the frequency of orofacial clefts in comparison to 206,244 unexposed infants at Brigham and Women's Hospital (BWH) in Boston.[48] However, this was not a true comparison population and other published reports of the frequency of orofacial clefts are higher than the BWH rate.[51] Additional women taking LTG during pregnancy must be identified in the various pregnancy registries in order to fully understand the risks of MCMs in general and the more specific risk of orofacial clefts.

Patient Preference

Quality of life (QOL) is impaired in epilepsy in part due to worry about seizures, functional impairments such as inability to drive, difficulties with relationships and depression as well as side effects of certain AEDs. Therefore, AEDs that improve seizure control and have low toxicity are likely to improve QOL. Good control of seizures in epilepsy depends in part on medication compliance. Convenience and frequency of dosing are inversely related to compliance.[52] In an assessment of compliance with long term antiepileptic medications, rates of compliance averaged 87% with once daily dosing, 81% with twice daily and dropped to 39% with four times daily dosing.[53] Therefore, AEDs that are available in once daily dosing are more likely to result in decreased seizure frequency due to increased compliance.

Initiation of LTG has been shown to improve QOL using various validated measures.[54–56] LTG also has favorable effects on seizure severity, mood and perceived internal control.[57] It appears to be less disruptive to sleep than some of the older AEDs,[58] improves sleep stability without changes in daytime somnolence, and has no effect on neuropsychological performance including attention, reaction time, concentration or memory.[59]

Place in Therapy

Lamotrigine is approved for use as adjunctive treatment of both partial onset and primary generalized tonic clonic seizures and the generalized seizures of Lennox Gastaut Syndrome in patients over 2 years of age as well as conversion to monotherapy in patients with partial seizures receiving treatment with either CBZ, PHT, PB, or VPA. There is some evidence that it is also useful in other generalized seizure types such as typical absence epilepsy[60] and juvenile myoclonic[61] but this is outside the scope of this review. Lamotrigine is a good choice for many patients due to its efficacy, low toxicity, minimal interactions, and linear pharmacokinetics, but it is especially useful in some specific patient populations.

Mood disorders

Lamotrigine is a particularly good choice for epilepsy patients suffering from mood disorders as it is also approved for the treatment of bipolar disorder. Most epilepsy patients have milder dysphoric symptoms rather that the overt manic episodes or major depression associated with bipolar disorder,[62] but in a secondary analysis from a randomized, double blind, placebo controlled trial of 70 patients with generalized epilepsy, LTG significantly improved all mood symptoms as compared with placebo.[63] Mood scores as measured by Profile of Mood States (POMS) questionnaires were improved on adjunctive and monotherapy LTG independent of efficacy for epilepsy.[62] In addition, an open label study in 158 patients who were not taking antidepressant medication showed mean scores on depression related self-reported questionnaires to be significantly improved after LTG was added to patients' medication regimen and those patients completing the study continued to improve on monotherapy LTG.[64] Further, adjunctive LTG improved a variety of mood variables when compared to adjunctive levetiracetam in individuals with partial seizures.[65]

Elderly

There has been a dramatic increase in the incidence of partial onset epilepsy in those over age 65[2] with

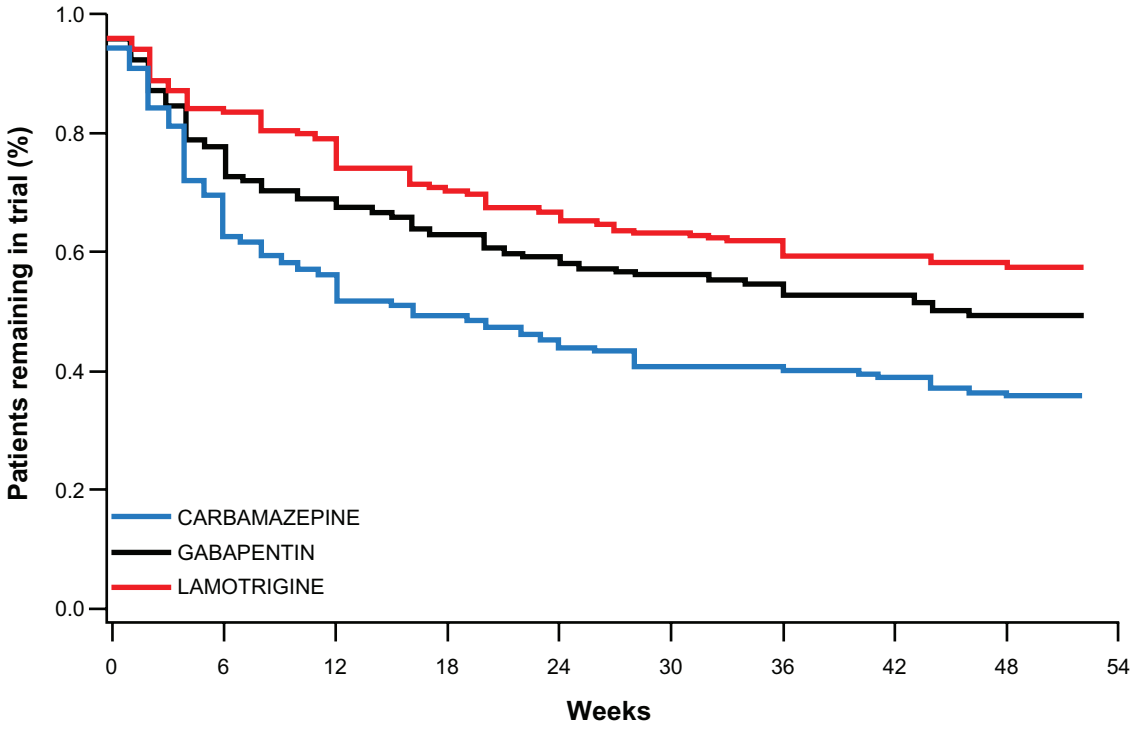

Figure 4. Percentage of elderly patients remaining in trial over 52 weeks. From Rowan, et al. *Neurology*. 2005.[70]

the most common causes being cerebrovascular disease[66,67] followed by dementia, trauma and neoplasm.[66] Given the symptomatic nature of most epilepsies in those over 60 and the high risk of seizure recurrence (90%), starting treatment after the first event should be considered.[66,68]

Unfortunately elderly patients are often excluded from clinical trials due to high co-morbidity and frequent polypharmacy.[66] There have been a few trials and reviews that have suggested that LTG is a better choice in the elderly population due to its lack of cognitive side effects, osteoporosis, influence on weight, and interaction with anticoagulants or antiplatelet agents.[67,69–72] It has also been suggested that LTG may provide some neuroprotective properties in animal models of cerebral ischemia.[73,74]

A VA Cooperative Trial assessed the tolerability and efficacy of LTG, GBP and CBZ in an 18 center, randomized, double blind, parallel study of 593 older patients with newly diagnosed epilepsy. The mean age of patients was 72 years with cerebral infarction the most common etiology of epilepsy. The patients had multiple medical conditions and took seven other medications on average. The primary outcome measure was retention in the trial for 12 months with the main limiting factor in patient retention being adverse drug reactions. Fewer LTG patients terminated for adverse reactions than patients taking either CBZ ($p < 0.0001$) or GBP ($p = 0.015$) (See Fig. 4). The efficacy was similar for all drugs but patients taking LTG had a higher seizure-free retention rate using an intent-to-treat analysis.[70]

Lamotrigine's linear kinetics are also an asset for elderly patients taking AEDs, but there are some slight pharmacokinetic modifications in this population. These include reduced absorption due to atrophy of the gastric mucosa and reduced intestinal motility, alteration in the volume of distribution due to reduction in total body water, reduction in binding with proteins, and reduced elimination from slowing of hepatic metabolism and glomerular filtration. Pharmacokinetic competition due to polypharmacy must also be carefully considered in this elderly population.[66]

Conclusions

Lamotrigine has been shown to be efficacious in the treatment of epilepsy and has a favorable side effect profile with only very rare instances of severe adverse events. It currently has multiple indications in epilepsy as well as mood disorders and is

well tolerated in most patients. Given LTG's linear kinetics and the possibility of once daily dosing either with the IR preparation for adjunctive therapy with VPA or the newly available XR preparation for adjunctive use with enzyme inducers such as PHT, CBZ and PB, LTG's convenience is obvious. As convenience and medication compliance are of utmost importance in seizure control, once daily dosing of LTG for use as adjunctive treatment in partial onset epilepsy is a great therapeutic option for many patients.

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