BJPsych | The British Journal of Psychiatry (2025)
1–3. doi: 10.1192/bjp.2025.10307

BJPsych Editorial

Lamotrigine treatment of mental health problems during the perinatal period

Holly A. Austin and David S. Baldwin

Summary

Lamotrigine is beneficial in bipolar disorder and is 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; breastfeeding.

Molecular and clinical pharmacology

Lamotrigine has complex pharmacological properties. It inhibits voltage-sensitive sodium channels, resulting in neuronal stabilisation, which probably underpins its anticonvulsant properties; however, the mechanisms underlying its mood-stabilising and antidepressant effects are uncertain. It blocks L-, N- and P-type calcium channels, weakly inhibits 5-HT_3 5-hydroxytryptamine receptors, inhibits the release of glutamate in ventral striatum limbic areas and reduces gamma-aminobutyric acid A receptor-mediated neurotransmission, but it has minimal effects on adrenergic, dopaminergic (D_1 and D_2), cholinergic, histaminic (H_1), 5-HT_2 and *N*-methyl-d-aspartate glutamate receptors. It exerts antioxidant and neuroprotective effects and weakly inhibits the enzyme dihydrofolate reductase (which is important in folate metabolism), although this effect is not associated with changes in serum or erythrocyte folate concentrations.

The metabolism of lamotrigine shows first-order kinetics with a 29-h 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 have not been established, nor is there any established level–response relationship in patients with affective disorders. Its 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]

Lamotrigine treatment always requires careful monitoring. The best-known adverse effect is development of skin rashes: between 5% and 10% of patients will develop some form of rash. Severe cutaneous adverse reactions are relatively uncommon (the incidence has been variably estimated as 1 in 1000 to 1 in 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 via a type IV hypersensitivity mechanism. Severe cutaneous adverse reactions 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; these 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 including 20 randomised controlled trials (RCTs) and 20 cohort studies (with a total of 12 307 lamotrigine-treated patients) examined its efficacy in acute treatment of bipolar depressive episodes, acute treatment of manic or hypomanic episodes, and maintenance treatment ('prophylaxis').[2] Studies were stratified by control (active medication or placebo) and strategy (monotherapy or add-on), and 24 studies were included in the meta-analysis (15 RCTs involving 950 lamotrigine-treated patients and nine cohort studies involving 812 lamotrigine-treated patients). For acute treatment of bipolar depressive episodes, there were insufficient data to establish superiority versus placebo for monotherapy; for add-on, there was superiority versus placebo but no difference versus comparators. For acute treatment of mania or hypomania, a single RCT found no difference compared with 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 its efficacy as an add-on treatment for bipolar depressive episodes and as maintenance treatment for prevention of relapse and recurrence.[2]

Lamotrigine treatment may be beneficial in management of comorbid substance use disorders in some bipolar patients. There are insufficient data to establish whether monotherapy is efficacious in acute treatment of patients with unipolar depression, and, although some have asserted that lamotrigine has broadly similar efficacy in unipolar and bipolar depressive episodes, the evidence for its efficacy as an 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.

https://doi.org/10.1192/bjp.2025.10307 Published online by Cambridge University Press

Lamotrigine in the period of reproductive potential

Awareness of the damaging effects of valproate-containing medicines in pregnancy and the resulting regulatory restrictions on their use in clinical practice have led to increased attention being paid to 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 recognised that women with bipolar disorder are at increased risk of relapse in the postpartum period, particularly if they have not taken medication during pregnancy. A meta-analysis of four randomised placebo-controlled maintenance studies – in which lamotrigine was administered at a dosage of 150–400 mg per day for up to 76 weeks to women aged 18–45 years – found that the median time to intervention for a mood episode (the primary outcome) was 323 days for lamotrigine, compared with 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 prevention of manic episodes. Lamotrigine was also generally well tolerated. During double-blind treatment, there was a similar incidence of adverse events and adverse events leading to withdrawal, the most common adverse effects being headache (16%, compared with 14% with placebo) and nausea (13%, compared with 11% with placebo).[3]

When considering possible prescription of any medication to a patient of reproductive potential, it is important to be aware of potential teratogenicity. An early retrospective study suggested that first trimester monotherapy (in 791 women) might increase 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 excess risk of oral clefts to be less than 1 in 550 exposed babies, with no significant increase in risk compared with controls.[4] Systematic reviews have found that lamotrigine exposure during pregnancy was not associated with increased risks of either birth complications or congenital malformations, compared with disease-matched controls and non-exposed controls. Prospective cohort studies have provided further reassurance: an international (47 countries) study including 10 121 pregnancies in individuals exposed to anticonvulsant monotherapy found a lower rate of major congenital malformations (MCMs) with lamotrigine (3.1%, 95% CI 2.5–3.7) 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 in individuals exposed to first-trimester lamotrigine monotherapy found no evidence of a higher risk of MCMs compared with pregnancies in those not exposed to anti-seizure medication (ASM), but there were higher risks of MCMs with valproate and topiramate compared with lamotrigine.[6]

There is no well-characterised lamotrigine withdrawal syndrome in adults, and neonatal withdrawal symptoms appear to be uncommon. There have been highly variable estimated of the correlation between maternal serum level and breast milk level (range: 0.6–90.3%). Potential effects of lamotrigine on breastfed 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 administered in utero has understandably focused attention on possible adverse effects of lamotrigine, including effects on neurodevelopment and on the 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 children or mothers prescribed lamotrigine for affective disorders.

A meta-analysis (including a total of 18 studies) of neurodevelopmental outcomes after epilepsy-indicated monotherapy in pregnancy found no influence of lamotrigine on overall neurodevelopmental outcomes (five studies; odds ratio 0.84; 95% CI: 0.66–1.06), language delay or disorders (seven studies; odds ratio 1.16; 95% CI: 0.67–2.00), diagnosis or risk of autism spectrum disorder (five studies; odds ratio 0.97; 95% CI: 0.61–1.53) or the diagnosis or risk of attention-deficit hyperactivity disorder (ADHD) (four studies; odds ratio 1.14; 95% CI: 0.75–1.72). However, lamotrigine exposure was associated with psychodevelopmental delay or disorders (four studies; odds ratio 2.68; 95% CI: 1.29–5.56) and with cognitive development delay in children less than 3 years old (two studies; odds ratio 3.42; 95% CI: 1.17–9.98).[7]

A cohort study of patients with epilepsy 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 of age. The cumulative incidence of autism spectrum disorder (after exclusion of children with chromosomal abnormalities) was 1.9% in the full population of children with no exposure to medication (4.2 million children), 4.2% in those with mothers with epilepsy but no exposure to medication (8815 children), 6.2% in those exposed to topiramate (1030 children), 10.5% in those with epilepsy exposed to valproate (800 children), and 4.1% in those with epilepsy exposed to lamotrigine (4205 children). The risk of autism spectrum disorder was higher among children exposed to anticonvulsant medication, although this risk was attenuated for lamotrigine (and topiramate, another anticonvulsant) after adjustment for confounders.[8]

A prospective population-based cohort study (in five Nordic countries, involving over 4.5 million singleton children) included 38 661 children of mothers with epilepsy and examined prenatal exposure to ASM at any time between 30 days before the last menstrual period and birth to ascertain the cumulative risks of diagnosis of any child or adolescent psychiatric disorder at 18 years of age (from patient registers). These were estimated as follows: ASM-unexposed children, 31.3% (95% CI: 28.9–33.6); children exposed to any ASM, 30.8% (95% CI: 29.2–32.3) (adjusted hazard ratio (aHR) 1.17; 95% CI: 1.09–1.25); valproate-exposed children, 42.1% (aHR 1.80; 95% CI: 1.60–2.03) (mainly neurodevelopmental disorders); and lamotrigine-exposed children, 24.1% (aHR 0.91; 95% CI: 0.82–1.02; i.e. no significant increase). 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. National Health Service advice is for high-dose folic acid to be taken throughout pregnancy

https://doi.org/10.1192/bjp.2025.10307 Published online by Cambridge University Press

Box 1 Characteristics of Lamotrigine

(a) 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 as an anti-epileptic.
(b) Dose in bipolar disorder– slow titration starting at 25mg for 14 days, up to British National Formulary recommended maintenance dose of 200 mg daily in 1-2 divided doses, maximum dose 400 mg/day
(c) Restart titration if more than 5 days of missed doses.
(d) There is no agreed therapeutic range of lamotrigine serum levels in affective disorders.
(e) Evidence suggests that lamotrigine use in pregnancy does not lead to increased rates of major congenital malformation in babies.
(f) 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.
(g) Lamotrigine can be used in breastfeeding mothers, with monitoring of the infant for somnolence and breathing difficulties.
(h) 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.

(5 mg rather than 400 μg). 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. Lamotrigine does not appear to be associated with congenital malformations. High-level evidence has identified no increased risk of autism spectrum disorder, ADHD, or other child and adolescent mental health disorders; however, the possible effects of in utero lamotrigine exposure on neurodevelopment need further investigation. It should be used cautiously in breastfeeding 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, owing to the need to consider both parent and child and to balance the potential risks of untreated illness and of exposure to medication, while recognising that such treatment decisions should not be avoided in clinical practice.

Holly A. Austin, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; **David S. Baldwin**, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; and University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

Correspondence: David S. Baldwin. Email: d.s.baldwin@soton.ac.uk

First received 14 Feb 2025, final revision 16 Apr 2025, accepted 6 May 2025

Acknowledgements

This article was based on an invited talk given by D.S.B. at the International Congress of the Royal College of Psychiatrists, Edinburgh, June 2024.

Author contributions

H.A.A. and D.S.B. both undertook literature appraisal and manuscript development.

Funding

This study received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

H.A.A. has been supported by the National Institute for Health and Care Research as an Academic Clinical Fellow. D.S.B. receives honoraria from Elsevier and Wiley for journal editorial work and reports funding from the Medical Research Council, National Institute for Health and Care Research, and Idorsia. D.S.B. is a member of the editorial board of the *British Journal of Psychiatry* but did not take part in the review or decision-making process for this article.

References

1 Methaneethorn J, Leelakanok N. Sources of lamotrigine pharmacokinetic variability: a systematic review of population pharmacokinetic analyses. *Seizure* 2020; **82**: 133–47.
2 Haenen N, Kamperman A, Prodan A, Nolen W, Boks M, Wesseloo R. The efficacy of lamotrigine in bipolar disorder: a systematic review and meta-analysis. *Bipolar Disord* 2024; **26**: 431–41.
3 Vieta E, Ghorpade S, Biswas A, Sarkar A, Phansalkar A, Cooper J. Lamotrigine efficacy, safety, and tolerability for women of childbearing age with bipolar I disorder: meta-analysis from four randomized, placebo-controlled maintenance studies. *Eur Neuropsychopharmacol* 2024; **78**: 81–92.
4 Dolk H, Wang H, Loane M, Morris J, Garne E, Addor M-C, et al. Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. *Neurology* 2016; **86**: 1716–25.
5 Battino D, Tomson T, Bonizzoni E, Craig J, Perucca E, Sabers A, et al. Risk of major congenital malformations and exposure to antiseizure medication monotherapy. *JAMA Neurol* 2024; **81**: 481–9.
6 Cohen JM, Alvestad S, Cesta CE, Bjørk MH, Leinonen MK, Nørgaard M. Comparative safety of antiseizure medication monotherapy for major malformations. *Ann Neurol* 2023; **93**: 551–62.
7 Peron A, Picot C, Jurek L, Nourredine M, Ripoche E, Ajiji P. Neurodevelopmental outcomes after prenatal exposure to lamotrigine monotherapy in women with epilepsy: a systematic review and meta-analysis. *BMC Preg Childbirth* 2024; **24**: 103.
8 Hernández-Díaz S, Straub L, Bateman BT, Zhu Y, Mogun H, Wisner KL. Risk of autism after prenatal topiramate, valproate, or lamotrigine exposure. *New Engl J Med* 2024; **390**: 1069–79.
9 Dreier JW, Bjørk MH, Alvestad S, Gissler M, Igland J, Leinonen MK, et al. Prenatal exposure to antiseizure medication and incidence of childhood-and adolescence-onset psychiatric disorders. *JAMA Neurol* 2023; **80**: 568.

https://doi.org/10.1192/bjp.2025.10307 Published online by Cambridge University Press