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Drug Profile

A pharmacological overview of lamotrigine for the treatment of epilepsy

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Abstract

Introduction:

Epilepsy is one of the most common neurological disorders, affecting about 2% of the population worldwide. Lamotrigine (LTG) is a second generation anti-epileptic drug (AED) with broad spectrum of activity, a favourable side-effect profile, simpler dosing than earlier drugs and efficacious in diverse epilepsy syndromes.

Areas covered:

The present review focuses on pharmacodynamics, pharmacokinetics, clinical efficacy, safety and tolerability of LTG and its effect on cognition, psychiatry, quality of life, women and pregnancy along with effect of enzyme inducing and enzyme inhibiting drugs over LTG and their effect on serum level fluctuations by collecting data from various studies over the years until 2016.

Expert Commentary:

Results from various studies and clinical trials indicate that LTG possessed a favourable profile of anticonvulsant activity and good tolerability as a monotherapy/or add-on therapy in children and adult patients against several types of seizures and syndromes. It has wide clinical dose range with favourable pharmacokinetic properties making it an excellent therapeutic option in epilepsy.

Keywords: Epilepsy, lamotrigine, pharmacokinetics, sodium channel blocker, women.

1. Introduction to the compound

LTG was first synthesised and developed by Wellcome research laboratories (Beckenham, Kent, England) in the early 1980s. Initial interest in aminopyrimidines similar to pyrimethamine led to the related compounds examination from which LTG was subsequently synthesised. It is a weak dihydrofolate reductase inhibitor. A hypothesis was developed initially because anti-folic acid agents (carbamazepine (CBZ), phenobarbital (PHB) and phenytoin (PHT)) were thought to be producing antiepileptic activity based on the observations from folic acid producing epileptogenic foci [1, 2]. However, a correlation between antifolate and antiepileptic activity has not been proven. In 1990, LTG was first approved for adult use in Ireland, the UK in 1991, and by US Food and Drug Administration (FDA), France in 1994 and 1995 respectively [3]. LTG is affected by both enzyme inducer and enzyme inhibitor drugs, so there is a need of slow-up titration of LTG to prevent rash/ Stevens-Johnson syndrome. Simultaneously up-titration is needed in women on LTG therapy with close monitoring of serum concentration, whereas in pregnant women already taking LTG achieving good serum levels is not an issue but it is a different situation in case of pregnant women started LTG newly, where clinical outcome is almost impossible as the slow up-titration together with progress of pregnancy decreases the likelihood to achieve good serum levels. In such cases, daily dosage levels can be exceeded to maximum dose by continuous monitoring under the supervision of a physician. From its genesis to till date, all significant studies and clinical trials of Lamotrigine in the treatment of epilepsy were given in table 1.

2. Methods

2.1. Search strategy

References for this review were identified from the authors files, relevant guidelines, patents, published articles, reviews and abstracts in PubMed/Medline (1820 - August 2016), EMBASE (1820 - August 2016), CINAHL, The Cochrane Controlled Clinical Trials Register (CCTR), The Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, clinicaltrials.gov and Web of Science.

In addition, the list of references of the retrieved articles, original research articles and previously published review articles were examined for further studies. Although we did not exclude citing older publications, we gave preference to major studies and clinical trials conducted from the genesis of lamotrigine.

Only articles published in English were reviewed.

2.2. Data extraction and assessment

Data extracted from each study included: study design, year of study, setting, age of patients, number of patients receiving LTG and comparator, study outcome, dose, type of seizure, type of therapy, summary of result, number and type of adverse events (AEs) for both LTG and the comparator drug(s) and the number of withdrawals along with reason for withdrawal. All studies were independently assessed by two reviewers; a third blinded reviewer was involved only if both reviewers did not agree on any study.

3. Chemistry and structure

LTG is an organic compound, white to pale-cream coloured powder with chemical name 6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine (table 2). It comes under the class phenyltriazine, structurally unrelated to other anti-epileptic drugs. Its molecular formula and molecular weight is $C_9H_7Cl_2N_5$ and 263.09g/mol respectively. It is having a solubility of 0.17mg/ml and 4.1mg/ml at 25ºC in water and 0.1M HCl respectively with pKa of 5.7. The

drug is commercially supplied as tablets for oral administration in various strengths like 5, 25, 50, 100, 150 and 200mg [18, 19].

4. Mode of action

LTG stabilises presynaptic neuronal membranes by acting at voltage-sensitive sodium channels and modulating presynaptic transmitter release of excitatory neurotransmitters such as aspartate and glutamate. *In-vitro* studies on rat cerebral cortex demonstrated ability of LTG in the inhibition of veratrine (sodium channel activator) induced aspartate, glutamate and it is found to be less effective in the inhibition of GABA or acetylcholine release without affecting potassium induced amino acid release. In conclusion, these studies suggest that LTG acts presynaptically at voltage-sensitive sodium channels [20]. In another study on mouse neuroblasts, LTG inhibited repetitive and sustained firing of sodium dependent action potentials suggesting its direct effect on voltage-activated sodium channels [21]. LTG may also influence and inhibit N- and P-type calcium currents in cortical neurons. These studies help in providing additional information on LTG and its anti-epileptic action at synaptic level [22, 23].

LTG has broad spectrum of activity against various seizures like absence seizures, focal seizures, tonic-clonic seizures and juvenile myoclonic epilepsy (JME) which was demonstrated in various animal preclinical studies. Seizures were induced in rats and mice using pentylenetetrazol (PTZ) infusion and repeated maximal electroshock (MES) methods, and when treated with LTG, termination of hind limb extension was observed, suggesting activity against focal seizures and tonic-clonic seizures. However at higher LTG doses, clonus latency was not increased in the PTZ test, suggesting ineffectiveness against absence seizures. But, in other models more predictive of human absence seizures, including the

photically evoked after-discharge test model in rats and the lethargic (lh/lh) mouse model, LTG was effective. LTG decreased electrically induced cortical after-discharge and hippocampal after-discharge duration in the marmoset, rat and dog, providing additional evidence of its efficacy against focal and dyscognitive seizures [24, 25, 26].

5. Pharmacokinetics

LTG has a half-life ($t_{½}$) of 24-34h in healthy individuals. It is highly metabolised by the liver enzymes, UDP-glucuronosyltransferase 1-4 and UDP-glucuronosyltransferase 1-3 involving glucuronic acid conjugation [18]. Pharmacokinetic studies of LTG in healthy volunteers and epilepsy patients have shown a complete absorption with absolute bioavailability of 0.976 ± 0.048 following first order kinetics at therapeutic dosage. LTG is ~ 55% protein bound with volume of distribution ~ 0.87 l/kg in healthy adults and ~ 1.25 l/kg in adult epileptic patients on anti-epileptic medication [27, 28, 29]. In various studies, LTG excretion through breast milk was examined in pregnant women. The results obtained from these studies are not similar, where median LTG plasma levels in nursed infants are ~ 30% of mother's plasma level without causing any adverse effects in infants. In "Medications and Mothers' Milk," LTG is rated as L3: moderately safe. In an another study to determine near bioavailability of LTG, a single 240mg dose of radio-labelled LTG was given to healthy adult volunteers. By the end of study, results have shown 2% of radioactivity recovery from faeces and ~ 94% of radioactivity recovery from urine; confirming LTG absolute bioavailability ~ 100%. The LD_{50} for LTG is 250mg/kg and >640mg/kg orally in rat and mice respectively with overdosing symptoms like lack of coordination, decreased conciousness, increased seizures etc [30].

6. Metabolism

LTG undergoes hepatic metabolism predominantly by glucuronic acid conjugation. UDP-glucuronosyltransferase 1-4 and UDP-glucuronosyltransferase 1-3 are the two major enzymes

involved in the LTG metabolism [31]. 70% of the oral LTG is recovered in urine as metabolite conjugate, LTG-2-*N*-glucuronide [32]. LTG ($t_{½}$) in adult healthy volunteers is ~ 25h and ~ 43h in chronic renal failure patients. The apparent plasma clearance of LTG in healthy volunteers taking single and multiple doses of LTG are 0.44mL/min/kg and 0.58mL/min/kg respectively. The rate of LTG metabolism is also affected by the concurrent medication taken by the volunteers. Rate of clearance drastically decreased to 0.18mL/min/kg thereby prolonging $t_{½}$ to ~ 59h in healthy volunteers taking multiple dose of LTG with valproate (VPA), an enzyme inhibiting drug [33]. On contrary, rate of clearance is increased to 1.12mL/min/kg in patients with epilepsy taking PHB or primidone, CBZ, VPA, PHT and multiple-dose LTG. This increase in rate of clearance and decrease in $t_{½}$ (~ 14h) of LTG on concurrent administration with other anti-epileptic drugs (AEDs) might be due to induction of hepatic cytochrome P450 enzyme by these drugs. To avoid this, the dose of LTG should be decreased or increased in presence of enzyme inhibitors or inducers as clinically indicated (testing of serum concentrations) [34]. In various randomised double blind, double blind add-on crossover trials and placebo-controlled studies, LTG add-on period was compared with the plasma levels of concomitant AEDs during a placebo period. From the results, it was clear that LTG has shown no significant effect on the concomitant AEDs plasma levels. Even LTG does not alter the steady-state plasma levels of PHT, primidone or PHB, CBZ and VPA [35-39].

7. Interactions

There are several reports of pharmacokinetic interactions of oral contraceptives with AEDs, which raise concern regarding increased risk of seizures. Some oral contraceptives decrease serum AED concentration by increasing AED metabolism. AED like LTG is affected by enzyme inducer and enzyme inhibitor drugs. It interacts with them and results in serum level fluctuations. Drugs like PHT, fosphenytoin, PHB, primidone, oxcarbazepine and olanzapine

increases LTG metabolism and results in reduced serum levels, whereas enzyme inhibitors like valproic acid, fluoxetine and sertraline inhibit LTG metabolism, resulting in raised serum levels [40]. But it does not influence the metabolism of drugs/components of some anti-depressants like bupropion. In some exceptional cases, oral contraceptives can also decrease the concentrations of AEDs such as LTG and, thereby, increase the risk of seizures. Since LTG is majorly eliminated by conjugation with glucuronic acid and ethinyl estradiol of the combined oral contraceptives, is a well-known inducer of uridine-diphosphate glucuronsyl transferase isoenzymes [41], the higher clearance rate of LTG was expected with oral contraceptives. The results of LTG and oral contraceptives interactions indicated that uridine-diphosphate glucuronsyl transferase metabolism of LTG was increased by a common combined oral contraceptive administration (ethinyl estradiol 35 μg/norgestimate 250 μg) [42]. Hence LTG levels should be checked before and after starting oral contraceptives and by monitoring clinically LTG levels and seizure control dose adjustments should be made.

Single oral dose of LTG was given in 12 healthy adult volunteers along with multiple oral doses of bupropion. As per results, pharmacokinetics of LTG did not show any signs of change on co-administration with bupropion [43]. In an 11days study on healthy adult volunteers, 300mg of LTG was co-administered with acetaminophen 900mg t.i.d. Study reported no significant interaction and change in pharmacokinetic parameters [44]. In some cases, LTG introduction causes pharmacodynamic interactions and it is a common consequence in patients established on high dose CBZ. Even though, LTG does not affect the metabolism and circulation time of CBZ, patient should be warned in prior about the amelioration of neurotoxic symptoms and possible interactions associated with reduction of CBZ dosage [45-48].

In another study, 150mg of LTG was given with oral contraceptive (ethinylestradiol 30μg/levonorgestrel 150μg) to 12 healthy volunteers for a period of 2 weeks. By the end of the study, LTG has shown no sign of effect on the steroid levels of contraceptives [49].

Enzyme inducing AEDS may interact with oral contraceptives and, thereby, reduce the efficacy of hormonal contraception. To partly overcome this limitation, formulations of oral contraceptives should contain at least 50 μg of estrogen and or supplementary or an additional barrier method or alternative methods should be considered, such as the classical IUDs (Intra Uterine Devices). The effectiveness of progesterone-only pills is also reduced if used in combination with enzyme-inducing AEDs. Further studies are clearly warranted to address critical issues, such as optimization of AED therapy for seizure control while achieving effective contraception with oral contraceptives. Patient-awareness programs on drug interactions with oral contraceptives may also help in improving contraception efficacy [50].

Therapeutic drug monitoring (TDM) plays a critical role in characterising the magnitude and course of alterations needed during treatment period. To assess the impact of TDM on seizure frequency, a prospective, observational study was conducted. In this study, cohorts of women were enrolled before conception or during pregnancy. Visits occurred every 1 to 3 months with review of seizure and blood sampling, examination and medication diaries. In the study free and total LTG clearance (Cl) during pregnancy and the postpartum period was assessed and calculated. The ratio to target concentration was compared between patients with and without increased seizures. It is evident that in second trimester, increase in seizure frequency was observed and it was associated with a lower ratio to target concentration ($p < 0.001$), and ratio to target concentration < 0.65 was a significant predictor of seizure worsening. Analysed samples also demonstrated an increased free and total LTG Cl in all trimesters above non-pregnant baseline ($p < 0.001$), with peak increase of 89% and 94% respectively in the third

trimester. Free LTG Cl was higher in white compared with black women. An empiric postpartum taper reduced the likelihood of maternal LTG toxicity without any malformations in new-borns [13].

8. Adverse effects

The side effect profile is different for different patients. The most common side effects associated with LTG are dizziness, nausea, vomiting, headache, tremor and ataxia. In few cases like JME, LTG can increase seizure frequency and background incidences along with irritability, confusion, aggression, agitation, psychosis, hallucination and rarely sedation. Death is a very rare phenomenon seen in patients taking LTG as monotherapy or in combination with other AEDs; it can be attributed to complication of seizure activity, as the clinical picture included disseminated intravascular coagulation, multi-organ failure. LTG was also linked to increased risk of Sudden Unexpected Death in Epilepsy (SUDEP) and pregnancy related deaths. As per FDA guidelines from December 2010, LTG carries a black box warning about aseptic meningitis and life threatening skin reactions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome [18, 31, 48, 51].

From a multicenter cross-sectional cohort study, reproductive endocrine health in pubertal females with epilepsy receiving antiepileptic drug like VPA, Levetiracetam (LEV) and LTG was evaluated. But the findings from the study do not allow us to clearly determine whether or not VPA, LEV, and LTG monotherapies considerably affect reproductive endocrine health in pubertal girls with epilepsy. Therefore, further screening tests should be recommended [52].

Rash is the commonest reason for discontinuing LTG treatment and it appears in the first 2-8 weeks of therapy. About 5% - 10% of patients develop rash, but only 1 in 1000 patients will develop a serious rash. If rash is mild, it may subside spontaneously or on reducing the dose

[53]. However some patients develop an accompanying systemic illness with fever, myalgia, eosinophilia, arthralgia and lymphadenopathy. In some cases, side-effects like fever, rash and fatigue are very serious, as they may indicate incipient DRESS syndrome or aseptic meningitis, toxic epidermal necrolysis and Stevens-Johnson syndrome. Very rarely it is also associated with reversible neutropenia and leukopenia [54].

9. Clinical efficacy

9.1. Placebo-controlled clinical and regulatory trials

Placebo-controlled, double blind clinical trials have demonstrated the efficacy and safety of LTG as an add-on therapy in patients with intractable epilepsy. Two of these studies had a parallel design and seven were crossover design.

In an Australian based placebo-controlled clinical trial, patients with intractable epilepsy were recruited. In this study, patients treating with valproic acid were given LTG as add-on therapy. It demonstrated that LTG was effective in controlling the seizures in the patients, refractory to treatment with valproic acid monotherapy [55]. In other placebo-controlled, double blind parallel study with 216 patients, statistically significant reductions in seizure frequency was observed with LTG 500mg compared to LTG 300mg or placebo. Reduction in the seizure frequency was significant and it was up to 36% in LTG 500mg treated patients compared with 20% for the 300mg group and 8% for the placebo group [56]. In another placebo controlled clinical trials, LTG was given to the patients with dyscognitive seizures. In 25% to 30% patients, about 50% of them have shown reduced seizure frequency [57-59]. Efficacy of LTG in tonic-clonic and Lennox Gastaut syndrome was proved by various case studies, anecdotal reports, uncontrolled studies and clinical trials [60-64].

120mg or 240mg of LTG single doses were given to 16 patients. After 24h, five patients with frequent interictal spikes showed reduction in spike frequency and six photosensitive patients

showed reduction (with abolition in two) in photosensitivity. The $t_{1/2}$ of LTG was also altered depending on the co-administered drugs [65]. In Australia LTG and vigabatrin were approved at the same time, but vigabatrin has greater efficacy with higher reimbursement than for LTG. During this, safety profile of LTG was taken into consideration. Consequently the approval terms were changed after adverse effects related to vigabatrin were taken into account.

Cross over trials was conducted in patients with tonic-clonic seizures and statistically significant decrease in seizure frequency was observed in the patients treated with LTG and placebo [35-39, 66, 67]. Group treated with LTG has shown ~30% of reduction in seizure frequency as compared with placebo treatment groups. The proportion of patients with significant improvement was 7 – 30% with seizure reduction > 50% [35, 38, 39].

From a cochrane review, randomised placebo-controlled trials of patients with drug-resistant partial epilepsy treated with LTG as add-on therapy for 4 to 12 weeks (baseline phases) and 8 to 36 weeks (treatment phases) were included from 14 studies with 1958 participants. The overall risk ratio for 50% or greater reduction in seizure frequency was 1.80 (95% CI 1.45 to 2.23; 12 randomised controlled trials) for 12 studies (n = 1322 participants) indicating that LTG was significantly more effective than placebo in reducing seizure frequency. The overall risk ratio for treatment withdrawal (for any reason) was 1.11 (95% CI 0.90 to 1.36; 14 randomised controlled trials) for 14 studies (n = 1958 participants). From the review it was concluded that LTG as an add-on treatment for partial seizures appears to be effective in reducing seizure frequency, and seems to be fairly well tolerated [68].

9.2. Comparative clinical trials of LTG

In order to assess the comparable efficacy of LTG and older AEDs various open label, prospective, double blind, multiple randomised, multi center studies were performed.

In a multi-center, randomised, double blind trial, LTG monotherapy was compared with gabapentin monotherapy, in patients with newly diagnosed epilepsy. Patients were

randomised and treated with a target dose of 150mg/day LTG or 1800mg/day gabapentin. In both the groups, similar proportion of patients became seizure free (LTG, 50%; gabapentin, 53%) [69].

In a multi-center, randomised, double blind parallel group trial, monotherapy of LTG and CBZ was given to patients with newly diagnosed epilepsy [70]. Patients with focal seizures and tonic-clonic seizures were randomised to either medication to undergo fixed dose escalation with a target dose of 150mg/day of LTG or 600mg/day of CBZ for a period of 4 weeks. Depending on the clinical outcome, doses were adjusted from 6 – 24 weeks. As evidenced, clinically similar efficacy was demonstrated by both medications in reducing seizures or becoming seizure free during the trial. But a greater portion of patients became tonic-clonic seizure free (LTG, 47%; CBZ, 47%) compared to patients with focal seizures (LTG, 35%; CBZ, 37%). Overall, fewer patients on LTG (15%) than on CBZ (27%) withdrew because of adverse events. The commonest side-effect leading to withdrawal with either drug was rash (9%, 13%). LTG and CBZ showed similar efficacy against focal seizures and tonic-clonic seizures in newly diagnosed epilepsy. LTG, however, was better tolerated.

Two major studies were performed by Standard and New Antiepileptic Drugs (SANAD) to compare the efficacy of LTG with older AEDs [71, 72]. In a randomised, unblinded controlled study, effectiveness of LTG, gabapentin, CBZ, oxcarbazepine or topiramate in the treatment of focal seizures was aimed to assess the LTG efficacy with regard to health economic outcomes, quality of life and long-term outcomes compared to the new AEDs. Total 1721 patients were recruited in this study and they were given with above mentioned AEDs keeping CBZ as standard treatment. The primary outcomes of this study were time to 1-year remission, time-to-treatment failure and the analysis was by both per protocol and intention to treat. For time to 1-year remission CBZ was significantly better than gabapentin (hazard ratio [HR] 0·75 [0·63–0·90]), and estimates suggest a non-significant advantage for

CBZ against LTG (0·91 [0·77–1·09]), oxcarbazepine (0·92 [0·73–1·18]), and topiramate (0·86 [0·72–1·03]). For time to treatment failure, LTG was significantly better than gabapentin (0·65 [0·52–0·80]), CBZ (0·78 [95% CI 0·63–0·97]), and topiramate (0·64 [0·52–0·79]), and had a non-significant advantage compared with oxcarbazepine (1·15 [0·86–1·54]). In a per-protocol analysis and intention to treat analysis, at 2 and 4 years the difference (95% CI) in the proportion achieving a 1-year remission (LTG-CBZ) is 0 (–8 to 7) and 5 (–3 to 12), suggesting non-inferiority of LTG compared with CBZ. Final results of the study proved that LTG was clinically better than CBZ, for time-to-treatment failure outcomes, the standard drug treatment and also considered to be an economical alternative for patients diagnosed with focal seizures [72].

In the second SANAD study, long term effectiveness of LTG, VPA and topiramate was compared in patient with tonic-clonic seizures or seizures that were difficult to classify. Total 716 patients were recruited in this study and for whom VPA was deemed to be standard treatment and randomly assigned to LTG or topiramate and valproic acid [71]. Primary outcomes of the trial were time to 12-month remission, time-to-treatment failure and assessment was by both per protocol and intention to treat. For time to 12-month remission VPA was significantly better than LTG overall (hazard ratio 0·76 [0·62–0·94]), and for the subgroup with an idiopathic generalised epilepsy 0·68 (0·53–0·89). For time to treatment failure, VPA was significantly better than topiramate, but there was no significant difference between VPA and LTG. For patients with tonic-clonic seizures, VPA was significantly better than both topiramate (1·89 [1·32–2·70]) and LTG (1·55 [1·07–2·24]. But there was no substantial difference between VPA and topiramate in either overall analysis or subgroup with tonic-clonic seizures. Interpretation of this study indicated that VPA is better and efficacious than LTG and topiramate. Based on the findings, VPA should remain as first choice of drug in patients with tonic-clonic seizures or unclassified seizures. But use of VPA

is limited in pregnant women, because of its known potential adverse effects and they have to be considered before the treatment.

It was pretty evident that SANAD studies suffered from a number of methodological limitations and especially results on LTG in focal seizures were biased by the inadequate use of CBZ. It was also not designed to and never possessed the power to examine the incidence of rare but serious idiosyncratic and chronic toxic effects and teratogenicity. It therefore leaves open a major area of concern around drug treatment of women in their child-bearing years with tonic-clonic seizures.

A joint Task Force of the European Academy of Neurology and the Commission on European Affairs of the International League against Epilepsy has published recommendations on when and how valproic acid should be used in the treatment of girls, women, and pregnant women with epilepsy. Following late 2014, European Medicines Agency announced restrictions over the use of valproic acid in pregnant women and emphasised the task force report based on the teratogenic effects caused by valproic acid. If valproic acid is prescribed, or considered, the physician is obligated to provide the complete and accurate information about the risks for any future children if the patient becomes pregnant. Data of overall congenital malformations in children exposed prenatally to different AED monotherapies were given in table 3 [81, 82, 83].

In a multicenter, randomised, open-label, controlled, parallel group trial, LTG was compared with LEV with regard to their efficacy and tolerability in the initial monotherapy for seizures. The trial included 409 patients aged ≥12 years with newly diagnosed focal or generalised seizures defined by either two or more unprovoked seizures or one first seizure with high risk for recurrence. Patients were titrated to 200mg/day of LTG or 2000mg/day of LEV for 22 or 71 days. Two dose adjustments by 500/50 mg were allowed. By the end of 6 weeks, proportions of seizure-free patients were LTG (64.0%) versus LEV (67.5%) and LTG

(47.8%) versus LEV (45.2%) during the whole treatment period of 26 weeks. Adverse events associated with study discontinuation occurred in LTG (8/201) versus LEV 17/204 patients. By the end of the trial, there were no significant differences with regard to efficacy and tolerability of LTG and LEV in newly diagnosed focal and generalised seizures despite more rapid titration in the LEV arm [15].

9.3. LTG as extended release formulations

In an open label study for 28 weeks in 121 patients, tolerability and efficacy of lamotrigine (LTG) extended-release (XR) as adjunctive therapy with optional conversion to monotherapy in patients ages ≥65 years with epilepsy was studied. This study included an 8- week Adjunctive Maintenance Phase, a 13-week Conversion and Monotherapy Phase or Adjunctive Optimization Phase, and a Follow-Up /Taper Phase. At the end of the Adjunctive Maintenance Phase, patients on a single concomitant AED were converted to LTG XR monotherapy (over 5 weeks) and then remained in the Monotherapy Maintenance Phase (for 8 weeks). All other patients remained in the study on concomitant AEDs for an additional 13 weeks in the Adjunctive Optimization Phase. Out of 121patients, 92 patients completed the Adjunctive Maintenance Phase, 74% (68 patients) were deemed by their treating physician to be eligible to proceed with monotherapy; the remaining 26% (24 patients) continued in the Adjunctive Optimization Phase. No serious adverse effects were reported. During the entire treatment period, the median percent change from baseline was 90% ($p<0.0001$). 52 (76%) patients out of 68 who entered the monotherapy phase successfully converted to monotherapy. The results of this study contribute for the establishment of safety, tolerability, and efficacy of LTG XR across age groups [84].

In a classic 2-period, crossover bioavailability study in elderly patients, relative and absolute bioavailability of LTG immediate-release (IR) and LTG-XR formulations under steady-state conditions were evaluated. On treatment days, every single subject's morning dose (IR or XR

LTG) was replaced with an intravenous 50mg dose of stable-labeled LTG and blood samples were collected and measured at 13 points between 0 and 96h. XR and IR lamotrigine formulations were similar with respect to steady-state average concentration ($C_{avg,\ ss}$), area under the concentration-time curve from 0 to 24 hours ($AUC_{0–24h\ ss}$), and trough concentration ($C_{t,\ ss}$). LTG XR relative to IR, a lower fluctuation in concentrations (33%) and delayed time to peak concentration ($T_{max,\ ss}$) 3.0h vs 1.3h was observed with an absolute bioavailability of 73% and 92%. In conclusion, the formulations were bioequivalent with respect to $AUC_{0–24h\ ss}$, $C_{t,\ ss}$, and $C_{avg,\ ss}$ indicating potential benefit of LTG-XR and its possibility to switch directly from IR to XR lamotrigine without changes in the total daily dose which in turn improves tolerability and seizure control by the lower fluctuation of steady-state concentrations compared with IR lamotrigine [85].

In a pooled analysis of three international, multi-center, randomized double-blind, open label clinical trials, tolerability and safety profile of LTG-XR was determined against LTG-IR. Total 662 patients in the integrated database were exposed to one or more doses of LTG-XR. Of the 662 patients who took at least one dose of LTG-XR in this pooled analysis, 82.5 % patients (546) were exposed to LTG-XR for ≥26 weeks, and 40.8 % patients (270) were exposed for ≥52 weeks. From pooled analysis data it is clear that LTG-XR administered as adjunctive therapy for partial or primary generalized tonic-clonic seizures or as monotherapy for partial seizures was generally well tolerated and contributes to a growing body of evidence in establishing the safety, tolerability and efficacy profiles of LTG-XR against LTG-IR [86, 87, 88, 89].

9.4. LTG in the treatment of paediatric patients

Number of studies has reported the administration of LTG in children. In several openlabel, prospective studies as well as randomised, placebo-controlled, add-on trials have demonstrated the safety and efficacy of LTG in children with focal seizures, myoclonic

absence, myoclonic seizures, tonic and atonic. Another report suggests that atypical absence and dyscognitive seizures responded best to LTG. In a review of 120 children treated in Paris showed that 10% of patients became seizure-free, 40% of the patients experienced at least a 50% reduction in total seizures [90]. A multi-center placebo-controlled trial was conducted in 201 children aged 2 - 16. They were treated with placebo and LTG and results demonstrated a significant 'r' mean reduction in seizure frequency in LTG group compared to placebo group (44% versus 12.8%, respectively). Patients free from all focal seizures during maintenance period were 1.3% in placebo group and 33% in LTG group. A statistically significant increase in days free of tonic-clonic seizures was also seen during the maintenance period (4.2% in placebo versus 53.7% in LTG, respectively) [89]. Another study was conducted in 59 students attending a special residential school for children with epilepsy. For automatic monitoring, 12 subjects were selected with spikewave discharges. Among them 6 subjects showed a reduction in their spikewave events with LTG treatment and conferred its benefit to the patients [92]. In other study, data from five openlabel, add-on studies was evaluated and pooled. About 31% of patients have experienced a reduction in ≥ 50% seizure frequency during the maintenance period [60].

9.5. LTG in the treatment of childhood absence seizures

In a retrospective analysis, patients with typical absence seizures refractory to VPA were treated with low-dose of LTG and treatment appeared to be effective [93]. In children and adults, 1.6 – 3mg/kg/day and 25 – 50mg/day of VPA was added to differing doses of LTG. In the treatment, 9 of 14 patients became seizure free and suggest the possibility of a therapeutic interaction between these two drugs.

In another 'responder-enriched' study design, 45 newly-diagnosed children and adolescents (aged 3 - 15) with absence seizures were treated with LTG monotherapy and treatment demonstrated to be effective [94]. Patients in placebo group became less seizure free

compared to LTG group (21% versus 62%, respectively). During escalation period in the protocol and intent-to-treat analysis, total 82% and 71.4% patients became seizure free. Throughout the study, no patients were withdrawn due to any significant changes in weight or adverse effects. Finally data concluded that, a significant difference in efficacy in LTG group compared to placebo group.

9.6. LTG in the treatment of tonic-clonic seizures

In an unblinded randomised controlled trial by SANAD in hospital-based outpatient clinics in UK, study was aimed to compare the longer-term effects of VPA, LTG, or topiramate in patients with tonic-clonic onset seizures or seizures that are difficult to classify. 716 patients were recruited and randomly assigned to VPA, LTG, or topiramate between Jan 12, 1999 and Jan 13, 2006. Primary outcomes were time to 1-year remission and time to treatment failure, and analysis was by both per protocol and intention to treat.

For time to treatment failure, there was no significant difference between VPA and LTG (hazard ratio 1·25 [0·94–1·68]), but VPA was better than topiramate (hazard ratio 1·57 [1·19–2·08]). For patients with tonic-clonic epilepsy, VPA (1·25 [0·94–1·68]) was significantly better than topiramate (1·89 [1·32–2·70]) and LTG (1·55 [1·07–2·24]). In patients with generalised and unclassified epilepsies VPA is efficacious and well tolerated than topiramate and LTG. But the known potential adverse effects of VPA during pregnancy are limiting its use. In such cases, LTG acts as a better alternative to other AEDS by limiting the extent of abnormalities and adverse effects caused to foetus and pregnant women (Table 3) [71]. But the increased SUDEP risk in pregnant women on LTG treatment should also be considered.

In a study, LTG was given to 677 adult patients with clonic, tonic and tonic-clonic seizures [95]. As per data obtained, among 40% of these patients 14% became seizure-free and 50% of these patients experienced reduction in seizure frequency. In some of them about 50% of

patients had at least 50% seizure reduction of their atypical absence and atonic seizures. In another study with 19 patients, 15 were reported to show at least 50% seizure reduction. Many other studies have reported LTG and its efficacy in various seizure types like clonic, tonic and tonic-clonic [63].

Recently, a retrospective, population-based analysis was performed on patient data of 4.1 million insurants from the German statutory health insurance. This data was based on the patients with newly diagnosed epilepsy between 2008 and 2014, where first anti-convulsive agent in a newly diagnosed epilepsy patient was validated against the clinical practice guideline. Data from the study shows a stable prescription of LTG around 20% and a very steep increase for LEV to 60% while CBZ and VPA decrease significantly. Overall, there is a significant increase in guideline compliant monotherapy in focal epilepsy syndromes, increasing from 20.1% (2008) to 44.1% (2014) ($p < 0.001$). In contrast, among patients with generalised epilepsies, the share of guideline compliant monotherapy decreases from 23.5% to 15.4% ($p < 0.001$), while the proportion of guideline noncompliant monotherapy increases significantly by 10% from 17.8% to 27.5% ($p < 0.001$). In Germany, both LTG and LEV are recommended as first choice of drugs in initial monotherapy of focal epilepsies since 2008. The huge difference in prescription between LTG and LEV likely affiliated due to favourable properties of LEV and not due to guideline adherence. Despite the careful study design, this retrospective study on health insurance data suffers from certain limitations inherent to such investigations [96].

9.7. LTG in the treatment of Lennox Gastaut syndrome and Juvenile myoclonic epilepsy

LTG was proved to be effective in the treatment of JME and seizures associated with Lennox–Gastaut syndrome.

In a double-blind, placebo-controlled, randomised trial, LTG was used as add-on therapy in patients with Lennox–Gastaut syndrome [62]. Initially during 4 week baseline period all the subjects received placebo, during which seizure frequency was 16.4 and 13.5counts/week in the LTG and placebo groups. Later all subjects were randomised to receive either placebo or LTG. After the 16-week treatment period, reduction in seizure frequency was observed in LTG and placebo groups (9.9 and 14.2counts/week, respectively).

Evidence for the efficacy of LTG in patients with JME was demonstrated in various retrospective, open-label monotherapy and pilot studies. In a 24 weeks open-label monotherapy study, patients with newly diagnosed JME and patients receiving VPA with poor seizure control or intolerable side effects were recruited. During this period, LTG was titrated for 8 weeks. As per results, new onset group became 75% seizure free and had no myoclonus. In patients previously on VPA treatment, 85% became seizure free and 70% myoclonus free [97, 98]. In another two retrospective studies, LTG was studied and demonstrated to be an effective alternative over VPA for the management of JME [99].

10. Safety and tolerability

10.1. Role and effect in psychiatry

LTG was initially developed as an anticonvulsant drug but later it emerged as new drug in psychiatry [100]. It is used as mood stabiliser and established for the treatment of bipolar disorders by the end of 1990s. Many clinical trials have confirmed its activity in bipolar maintenance treatment to prevent relapse to both depressive and manic phases in patients aged 18years and over [19]. LTG is currently licensed for the maintenance treatment of bipolar disorder (depressive episodes in bipolar type II). Although, LTG is less effective than lithium but there is an evidence of its efficacy in treating refractory bipolar disorder, bipolar depressive episodes and as an augmentation agent for treatment resistant unipolar depression. The use of lithium is highly discouraged and less widely used than previously due to its

known teratogenesis, possibility of permanent renal problems and its concern about true efficacy.

In a trial, LTG was compared with other mood stabilisers and often better tolerated. A study conducted in 28 patients with borderline personality disorder suggested, LTG may reduce impulsivity associated with this disorder [101]. In another study, women with borderline personality disorder were treated with LTG and demonstrated its efficacy in reducing aggression [102]. In patients receiving antipsychotic treatment to treat schizophrenia [103], conjunctive treatment with LTG proved to be ineffective. LTG is superior to placebo for the treatment of post-traumatic stress disorder [104] and depersonalization disorders [105]. LTG did not differ from placebo for the treatment of autistic disorder [106], cocaine dependence [107] and binge eating with obesity [108].

Recently, there is an increased emphasis on use of mood stabilisers by clinical psychiatrists for the treatment of bipolar illness. But the adverse effects like weight gain, sedation, polycystic ovary (PCO) syndrome, enzyme induction and enzyme inhibition associated with valproic acid, CBZ and most of second-generation anti-psychotic drugs are limiting their usage. To avoid above problems and to seek patient compliance, LTG was used as an alternative. Rapid introduction of LTG causes severe rash.

10.2. Role and effect on cognitive function

Association of anti-epileptic therapy with cognitive impairment represents a particular problem, especially in the young and elderly. Existing data suggest that LTG is an effective, well tolerated new generation AED. It does not show any sign of cognitive deficits which are commonly associated with other AED therapies. This was supported by various volunteers, monotherapy and add-on clinical studies. In a volunteer acute study of 1 day, LTG (120mg and 240mg) was given to 12 healthy adults [109]. There was no significant change in any of the neurocognitive functions relative to baseline performance. In another study, effect of LTG

on cognitive functioning has been compared with those of CBZ in patients with newly diagnosed epilepsy [109]. Patients were tested for attention, mental flexibility (stroop test, trial making test and logical reasoning), verbal learning and memory tests at baseline and then periodically up to 48 weeks. Results from the study concluded that LTG may have a favourable long term effect on cognitive function when compared with CBZ. Data from different studies suggest improvement in cognitive functioning with LTG treatment which is not seen with standard AEDs.

10.3. Role and effect on neuronal damage

Status epilepticus causes neuronal damage and cognitive impairment. In a study on wistar rats for 2 weeks, LTG was compared with CBZ for their effect on status epilepticus-induced temporal lobe damage and memory impairment. Rats were induced with status epilepticus by electric stimulation of the perforant pathway (PP), after which they were treated with either LTG (12.5mg/kg, twice a day) or CBZ (30mg/kg, twice a day) and both groups were compared. Final data demonstrates that group treated with LTG has shown mild neuroprotective effect over the group treated with CBZ in status epilepticus-induced neuronal damage, even when administered after the beginning of status epilepticus [110]. Many studies have confirmed the activity of LTG to protect neurons against experimentally induced ischemic or toxic lesions *in-vivo* [111, 112, 113].

10.4. Role and effect on women and pregnancy

Among all the AEDs and mood stabilisers, CBZ and valproic acid are widely used. But teratogenesis is one of the major concerns with them; to avoid this LTG is preferred (Table 3). In a study conducted by International Registry of Antiepileptic Drugs and Pregnancy (EURAP), lowest rate of fetal malformations was observed in more than 4000 pregnant women when given LTG doses up to 300mg daily when compared with commonly used AEDs [114]. LTG was marketed as an ideal AED for pregnant women, claiming to be

equally effective to valproic acid. It is also free from causing any effect on cognitive development of the foetus and foetal malformations.

The main problem with the use of LTG in pregnancy is the slow introductory dose schedule, which is necessary to prevent serious, occasionally catastrophic, adverse effects. LTG introduction regimen starts with 12.5mg doses on alternate days, for 2 weeks. Then the dose will be doubled every week till 200mg per day has been reached (in rare cases, daily dosage can be exceeded to 1000mg/day). The major limitation of LTG use in pregnancy is its slow dosage regimen introduction, serum level measurements and lack of efficacy to stop seizures during initial dose adjustments periods. With respect to lactation, human milk is a complex, sophisticated infant support system by providing both non-nutritive and food/ nutritive components [115]. From mother to infant, considerable amount of LTG excretion was observed through breast milk. Especially in preterm or small babies, close monitoring for drug toxicity is required [116]. Overall, LTG can be used till it outweighs the unknown potential risk to foetus [117].

10.5. Role and effect on quality of life

The aim of the AED therapy is to give the patient a better quality of life. It was assessed in number of patients by using questionnaires. The Side Effect and Life Satisfaction (SEALS) inventory is a patient-complete questionnaire containing five categories (cognition, temper, worry, dysphoria and tiredness) designed to assess patients psychosocial functioning [118]. SEALS was studied and validated in a large group of 923 patients [119]. Patients taking LTG along with one other AED was found to have fewer symptoms than patients taking two or more AEDs. Furthermore, when compared with patients taking CBZ, LTG monotherapy showed a greater improvement on all five SEALS categories in newly diagnosed epileptic patients.

In a study both SEALS inventory and Quality of Life in Epilepsy - 31(QOLIE-31) have been used to assess health related quality of life [120]. Effect of switching to a monotherapy regimen of either LTG or VPA was examined in total 246 patients and a report was prepared based on the data collected from the patients. Three of five subscales for the SEALS inventory (cognition, tiredness and dysphoria) and five of seven subscales for the QOLIE inventory (cognition, overall QOL, medication, social functioning and energy-fatigue) improved more than twice in the patients treated with LTG when compared with valproic acid. Data suggests that LTG exerted a favourable profile in terms of both impact of side effects and the underlying condition including patients perceived cognitive abilities [120].

In another randomised controlled clinical trial, LTG was compared with PHT [121]. Both of them have shown similar therapeutic activity in controlling seizures in a group of newly diagnosed patients with untreated focal seizures or tonic-clonic seizures. SEALS scores were recorded for both the drugs and scores were found to be a slight higher in PHT group. According to the study, LTG has shown lower central nervous system side effects when compared with PHT [121]. From the studies, it was reported that LTG showed a statistically significant improvement in patients' happiness and quality of life.

11. Safety concerns

The main competitor for LTG is VPA but VPA causes PCO syndrome, hirsutism, infertility, menstrual abnormalities and hyperinsulinism. Like other traditional AEDs, VPA was also claimed to be affecting the sperm count, motility and increase in spermatic fluid viscosity leading to the impairment of male fertility. But from the studies reported from Finland, LTG has shown no effect on sperm count or motility in contrast to other traditional AEDs [122, 14].

In studies on dogs, LTG is metabolised to form a metabolite (2 –*N*-methyl lamotrigine) [18]. This metabolite has produced dose dependent prolongation of the PR and QRS intervals.

However, such metabolites are not been observed in human plasma even after a long treatment with LTG but first degree AV block was significantly observed, although no causal relationship could be established. But none of the patient's discontinued LTG treatment due to the development of AV block [18, 55, 123].

LTG is also reported to be a weak inhibitor of dihydrofolate reductase in *in-vitro* studies. In both animal and human studies, use of LTG as a chronic therapy has shown no significant haematological effects. Except, few patients in human studies have reported aplastic anaemia and pancytopenia [18].

Idiosyncratic reactions are a major source of safety concern because they encompass most life-threatening effects of AEDs, as well as many other reactions requiring discontinuation of treatment. Specified reaction has been reported for LTG for liver toxicity, pancreatitis, aplastic anaemia and the adverse reactions associated with a warning box in the U.S. prescribing information monographs for Stevens-Johnson syndrome and toxic epidermal necrolysis. Serious consequences of idiosyncratic reactions can be minimized by cautious dose titration, knowledge of risk factors, avoidance of specific AEDs in sub-populations at risk, and careful monitoring of clinical response [124].

12. Dosing

LTG has no well-defined therapeutic range and its dosing differs from patient to patient depending on the concomitant use with an enzyme-inducing or enzyme-inhibiting AEDs. So based on patients clinical response and/or adverse effects, dose adjustments should be done to establish a safe therapeutic plasma level [125, 126]. LTG with enzyme inducing AEDs like PHT, recommended initial dose is 50mg/day for 2 weeks, followed by 50mg t.i.d. for 2 weeks. Therefore, depending on the patient clinical response, further dose increases can be made up to 100 – 500mg/day (1 or 2 divided doses) for the usual maintenance.

In patients receiving LTG with enzyme inhibiting AEDs like VPA, an initial dose of 25mg every other day is recommended for 2 weeks, followed by 25mg daily for 2 weeks. Further dose is increased to 25 – 50mg/day every 2 weeks up to a maximum dose of 300 – 500mg/day. Maintenance doses as high as 700 mg/day have been used. However relationship between plasma concentration and clinical response and/or adverse effects is not yet clear, although a clinically applicable therapeutic range of drug plasma concentration is 3 – 14 mg/l [46]. The value of routine monitoring of LTG plasma concentration is not yet established but it should be followed stringently in pregnant women [125, 126, 127].

13. Expert Commentary and Five Year View

LTG is a second generation AED with broad spectrum of efficacy. It acts on voltage-sensitive sodium channels and modulates the excitatory neurotransmitters at synaptic level. Preclinical studies in animals have demonstrated the efficacy of LTG against various seizure types including focal motor, absence seizures, tonic-clonic, juvenile myoclonic and Lennox-Gastaut syndrome. LTG is also drug of choice in pregnant women with excellent tolerability and safety profile and it was confirmed by various studies on rats and pregnant women. Even though, LTG has shown no effect on concomitant AEDs and their plasma levels, but it is highly affected by enzyme inducer and enzyme inhibitor drugs. The use of enzyme inducer drugs concomitantly reduces the $t_{½}$ of LTG, whereas the use of enzyme inhibitors increases the $t_{½}$ and serum levels by decreasing the metabolism. But LTG is not influenced or/influence the metabolism of anti-depressants but whereas oral contraceptives can enhance the clearance of lamotrigine, which eventually raise concern regarding increased risk of seizures.

Compared to other AEDs, LTG have some common side effects except rash and in almost all cases it can be minimised by titrating the dose levels. Placebo-controlled trials show LTG efficacy in treating intractable epilepsy and significant improvement in seizure reduction, whereas comparative clinical trials confirmed that LTG is at least as effective as the standard

old AEDs. Studies conducted by SANAD also proved the clinical efficacy of LTG over other AEDs and also considered it as an economical alternative.

Pooled data analysis from various clinical trials demonstrates the potential benefit of LTG-XR to improve tolerability and seizure control by the lower fluctuation of steady-state concentrations compared with LTG-IR.

Several prospective and retrospective studies have demonstrated the safety and efficacy of LTG in treating children with various seizure types including focal and childhood absence seizures. A long term effect of AEDs on patients with tonic-clonic seizures was studied by SANAD in unblinded randomised trial and reported LTG as a better alternative. Data from the studies suggest that, LTG is not associated with impaired cognitive functioning. Studies even suggest that in many cases, use of LTG can lead to improved cognition and associated improvements in health related quality of life. Studies also confirm LTG as an ideal AED in pregnant women because of its minimal effect on foetus and foetal malformations compared to other AEDs and it was proved and established by various countries prospective registries. Even LTG has better safety profile than alternative AEDs and drug selection should be a shared decision between the clinician and the informed patient based on careful risk–benefit assessment.

Trials suggest LTG will have an important role in treatment of epilepsy. Although there are challenges to the use of LTG, particularly rash development, but its broad efficacy, well tolerability, favourable pharmacokinetics properties, neuroprotection, lack of cognitive impairment or/side effects, improved quality of life, low drug-drug interaction potential and its safety profile in pregnant women is making it as an excellent therapeutic option in epilepsy. However from population-based analysis, it is clear that change in prescription patterns are very difficult to foresee. Further evaluations should address the question of

whether patients treated in line with the guidelines have a favourable outcome, compared to patients not treated in line with current guidelines.

14. Key Issues

- Lamotrigine has broader clinical spectrum of activity against various seizures.
- It is well tolerated and widely used.
- Main adverse events are rash.
- In pregnant women, lamotrigine is a drug of choice with excellent tolerability and safety profile by showing minimal effect on foetus and foetal malformations.
- Role of lamotrigine and its safety, tolerability on cognitive function, neuronal damage, women and pregnancy, quality of life was discussed.

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Table 1: The characteristics of lamotrigine

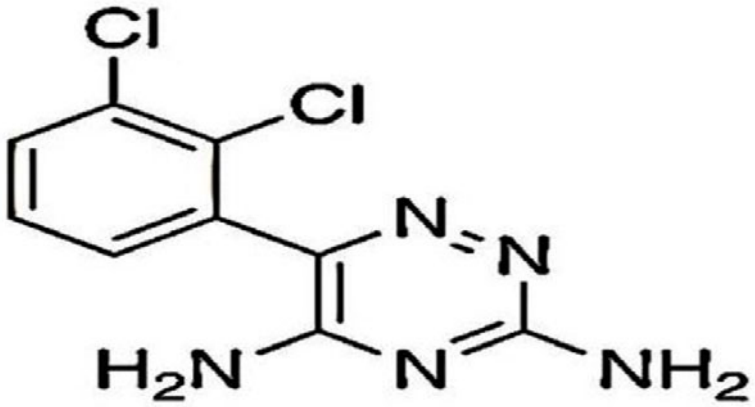
Drug name	Lamotrigine
Phase	Launched
Approved Indication	Epilepsy
Pharmacology description	Sodium channel blocker
Route of administration	Self-administration by purposely-trained patients
Chemical structure	
Regulatory approval	1990 HPRA, 1991 MHRA 1994 USFDA, 1995 ANSM
Pivotal trails	[52, 67, 68, 86, 87, 108, 113, 114]

Table 2: Key studies and clinical trials of Lamotrigine in epilepsy

S.No.	Research group	Study design	Follow-up period (Weeks/Months)	Results
1	Cocito et al., 1994 [4]	Non-comparative open label	15-38 Months	Over a period of 1 year, LTG was effective in significantly reducing seizure frequency. But the number of patients in the study was small. This study confirms the moderate efficacy and low toxicity of long-term LTG in severe epilepsy.
2	Brodie et al., 1995 [5]	Double-blind, randomised, parallel-group comparison	48 Weeks	The proportion of patients remaining seizure free was similar with LTG and with CBZ. LTG, however, was better tolerated.
3	Brodie et al., 2002 [6]	Multicenter, double-blind, randomized, parallel-group	30 Weeks	GBP and LTG monotherapy were similarly effective and well tolerated in patients with newly diagnosed epilepsy.
4	Marson et al., 2007 [7]	Unblinded randomised controlled	72-96 Months	LTG is clinically better than the standard drug treatment and cost-effective alternative for patients diagnosed with partial onset seizures.
5	Pennell et al., 2008 [8]	Prospective, observational	25-30 Months	Novel data from this study contribute to a rational treatment plan and dosing paradigm for LTG use during pregnancy, parturition,

				and the postpartum period.
6	Tomson et al., 2011 [9]	Observational cohort	14-16 Months	Data from this study suggest that lower doses of LTG, CBZ with dose adjustments during and later pregnancy period helps in controlling seizures; it also seems to be associated with low malformation rates.
7	Rosenow et al., 2012 [10]	Multicenter, randomised, open-label, controlled, parallel group	26 Weeks	The proportions of seizure-free patients were LEV (45.2%) versus LTG (47.8%) during the whole treatment period of 26 weeks. Data suggests no significant differences with regard to efficacy and tolerability of LTG and LEV in newly diagnosed focal and generalised seizures despite more rapid titration in the LEV arm.
8	Meador et al., 2013 [11]	Prospective, observational, assessor-masked, multicentre	72 Months	Over a period of 6 years, LTG was proved to be safe by not showing much effect on cognitive outcome in children when compared with other AEDs.
9	Yasumoto et al., 2015 [12]	Multicenter, uncontrolled, open-label	24 Months	LTG monotherapy in children with typical absence seizures was well tolerated and at the end of maintenance phase 35.0% of patients were seizure free.
LTG as add-on therapy				

10	Matsuo et al., 1993 [13]	Multicenter, randomized, double-blind, parallel-group, placebo-controlled	39 Weeks	34% of patients had a 50% or greater reduction in seizure frequency with LTG. LTG as add-on therapy was safe, effective, and well tolerated for refractory partial seizures.
11	Motte et al., 1997 [14]	Double-blind, placebo controlled	16 Weeks	The addition of LTG to standard anticonvulsant therapy reduced the generalized seizures frequency by 50% or more. LTG was an effective and Well - tolerated treatment for seizures associated with the Lennox–Gastaut syndrome.
12	Beran et al., 1998 [15]	Multicenter, randomised, double-blind, placebo-controlled, crossover	24 Weeks	Significant reduction (≥ 50%) in seizure frequency was observed in 50% cases of tonic-clonic and 33% of absence seizures. The number of patients recruited in this study was small. LTG as add-on therapy was effective in patients with refractory generalised epilepsies.
LTG as adjunctive therapy				
13	Duchowny et	Placebo-controlled	24-26 Weeks	LTG was found to be safe and effective for

	al., 1999 [16]			the adjunctive treatment of partial seizures in children.
14	Biton et al., 2005 [17]	Randomized, double-blind, Placebo controlled	20-25 Weeks	LTG as adjunctive therapy is effective in the treatment of primary generalized tonic-clonic seizures and has a favourable tolerability profile.

LTG-Lamotrigine; CBZ – Carbamazepine; GBP – Gabapentin; LEV – Levetiracetam;

Table 3: Major congenital malformations (malformed/exposed) frequency in prenatally exposed children to different monotherapies.

Register	Follow-up after birth	General population	Untreated epilepsy	CBZ	LEV	LTG	OXCBZ	PHT	PHB	TPM	VA
EURAP (14)	1 year	---	---	79/1402 (5.6%)	2/126 (1.6%)	37/1280 (2.9%)	6/184 (3.3%)	6/103 (5.8%)	16/217 (7.4%)	5/73 (6.8%)	122/1224 (10.0%)
NMBR (73)	Birth	2.9%	106/3773 (2.8%)	20/685 (2.9%)	2/118 (1.7%)	28/833 (3.4%)	1/57 (1.8%)	---	2/27 (7.4%)	2/48 (4.2%)	21/333 (6.3%)

SMBR (74)	Birth	2.1%	---	38/1430 (2.7%)	0/61 (0%)	32/1100 (2.9%)	1/27 (3.7%)	8/119 (6.7%)	---	4/52 (7.7%)	29/619 (4.7%)
UK EPR (75-77)	3 months	---	---	43/1657 (2.6%)	2/304 (0.7%)	49/2098 (2.3%)	---	3/82 (3.7%)	---	3/70 (4.3%)	82/1220 (6.7%)
NAAPR (78)	3 months	---	5/442 (1.1%)	31/1033 (3.0%)	11/450 (2.4%)	31/1562 (2.0%)	4/182 (2.2%)	12/416 (2.9%)	11/199 (5.5%)	15/359 (4.2%)	30/323 (9.3%)
AUS (79)	---	---	5/153	19/346 (5.5%)	2/84 (2.4%)	14/307 (4.6%)	1/17 (5.9%)	1/41 (2.4%)	---	1/42 (2.4%)	35/253 (13.8%)

			(3.3%)								
GSK (80)	---	---	---	---	---	35/1558 (2.2%)	---	---	---	---	---

Data collected from different prospective registers. Data are n/N (%).
CBZ- Carbamazepine; LEV- Levetiracetam; LTG- Lamotrigine; OXCBZ- Oxcarbazepine; PHT- Phenytoin; PHB- Phenobarbital; TPM- Topiramate; VA-Valproic acid; EURAP-An International Register of Antiepileptic Drugs and Pregnancy; NMBR-Medical Birth Register of Norway; SMBR-Swedish Medical Birth Register; UK EPR-UK Epilepsy and Pregnancy Register; NAAPR-North American Antiepileptic Drug Pregnancy Register; AUS-*Australian* Register of *Antiepileptic Drugs; GSK*-GSKs International Lamotrigine Registry