Lamotrigine

Use in Bipolar Disorder

AMBER 2

Lamotrigine has been licensed for the treatment of epilepsy for many years. In 2009 the license was extended to include the prevention of depressive episodes in adults with bipolar I disorder who experience predominantly depressive episodes[1].

Guidance on Use

- Initiation should be by or on the recommendation of a specialist.
- Lamotrigine may be an alternative to olanzapine, valproate and lithium as a long-term prophylactic treatment, particularly for patients with bipolar disorder with chronic or recurrent depression.[2]
- Lamotrigine may be combined with other agents (e.g. lithium, valproate, olanzapine) in patients who relapse frequently, or have symptoms continuing to cause functional impairment, or with rapid-cycling bipolar disorder.[2]
- Lamotrigine is not licensed or recommended for treatment of acute mania.[1,2]
- Lamotrigine is not licensed or recommended in the routine management of treatment-resistant unipolar depression because of the lack of positive data to support its use.[1,3]
- There is some evidence to support a trial of lamotrigine augmentation in patients with schizophrenia unresponsive to clozapine, although this would always be initiated by a psychiatrist.[4]

Dose Regimen

- Lamotrigine is available as 25mg, 50mg, 100mg and 200mg tablets and 25mg and 100mg dispersible tablets, which may be chewed.
- There are no bioavailability concerns between generic and branded preparations in bipolar disorder.[5]
- It may be administered ONCE or TWICE a day.
- *Dose should be titrated upwards gradually (even slower if co-prescribed valproate) to minimise the risk of rash, including the rare but potentially life-threatening Stevens-Johnson syndrome, toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):*
  - Initial dose is usually 25mg once daily for 2 weeks, followed by 50mg daily for 2 weeks in 1-2 divided doses, then 100mg daily in 1-2 divided doses for a further week. The usual maintenance dose is 200mg daily in 1-2 divided doses (with a max of 400mg daily).
  - In *combination with valproate* the initial dose is usually 25mg on alternate days for 2 weeks, followed by 25mg once daily for 2 weeks, then 50mg daily in 1-2 divided doses for a further week. The usual maintenance dose is 100mg daily in 1-2 divided doses (with a max of 200mg daily).
  - In *combination with carbamazepine, phenytoin, rifampicin, lopinavir, ritonavir or other enzyme inducing agents* the initial dose is usually 50mg once daily for 2 weeks, then 50mg twice daily for a further 2 weeks then 100mg twice daily for a further week, then 150mg twice daily for a further week. The usual maintenance dose is 200mg twice daily.
- Dose adjustments may be necessary for patients who have been stabilised on lamotrigine and require additions or deletions of enzyme inducing/inhibiting drugs to their treatment regimen (refer to SPC).[1]
- When stopping lamotrigine in bipolar disorder the dose should be gradually reduced over at least four weeks to minimise the potential for destabilisation.[2]
- If lamotrigine has been stopped for any reason (e.g. non-compliance) consider re-titrating the dose to minimise risk of serious skin rash, particularly if interval exceeds five half-lives (see below):

	Mean half-life	*Five half-lives*
Healthy adult	24-35 hrs	1 week
Co-prescribed enzyme-inducer (e.g. carbamazepine)	14 hrs	3 days
Co-prescribed enzyme-inhibitor (e.g. valproate)	70 hrs	2 weeks

Contraindications

- Patients with a known hypersensitivity to lamotrigine or to any of its excipients.

Monitoring

- People with bipolar disorder have higher levels of physical morbidity and mortality than the general population, particularly cardiovascular disease, stroke, pulmonary embolus, and renal disease. All patients should be offered a *baseline* and *annual physical health check* (normally in primary care) to include: smoking status, alcohol intake, blood pressure, pulse, body weight or BMI, diet, level of physical activity, fasting blood glucose, HbA1c, blood lipid profile, liver function (LFTs), full blood count, renal function and thyroid function (if clinically indicated, every 6 months in rapid-cycling bipolar disorder).[2]
- In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder.[1] Be alert for signs throughout treatment and discuss any concerns with the specialist.
- Prescribe limited quantities of psychotropic drugs during periods of high suicide risk.
- Encourage patients to keep a regular mood diary to monitor changes in severity and frequency of symptoms and the impact of interventions.
- There is no need to routinely check lamotrigine blood levels.
- If lamotrigine serum concentrations are indicated (e.g. in pregnancy) the sample should be taken as a trough level. The exact therapeutic range may vary between individuals but is suggested to be 2-15mg/L.[6] Discuss with specialist.
- **Additional patient counselling point**: Patients and their carers should be alert for signs and symptoms suggestive of bone marrow failure such as anaemia, bruising, or infection. Aplastic anaemia, bone marrow depression and pancytopenia have been rarely associated with lamotrigine.[7] Routine FBC monitoring is however not recommended.[2,7]

SIDE EFFECTS[1]	ACTION
Rash (usually maculopapular) *(very common: ≥1/10)*	Usually occurs within first 8 weeks. Advise patient to stop lamotrigine and contact a doctor immediately if rash develops. Stop lamotrigine, unless it is clear that the rash is not related to it. Often difficult to distinguish between serious and more benign rash. If rash is trivial and disappears re-start lamotrigine but at a slower rate. More common if the dose is increased too quickly, however, see below.
More serious skin reactions, associated with influenza-like symptoms, lymphadenopathy, facial swelling, and hypersensitivity syndrome, progressing to Stevens-Johnson syndrome *(rare: ≥1/10,000 to <1/1000)* and toxic epidermal necrolysis or DRESS *(very rare: <1/10,000)*	Stop lamotrigine immediately and seek specialist advice. Associated with high initial doses, rapid dose titration or when co-prescribed with valproate.
Bone marrow depression - may show as anaemia, bruising or infection *(very rare: <1/10,000)*	Stop lamotrigine and seek specialist advice.
Increased risk of suicidal thoughts and behaviour *(uncommon: ≥1/1000 to <1/100)*	Be alert for signs throughout treatment. Discuss with specialist.[8]
Headache *(very common: ≥ 1/10)*	Try dividing, then reducing the dose.
Nausea, vomiting *(common: ≥1/100 to <1/10)*	Taking with or after food may help.
Dizziness *(common: ≥1/100 to <1/10)*	Try dividing, then reducing the dose.
Drowsiness *(common: ≥1/100 to <1/10)*	Try dividing, then reducing the dose.

OTHERS (not exhaustive):
Diplopia, blurred vision, diarrhoea, tremor, ataxia, agitation, dry mouth, arthralgia, alopecia.

Cautions

- Elderly patients require no dosage adjustment from that recommended for adults.
- Doses should be generally be reduced by 50% in moderate and by 75% in severe hepatic impairment.
- Reduced maintenance doses may be effective in patients with significant renal impairment.
- Pregnancy – lamotrigine should only be used during pregnancy where the benefits of treatment are considered to outweigh any potential risks. The available data on lamotrigine use in pregnancy are derived mainly from studies of women with epilepsy; the majority of the data do not provide evidence that lamotrigine use is associated with an increased risk of overall malformation or a number of specific malformations[9]. All women of child-bearing potential should be advised to use a robust method of contraception (see below) and the importance of planning a pregnancy explained. If patient becomes pregnant whilst taking lamotrigine discuss options with specialist. High-dose folic acid (5mg/day) is recommended whilst trying to conceive and during the first trimester of pregnancy.[9]
- Some reports have shown decreased plasma levels of lamotrigine during pregnancy and the potential for lamotrigine levels to increase rapidly after birth. Therefore, lamotrigine serum concentrations should be monitored before, during and after pregnancy, including shortly after birth. Doses should be amended accordingly to maintain the lamotrigine serum concentration at the same level as before pregnancy or adapted according to clinical response. Dose related side effects should be monitored after birth,[10]
- Lamotrigine should be used with caution in breast feeding and the infant monitored for rash, sedation, poor feeding, adequate weight gain and developmental milestones. Withdrawal effects may occur in infants if a mother suddenly stops breastfeeding.[11] Discuss with specialist.

Drug Interactions

- The contraceptive efficacy of hormonal contraceptives may be reduced by concurrent use of lamotrigine although the clinical significance of this effect is unknown.[12]
- Combined hormonal contraceptives (CHC) are not usually recommended due to both the risk of reduced lamotrigine blood levels (with worsened control of mental health symptoms) whilst on CHC, and the potential increased lamotrigine blood levels and toxicity in the CHC-free week.[12] The progestogen-only pill may increase lamotrigine levels so monitor for side-effects.[12]
- Dose adjustments of lamotrigine may be required when patients taking a maintenance dose of lamotrigine are either started on, or stop taking CHCs (refer to SPC).[1]
- Enzyme inducing drugs (e.g. carbamazepine, phenytoin, rifampicin, atazanavir/ritonavir, lopinavir/ritonovir) enhance the metabolism of lamotrigine and may therefore double dose requirements. If added to or discontinued from a maintenance dose of lamotrigine then dose adjustment of lamotrigine may be necessary (refer to SPC).[1]
- Valproate reduces the metabolism of lamotrigine and may halve dose requirements (refer to SPC).[1]
- St John's wort may increase the metabolism of lamotrigine.[13]

Patient Information

In addition to the manufacturers PIL there are a wide range of patient information leaflets on lamotrigine and other medicines used for the management of bipolar disorder that can be downloaded and printed from our website at: http://www.choiceandmedication.org/nottinghamshirehealthcare/. There is also a UKTIS BUMPS patient information leaflet on lamotrigine use in pregnancy available on the medicines in pregnancy website.

Please consult the SPC[1] for detailed prescribing information. For further advice please contact the specialist.

References

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Version Control - Lamotrigine – Use in Bipolar Disorder			
Version	Author(s)	Date	Changes
1.0	John Lawton	June 2014	
2.0	John Lawton	October 2017	Information on worsening depression/suicidal ideation added, updated information on interactions with oral contraceptives and inclusion of patient information from UKTIS.
3.0	John Lawton, Hannah Godden	November 2020	Pregnancy advice amended as per updated UKTIS monograph January 2020. Monitoring requirements of AHC brought in line with NICE CG185. Amended 'consultant psychiatrist' to 'specialist' in view of NMP roles.
4.0	John Lawton, Hannah Godden, Anjli Khatri	November 2023	References updated. Information on plasma concentrations in pregnancy updated as per MHRA advice published in January 2021. Added plasma level monitoring information. NICE CG 90 has been updated and replaced by NICE guideline NG222.