

Introduction

Lamotrigine (Lamictal) is increasingly being recognised as an effective mood stabiliser for many with a bipolar disorder and, in particular, for bipolar II disorder. It has relatively few side-effects. However, it has the potential to cause Stevens-Johnson syndrome, a rare but dangerous reaction. This has led to a pre-emptive strategy of slow titration, increasing the adult dose from an initial 25mg at night by 25mg each week to a general maximum dosage of 200mg/day. This fact sheet seeks to inform practitioners and patients about this side-effect.

The key message

Patients need to be warned about the possibility of **severe dermatological reactions** – not only of a Stevens-Johnson syndrome – and that the appearance of a rash may foreshadow serious consequences. The general recommendation is that patients should stop the drug at the first sign of a rash, regardless of its type or severity, unless the rash is clearly non-drug related. However, as will be noted, systemic (bodily) symptoms may precede the rash.

The dermatological events associated with lamotrigine use

The clinical presentations of rashes associated with lamotrigine use are highly variable. They range from common, transient and benign erythema that commences 6-9 days after the introduction of the drug, to the most severe forms that affect 1/1000 to 1/10,000 users.

- 1) the most common dermatological event is a **hypersensitivity reaction** which can occur in association with most medications, and which can present with fixed eruptions*, an exanthematous rash*, urticaria*, oedema* or pruritis*
- 2) a mixed group of dermatological events with different pathophysiologies can occur causing non-life threatening rashes and which includes photosensitivity*, alopecia*, and drug-induced pigmentation
- 3) the most severe and life-threatening rashes include erythema multiforme, Stevens-Johnson syndrome or SJS (10% mortality rate), Toxic Epidermal Necrolysis or TEN (45% mortality rate), severe hypersensitivity reactions, and exfoliative dermatitis or erythroderma
- 4) finally, worsening of common skin disorders such as acne, psoriasis, seborrhoea and hyperhidrosis* can occur.

Characteristics of the rashes

Life threatening lamotrigine-associated rashes do not correlate with plasma drug levels. However, exceeding the recommended initial dosage or dosage escalation of the drug may increase the risk of rash.

The majority of the reactions consist of a simple benign morbilliform rash – a fine discrete maculopapular rash that resembles the rash of measles, which may or may not be itchy, occurring in 5-15% of patients between day 5 and week 8 after taking lamotrigine.

A minority of the reactions are severe and include:

- a) an anticonvulsant hypersensitivity syndrome. This usually presents with fever, rash and internal organ involvement (lymphadenopathy, hepatitis and haematological abnormalities). There is no mucous membrane involvement. Liver failure due to fulminant hepatitis is the most common cause of death (10-40% of untreated cases). Cross-reactivity between carbamazepine, oxcarbazepine, valproate and lamotrigine is 50-80%
- b) erythema multiforme, which predominantly involves the skin with classical target lesions with a pink-red ring around a pale centre and gradually increasing mucocutaneous and systemic (bodily) involvement
- c) a Stevens-Johnson syndrome, which is characterised by high fever and 'flu-like' symptoms followed by skin erythema, tenderness, and cutaneous and mucosal exfoliation which is progressive and associated with a 10% mortality rate mainly due to sepsis
- d) Toxic Epidermal Necrolysis (TEN), which is an extreme variant of the Stevens-Johnson syndrome, and associated with epidermal detachment in more than 30% of cases. It presents similarly to a Stevens-Johnson syndrome but is more rapidly (over 1-5 days) progressive. It is associated with up to 45% mortality rate due to sepsis of the denuded skin and lungs

e) erythroderma or exfoliative dermatitis (ED) is a syndrome characterised by generalised inflammatory erythema* (redness), and scaling, sometimes in large sheets. The resulting loss of large amount of proteins in the scales has adverse metabolic consequences for the body.

To rechallenge or not

It is recommended that lamotrigine should be discontinued at the first sign of a rash, unless it is clearly non-drug related. This will ensure that the drug is discontinued in instances of serious rash, but may lead to unnecessary discontinuation of a valuable treatment in cases of non-serious rash. Thus, can it be reintroduced or 'rechallenged'?

A literature review¹ reported that, in 42 cases of lamotrigine-associated rashes in epileptic patients, 84% were successfully rechallenged with a lower dosage and slower titration of the drug. There are only two case reports in the literature of rechallenge in patients with a lamotrigine-associated rash in bipolar disorder. One was successful in the rechallenge – the other did not involve lowering the introductory dose or slowing the titration of the dosage during the rechallenge and the rash returned.

Given the usefulness of the drug as a mood stabiliser in bipolar disorder, rechallenge may be cautiously considered as a management option. The risks and benefits need to be assessed for the individual patient and careful evaluation of the characteristics of the rash established as being a benign rash or not. If benign, reintroduction of lamotrigine after six months and with a lower starting dose (5-12.5 mg/day) and slower titration than currently recommended in the prescribing guidelines is suggested. Close monitoring of the patient must continue and the lamotrigine ceased if the rash worsens or other symptoms appear.

Suggested management of lamotrigine-associated rash

A rash that occurs in the first 5 days of lamotrigine therapy is probably non-drug related (except for hypersensitivity reaction). The patient should, however, stop the drug and contact their physician. The rash is most likely benign if it has the following characteristics:

- (a) peaks within days and settles in 10-14 days
- (b) is spotty, non-confluent*, non-tender
- (c) there is an absence of systemic features, or
- (d) a full blood count, liver function tests, blood urea, serum creatinine, and urine analysis are within normal limits.

If the rash is pruritic (itchy), antihistamines or topical corticosteroids can be prescribed. After careful evaluation of the rash, exclusion of possible risk factors and assessment of the benefits of continuing treatment, the patient may be challenged at a lower dose and with slower titration along with careful monitoring and withdrawal of the drug if rash worsens or new symptoms emerge.

A rash occurring between 5 days and 8 weeks is probably lamotrigine related. The patient should stop taking lamotrigine and contact their physician immediately. Features suggestive of the development of a severe dermatological event include:

- (a) a confluent and widespread rash
- (b) a purpuric* and tender rash
- (c) a rash with associated fever, malaise, pharyngitis, lymphadenopathy or anorexia (lack of appetite)
- (d) abnormalities in the laboratory tests listed above
- (e) any involvement of eyes, lips, mouth, or other mucous membranes, or
- (f) prominent involvement of the neck or upper trunk.

In such circumstances the lamotrigine should be discontinued and the patient closely monitored for internal organ involvement with hospitalisation and dermatological consultation obtained. In this situation, there should be no rechallenge with lamotrigine.

Key points to remember

Possible drug interactions need to be considered – concomitant anticonvulsant use may play a part in the increased incidence of side-effects – e.g. valproate (Epilim) increases the half life of lamotrigine from 25 hours to 70 hours.

Key to terms used

*Fixed eruptions – fresh lesions are well defined, round or oval patches of redness and swelling of the skin sometimes surmounted by a blister which fades to a purplish or brown colour and usually develop within 30 minutes to 8 hours after taking the drug. Often a single lesion initially, but with repeated attacks new lesions appear and existing ones may increase in size. The rash appears on the limbs including hands and feet more than the trunk but also around the mouth and eyes and perianal area. Local or general symptoms such as fever are mild or absent.

*Exanthematous rash – a maculo-papular rash similar to the rash of viral infections such as measles.

*Urticaria – evanescent wheals (hives) associated with itching.

*Oedema – swelling from excessive accumulation of watery fluid in cells, tissues or serous cavities

*Pruritis – itch.

*Alopecia – hair loss, either patchy or generalised.

*Hyperhidrosis – excessive sweating.

*Erythema – redness of the skin caused by capillary congestion.

*Purpuric rash – a purplish discoloration of the skin produced by small bleeding vessels near the surface. When purpura is pressed with the finger it does not blanch as other rashes do. It may also occur in the mucous membranes especially the mouth or the internal organs. When the spots are small (<1cm in diameter), they are called petechiae. Larger deeper purpura is called ecchymosis or bruising.

*Non-confluent – separate; not merging together to form a mass

References

¹ Boris Lorberg, Nagy A. Youssef and Zubin Bhagwagar (2009). 'Lamotrigine-associated rash: to rechallenge or not to rechallenge?' *International Journal of Neuropsychopharmacology* ; 12: 257-265.

[Also – see our Fact Sheet “Lamotrigine-associated Rash” for patients](#)