Editors' Note: Correspondence in WriteClick this week references the article by Drs. Simms, Kortepeter, and Avigan, "Lamotrigine and aseptic meningitis." Drs. Tatum and French point out that most physicians will never see a case of lamotrigine-associated aseptic meningitis and that, in pregnancy, lamotrigine has one of the safest clinical profiles despite its category C ranking. Dr. Sethi cautions that aseptic meningitis should still be a diagnosis of exclusion in any patient and that physicians should not be deterred from using this highly effective medication. The authors agree with Dr. Sethi on both points and offer that data collected since lamotrigine was approved in 1994 support that aseptic meningitis is a very rare complication.

Megan Alcauskas, MD, and Robert C. Griggs, MD

LAMOTRIGINE AND ASEPTIC MENINGITIS

William Tatum, Jacksonville, FL; Jacqueline French, New York:

An association between lamotrigine and aseptic meningitis is predicated on a complete clinical and CSF investigation to exclude another source. Inflammatory and infectious processes may overlap with aseptic meningitis. The cases reported by Simms et al.¹ are solely validated on historical reporting of available evidence. With the current number of cases of aseptic meningitis reported and the prevalence of lamotrigine use, most neurologists are unlikely to see an affected patient. A more common scenario is lamotrigine-associated headaches without aseptic meningitis. Food and Drug Administration drug warnings are "red flags" yet the entire spectrum of the clinical association may not be evident.² In 2006, a warning was issued related to oropharyngeal clefting in infants born to women taking lamotrigine during pregnancy.³ As Dr. Sethi mentioned, lamotrigine is a category C drug in the United States. World ranking includes category D status by the Australian Drug Evaluation Committee.⁴ Nevertheless, lamotrigine has retained one of the safest clinical profiles during pregnancy irrespective of risk category.⁵ Lamotrigine has proven to be a safe, effective, broad-spectrum antiepileptic drug (AED) well tolerated by many different subpopulations with epi-

lepsy. In the end, it is the clinician who is responsible for ensuring the best outcome from its use.

Nitin K. Sethi, New York: Simms et al. discuss the risk of aseptic meningitis with lamotrigine use,¹ a drug which is fast becoming the drug of choice for patients with both partial and primary generalized epilepsies. By definition, aseptic meningitis refers to meningitis characterized by lymphocytic pleocytosis and culture-negative CSF. Viral meningitis, fungal meningitis, drug-induced meningitis, bacterial and even tubercular meningitis—which has a very high morbidity and mortality—may be classified as aseptic meningitis depending upon when and to what extent the CSF is sampled during the disease course. Hence, the term itself is a misnomer and the diagnosis remains one of exclusion. Further studies are warranted before this risk is causally attributed to lamotrigine use as this may deter neurologists, psychiatrists, and primary care physicians from using this highly effective drug with an extremely favorable side-effect profile. Recent data from pregnancy registries attest to the low incidence of congenital malformations associated with lamotrigine use during pregnancy.⁶ It remains a category C drug and not a category D drug as erroneously reported by Tatum and French.⁷

Author Response: Kelley M. Simms, Cindy Kortepeter, Mark Avigan, Silver Spring, MD: We agree with Dr. Sethi that the clinical diagnosis of aseptic meningitis is one of exclusion and is an umbrella category for meningitides which are associated with a number of different causes. Our article also reinforces the notion that bacterial etiologies be excluded first due to the potential for serious sequelae with untreated bacterial meningitis.

Since approval in 1994, an estimated 46 million prescriptions of lamotrigine products have been dispensed in the United States. Only 40 cases of aseptic meningitis were identified with lamotrigine from the Adverse Event Reporting System database, thus suggesting that this is an uncommon event. Regarding causality, a positive dechallenge was reported in 27 cases and it was compelling that 15 cases reported a positive rechallenge,

with recurrence of features of meningitis within a short time after readministration of lamotrigine.

The mechanisms that underlie lamotrigine-associated meningitis are unclear and the factors responsible for increased susceptibility among patients who take lamotrigine require further research. Our intent is not to discourage clinicians from prescribing lamotrigine, but rather to raise awareness that there have been reports of aseptic meningitis in patients taking lamotrigine and to consider this possibility in their differential diagnoses.

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William Tatum, Nitin K. Sethi, Kelley M. Simms, et al.

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