

Lamotrigine and Rash: Scratching Beneath the Surface

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That lamotrigine is an effective medication in the treatment of epilepsy and psychiatric disease is not debatable. Numerous well-designed clinical trials have demonstrated efficacy and safety in both neurologic and psychiatric disorders.¹⁻⁴ Why, then, do many practitioners in neurology as well as psychiatry steer away from using this medication? Clearly, it seems that the “rash issue” taints the perception of safety.

Rash, both benign and serious, has been associated with lamotrigine and many other antiepileptic medications for quite some time. The rashes seen with lamotrigine use have been either benign or serious (Stevens-Johnson syndrome or toxic epidermal necrolysis). While none of us wish to cause our patients discomfort, the benign rash is just that and should not be a reason for withholding a medication. The risk of Stevens-Johnson syndrome or toxic epidermal necrolysis is of concern and should be taken seriously. The prescribing information for lamotrigine reports a 1% risk of Stevens-Johnson syndrome in the pediatric population and 0.3% in adults.⁵ Calabrese et al.⁶ have reviewed the prospectively collected data from the double-blind studies of lamotrigine in the treatment of mood disorders and report that the risk of serious rash was nil, even lower than the placebo group that had a single case of serious rash. Which number is correct and how should we use these data in deciding

when and how to prescribe this medication? If, in fact, 3 of every 1000 adults and 1 of every 100 children exposed to lamotrigine may be at risk of a life-threatening rash, the use of this medication should be limited. However, recent German data should allow us to feel more comfortable in the use of lamotrigine.⁷

The German Registry for Serious Cutaneous Reactions attempts to identify all cases of Stevens-Johnson syndrome and toxic epidermal necrolysis independent of etiology. Estimates suggest that they have successfully identified 96% of all hospitalized cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in Germany, allowing a comparison of etiologies regarding exposure to medication.⁷ A recent presentation at the American Academy of Neurology⁷ reviewed the data regarding confirmed cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. Estimates were made of the frequency of Stevens-Johnson syndrome or toxic epidermal necrolysis due to several different antiepileptic medications in both adults and children. Data for lamotrigine, carbamazepine, phenytoin, and phenobarbital were compared. In adults, the rates for serious rash ranged from 0.003 cases/1000 prescriptions for phenobarbital to 0.011/1000 for both lamotrigine and phenytoin (no statistical difference between any of the 4 medications). Interestingly, in children, the rates were lowest for carbamazepine and highest for phenytoin (0.023/1000 and 0.143/1000, respectively), but, again, there was no statistically significant difference between the 4 compounds.

The data from this registry also provide good estimates of the overall risk of lamotrigine-induced Stevens-Johnson syndrome or toxic epidermal necrolysis.⁷ The calculated risks based on new exposures to the medication since 1993 are 2.4/10,000 for children and 2.0/10,000 for adults. These rates are considerably lower than those

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suggested by the prescribing information, especially for children. The difference can quite likely be attributed to an artifact of data acquisition for the prescribing information. The relatively higher rate in children can be blamed on a single study of children with Lennox-Gastaut syndrome in which 2 of fewer than 100 children developed serious rash. Nearly all of these children were taking valproate, a drug now known to increase the risk of lamotrigine-induced rash. When one looks at the total postmarketing experience for serious rash associated with lamotrigine, the numbers are much closer to the German experience. These data should help put us at ease that the risks associated with lamotrigine are no greater than those associated with other medications that are typically considered to be "safer."

This then leaves us with the problem associated with benign rash. In their study, Calabrese et al.⁶ determined the rate of benign rash to be 8%. This is on par with the postmarketing experience and with our own experience. In fact, the rate of rash was considerably higher prior to the recognition that it was related to both the rate of titration and the concomitant administration of valproate. Once these observations were factored in and the recommended titration rates were put in place, the rate of rash has stabilized at the current level (approximately 10%). While this rash is a nuisance for patients, the recommendations in the flow chart provided by Calabrese et al. provide very reasonable advice on both how to distinguish it from more serious rash and how to manage it.

This study by Calabrese and colleagues⁶ confirms my observation in clinical practice that the risk of serious rash associated with the use of lamotrigine is rare. In fact, in

our practice, this drug is arguably the best-tolerated anti-epileptic medication that we prescribe. This may, in fact, be due to the mood-elevating properties associated with this medication as well as its (overall) mild side-effect profile. Given that the risk of rash is essentially "front-loaded" (i.e., limited to the first 8–12 weeks), there seems to be minimal justification for limiting its use in clinical practice. When you scratch beneath the surface, what you find is a medication that is effective in the treatment of both neurologic and psychological disease, well tolerated by patients, and safe to use.

Drug names: carbamazepine (Tegretol and others), lamotrigine (Lamictal), phenobarbital (Donnatal and others), phenytoin (Dilantin and others).

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