**Lamotrigine treatment of mental health problems during the perinatal period**

Holly A. Austin1 and David S. Baldwin1,2

1 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, United Kingdom

2 University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

Corresponding author: [d.s.baldwin@soton.ac.uk](mailto:d.s.baldwin@soton.ac.uk). Address: University Department of Psychiatry, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3DT, United Kingdom

**Summary**

Lamotrigine is beneficial in bipolar disorder and often prescribed to patients during their period of reproductive potential. We summarise aspects of the pharmacology of lamotrigine, highlight its uses in psychiatric practice, drawing attention to recent findings relating to potential hazards arising from lamotrigine exposure *in utero* and make some suggestions for clinical management.

**Keywords**

Lamotrigine, pregnancy, teratogenicity, neurodevelopment, breast-feeding

**Molecular and clinical pharmacology**

Lamotrigine has complex pharmacological properties. It inhibits voltage-sensitive sodium channels, resulting in neuronal stabilization, which probably underpins its anticonvulsant properties: however, the mechanisms underlying its mood-stabilizing and antidepressant effects are uncertain. It blocks L-, N-, and P- type calcium channels, weakly inhibits 5-hydroxytryptamine (5-HT) 5-HT3 receptors, inhibits the release of glutamate in ventral striatum limbic areas, and reduces gamma-aminobutyric acid (GABA) GABA-A receptor-mediated neurotransmission, but has minimal effects on adrenergic, dopaminergic (D1 and D2), cholinergic, histaminic (H1), 5-HT2 and N-methyl-D-aspartate (NMDA) glutamate receptors. It exerts antioxidant and neuroprotective effects and weakly inhibits the enzyme dihydrofolate reductase (important in folate metabolism), though this effect is not associated with changes in serum or erythrocyte folate concentrations.

Metabolism shows first-order kinetics with a 29-hr half-life. It undergoes rapid and complete absorption, with 98% absolute bioavailability that is unaffected by food. It is inactivated by hepatic glucuronidation, the major metabolite being inactive. Optimal therapeutic levels in patients with epilepsy are not established and there is no established level-response relationship in patients with affective disorders. Pharmacokinetics are influenced by genetic polymorphisms, weight, and some concomitantly prescribed medicines. Clearance is increased in pregnant women, and during concomitant treatment with oestrogen-containing oral contraceptive pills.1

Treatment requires careful monitoring. The most well-known adverse effect is development of skin rashes: between 5-10% of patients will develop some form of rash. Severe cutaneous adverse reactions (SCARS) are relatively uncommon (incidence variably estimated as 1/1000 - 1/2500), but include drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome (with involvement of <10% of skin) and toxic epidermal necrolysis (more than 30% of skin), usually occurring as a Type IV hypersensitivity mechanism. SCARS with lamotrigine should be regarded as potentially life-threatening, necessitating admission to an intensive care or burns unit - the potential fatality rate with Stevens-Johnson syndrome is around 5-10%. Multiple risk factors for dermatological reactions have been identified, and include female sex, younger age, inappropriately rapid dosage titration, and concomitant use of valproate-containing medicines.

**Lamotrigine in patients with affective disorders or other conditions**

Lamotrigine can be beneficial as part of overall clinical management in patients with bipolar disorder. A systematic review included twenty randomised controlled trials (RCTs) and twenty cohort studies (with a total of 12307 lamotrigine-treated patients) and examined its efficacy in acute treatment of bipolar depressive episodes, acute treatment of manic or hypomanic episodes, and in maintenance treatment (‘prophylaxis’).2 Studies were stratified by control (active medication or placebo) and strategy (monotherapy or add-on), and twenty-four studies could be included in meta-analysis (fifteen RCTs involving 950 lamotrigine-treated patients, and nine cohort studies involving 812 lamotrigine-treated patients). In acute treatment of bipolar depressive episodes, there were insufficient data to establish superiority *vs*. placebo for monotherapy; for add-on, there was superiority *vs*. placebo, but no difference *vs*. comparators. For acute treatment of mania or hypomania, a single RCT found no difference from lithium as monotherapy. In maintenance treatment, monotherapy was superior to placebo but no different to lithium, and add-on therapy resulted in a longer median time to relapse (10 months) than placebo (3.5 months). Furthermore, five high-quality register-based studies found that lamotrigine was associated with lower hospital admission rates than other commonly used treatments. The authors emphasised the efficacy as add-on treatment in bipolar depressive episodes and as maintenance treatment for preventing relapse and recurrence. 2

Lamotrigine treatment may be beneficial in the management of comorbid substance use disorders in some bipolar patients. In acute treatment of patients with unipolar depression, there are insufficient data to establish whether monotherapy is efficacious, and although some have asserted that lamotrigine has broadly similar efficacy in unipolar and bipolar depressive episodes, the evidence for efficacy of add-on treatment is inconclusive. However, it is superior to placebo, in reducing positive and negative symptoms as an augmentation therapy in patients with schizophrenia being treated with clozapine.

**Lamotrigine in the period of reproductive potential**

Awareness of the damaging effects of valproate-containing medicines in pregnancy and the resulting regulatory restrictions on use in clinical practice, have led to increased attention on the use of lamotrigine in women of reproductive potential. The ability of lamotrigine to prevent depressive episodes in women of reproductive age with bipolar disorder can be of enormous benefit. It is recognized that women with bipolar disorder are at an increased risk of relapse in the postpartum period, particularly if they are not taking medication during pregnancy. A meta-analysis of four randomised placebo-controlled maintenance studies, in which lamotrigine was administered at a dosage 150-400 mg/day for up to 76 weeks, in women aged 18-45 years, and where the primary outcome was the median time to intervention for a mood episode (TIME), found that the median TIME was 323 days for lamotrigine, compared to 127 days for placebo (for all episodes): much of the benefit of lamotrigine was because of its superior efficacy in preventing depressive episodes, as it was not superior to placebo in preventing manic episodes. Lamotrigine was also generally well tolerated. During double-blind treatment, there was a similar incidence of adverse events and of adverse events leading to withdrawal, the most common adverse effects being headache (16%, compared to 14% with placebo) and nausea (13%, compared to 11% with placebo). 3

When considering possible prescription of any medication to a patient of reproductive potential, it is important to be aware of its potential teratogenicity. An early retrospective study suggested first trimester monotherapy (in 791 women) might raise the risk of oral clefts (lip or palate), although a population-based case-control study of infants with congenital malformations (226,806 pregnancies) found the risk of oral clefts to be less than 1 in every 550 exposed babies, not significantly raised compared to controls.4 Systematic reviews have found that lamotrigine exposure during pregnancy was not associated with increased risks of either birth complications and /or congenital malformations, compared to disease-matched controls or non-exposed controls. Prospective cohort studies provide further reassurance: an international (47 countries) study including 10121 pregnancies exposed to anticonvulsant monotherapy found a lower rate of major congenital malformations (MCMs) with lamotrigine (3.1%) than with most other anti-epileptics (whereas there were dose-dependent effects for carbamazepine, phenobarbital and valproate) 5; and a population-based cohort study (in five Nordic countries), of 8339 pregnancies exposed to first-trimester lamotrigine monotherapy, found no evidence of higher risk of MCMs compared to pregnancies not exposed to anti-seizure medication, but higher risks of MCMs with valproate and topiramate when compared to lamotrigine.6

A lamotrigine withdrawal syndrome in adults is not well characterized, and neonatal withdrawal symptoms appear uncommon. The correlation between maternal serum level and breast milk level has been estimated highly variably (range 0.6%-90.3%). Potential effects of lamotrigine on breast-fed infants, described in case reports, include breathing difficulties and somnolence, however clinical advice is that lamotrigine treatment is not a reason to discontinue breastfeeding

**Neurodevelopment and mental disorders in childhood and adolescence**

Increasing awareness of the hazards of valproate-containing medicines when taken *in utero* has understandably focused attention on possible adverse effects of lamotrigine: both on neurodevelopment and on emergence of mental health problems in children and adolescents. Most data are derived from studies of the offspring of mothers with epilepsy and may not necessarily be fully applicable to considerations of developmental conditions among the children or mothers prescribed lamotrigine for affective disorders.

A meta-analysis (total of 18 studies) of neurodevelopmental outcomes after epilepsy-indicated monotherapy in pregnancy found no influence of lamotrigine on overall neurodevelopmental outcomes (5 studies), odds ratio (OR) 0.84 [CI 0.66- 1.06]), language delay or disorders (7 studies, OR 1.16 [CI 0.67, 2.00]), the diagnosis or risk of autism spectrum disorder (5 studies, OR 0.97 [CI 0.61-1.53]), or the diagnosis or risk of attention deficit hyperactivity disorder (ADHD) (4 studies, OR 1.14 [CI 0.75-1.72]): however, lamotrigine exposure was associated with psychodevelopmental delay or disorders (4 studies, OR 2.68 [CI 1.29, 5.56]), and with cognitive development delay (2 studies) in children less than 3 yrs (2 studies, OR 3.42 [CI 1.17-9.98]). 7

A pregnancy with epilepsy cohort (involving over 4 million pregnancies) evaluated those exposed to anti-epileptic drugs between pregnancy Week 19 and delivery, with linkage to health records of children before 8 years. The cumulative incidence of autistic spectrum disorder (after exclusion of children with chromosomal abnormalities) in the full population, with no exposure to medication (4.2 million children) was 1.9%; in those with epilepsy, but no exposure to medication (8815 children) was 4.2%; in epilepsy, with topiramate (1030 children) was 6.2%; in epilepsy, with valproate (800 children) was 10.5%; and in epilepsy, with lamotrigine (4205 children) was 4.1%. The risk of autistic spectrum disorder was higher among children exposed to anticonvulsant medication, although this risk was attenuated for lamotrigine (and topiramate, another anticonvulsant) after adjusting for confounders. 8

A prospective population-based cohort study (in five Nordic countries, involving over 4.5 million singleton children), that included 38,661 children of mothers with epilepsy and which examined prenatal exposure to anti-seizure medication (ASM), at any time between 30 days before last menstrual period and birth, ascertained the cumulative risks of diagnosis of any child-adolescent psychiatric disorder at 18 years (from patient registers). These were estimated as follows: ASM-unexposed children 31.3% (28.9-33.6%), any ASM-exposed children 30.8% (29.2-32.3%) (adjusted hazard ratio aHR 1.17, CI 1.09-1.25), valproate-exposed children 42.1% (aHR 1.80, CI 1.60-2.03) (mainly neurodevelopmental disorders), and lamotrigine-exposed children 24.1% (aHR 0.91, CI 0.82-1.02: i.e. not significantly increased). However, there were associations between topiramate and ADHD, and between levetiracetam (another anticonvulsant) and both ADHD and anxiety disorders. 9

**Guidance on lamotrigine prescribing**

When making treatment decisions, it makes sense to rely on the highest-level evidence (i.e. meta-analyses and prospective population studies), rather than findings from isolated case reports or limited case series. The possible importance of effects of lamotrigine on dihydrofolate reductase and hence on folate metabolism are worth remembering, as folate deficiencies are associated with an increased risk of congenital malformations. NHS advice is for high dose folic acid throughout pregnancy (5mg rather than 400 micrograms). Similarly, clinicians should be aware that lamotrigine pharmacokinetics are altered during pregnancy and levels should be monitored and the dose adjusted.

High-level evidence indicates that lamotrigine is effective in the prevention of depression in patients with bipolar disorder. When prescribing lamotrigine, great caution is needed when titrating the dosage, to reduce the likelihood of adverse dermatological reactions. It does not appear to be associated with congenital malformations. High-level evidence has identified no increased risk of autism spectrum disorder, ADHD, or increased risk of other child and adolescent mental health disorders, but the possible effects of *in utero* lamotrigine exposure on neurodevelopment need further investigation. It should be used cautiously in breast-feeding mothers.

All conclusions relating to safety of medicines during the perinatal period are necessarily tentative. Treatment decisions for managing mental health problems in patients of reproductive potential are complex, due to the need to consider both parent and child, and to balance potential risks of untreated illness and of exposure to medication: whilst recognizing that such treatment decisions should not be avoided in clinical practice.

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**Contribution of Authors**

*Author Contributions*. HAA and DSB both undertook literature appraisal and manuscript development.

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**Key Facts**

* Lamotrigine is effective as an add-on treatment in bipolar depressive episodes and as maintenance treatment for preventing relapse in bipolar disorder. It is also used an anti-epileptic.
* Dose in bipolar disorder– slow titration starting at 25mg for 14 days, up to *British National Formulary* recommended maintenance dose of 200mg daily in 1-2 divided doses, maximum dose 400 mg/day
* Restart titration if more than 5 days of missed doses.
* There is no agreed therapeutic range of lamotrigine serum levels in affective disorders.
* Evidence suggests that lamotrigine use in pregnancy does not lead to increased rates of major congenital malformation in babies.
* In pregnancy lamotrigine pharmacokinetics are altered and serum levels may be useful; patients tend to require higher doses in the third trimester and a reduction in dose after delivery.
* Lamotrigine can be used in breastfeeding mothers, with monitoring of the infant for somnolence and breathing difficulties.
* Side effects – the development of skin rashes affects between 5-10% of patients; severe cutaneous adverse reactions (SCARS) are relatively uncommon (incidence variably estimated as 1/1000 - 1/2500) but can be life threatening. Patients should be made aware to stop lamotrigine and seek medical attention if a rash occurs. Other side effects include nausea, headache, drowsiness and dry mouth.

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