18 - 29.18 Lamotrigine

29.18 Lamotrigine

effects (e.g., cardiac, hypotensive, epileptogenic, sexual, and allergic) with the lowpotency drugs. If sedation is a desired goal, either a low-potency antipsychotic can be given in divided doses or a benzodiazepine can be coadministered. An unpleasant or dysphoric reaction (a subjective sense of restlessness, oversedation, and acute dystonia) to the first dose of an antipsychotic predicts future poor response and noncompliance. Prophylactic use of antiparkinsonian medications may prevent this reaction. In general, clinicians should be vigilant about serious side effects and adverse events (described above) regardless of which drug is used. REFERENCES Cameron K, Kolanos R, Vekariya R, De Felice L, Glennon RA. “Mephedrone and methylenedioxypyrovalerone (MDPV), major constituents of “bath salts,” produce opposite effects at the human dopamine transporter”: Erratum. Psychopharmacology. 2013;227(3):501. Dean AC, Groman SM, Morales AM, London ED. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology. 2013;38(2):259–274. Jones PB, Barnes TR, Davies L, Dunn G; Lloyd H. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63:1079. Leucht S, Cores C, Arbter D, Engel R, Li C, Davis J. Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis. Lancet. 2009;373:31. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A metaanalysis of randomized controlled trials. Schizophr Res. 1999;35(1):51. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigators. N Engl J Med. 2005;353:1209. Marder SR, Essock SM, Miller AL, Buchanan RW, Davis JM. The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophr Bull. 2002;28(1):5. Pacciardi B, Mauri M, Cargioli C, Belli S, Cotugno B, Di Paolo L, Pini S. Issues in the management of acute agitation: how much current guidelines consider safety? Front Psychiatry. 2013;4:26. Smith RC, Segman RH, Golcer-Dubner T, Pavlov V, Lerer B. Allelic variation in ApoC3, ApoA5 and LPL genes and first and second generation antipsychotic effects on serum lipids in patients with schizophrenia. Pharmacogenomics J. 2008;8:228. van Kammen DP, Hurford I, Marder SR. First-generation antipsychotics. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3105. Wu B-J, Chen H-K, Lee S-M. Do atypical antipsychotics really enhance smoking reduction more than typical ones? The effects of antipsychotics on smoking reduction in patients with schizophrenia. J Clin Psychopharmacol. 2013;33(3):319– 328. 29.18 Lamotrigine Lamotrigine (Lamictal) was developed as a result of screening folate antagonists as anticonvulsants.

Lamotrigine proved effective in several animal models of epilepsy, was

developed as an antiepileptic drug, and was marketed for the adjunctive treatment of partial seizures in the United States in 1995. Initial, postmarketing, open, clinical experience suggested efficacy in a variety of neurological and psychiatric conditions, coupled with good tolerability (aside from the risk of rash). Later, double-blind, placebocontrolled studies revealed that lamotrigine was useful for some, but not all, of the neurological and psychiatric conditions reported in open studies. Therefore, lamotrigine appeared effective as maintenance treatment for bipolar disorder and was approved for maintenance treatment of bipolar I disorder in 2003. Lamotrigine also appeared to have potential utility in acute bipolar depression, but the magnitude of the effect was too modest to yield consistently superior performance compared with placebo, and hence lamotrigine did not receive approval for the treatment of acute bipolar depression. Similarly, limited data suggested lamotrigine had potential utility in rapid-cycling bipolar disorder. Lamotrigine did not appear to be effective as a main intervention in acute mania. Thus, lamotrigine has emerged as an agent that appears to “stabilize mood from below” in the sense that it may maximally impact the depressive component of bipolar disorders. PHARMACOLOGICAL ACTIONS Lamotrigine is completely absorbed, has a bioavailability of 98%, and has a steady-state plasma half-life of 25 hours. However, the rate of metabolism of lamotrigine varies over a sixfold range, depending on which other drugs are administered concomitantly. Dosing is escalated slowly to twice-a-day maintenance dosing. Food does not affect its absorption, and it is 55 percent protein bound in the plasma; 94% of lamotrigine and its inactive metabolites are excreted in the urine. Among the better-delineated biochemical actions of lamotrigine are blockade of voltage-sensitive sodium channels, which in turn modulates release of glutamate and aspartate, and has a slight effect on calcium channels. Lamotrigine modestly increases plasma serotonin concentrations, possibly through inhibition of serotonin reuptake, and is a weak inhibitor of serotonin 5-HT3 receptors. THERAPEUTIC INDICATIONS Bipolar Disorder Lamotrigine is indicated in the treatment of bipolar disorder and may prolong the time between episodes of depression and mania. It is more effective in lengthening the intervals between depressive episodes than manic episodes. It is also effective as treatment for rapid-cycling bipolar disorder. Other Indications There have been reports of therapeutic benefit in the treatment of borderline personality disorder and in the treatment for various pain syndromes.

PRECAUTIONS AND ADVERSE REACTIONS Lamotrigine is remarkably well tolerated. The absence of sedation, weight gain, and other metabolic effects is noteworthy. The most common adverse effects—dizziness, ataxia, somnolence, headache, diplopia, blurred vision, and nausea—are typically mild. Anecdotal reports of cognitive impairment and joint or back pain are common. The appearance of a rash, which is common and occasionally very severe, is a source of concern. About 8 percent of patients started on lamotrigine develop a benign maculopapular rash during the first 4 months of treatment, and the drug should be discontinued if a rash develops (see Color Plate 29.18-1). Even though these rashes are benign, there is concern that in some cases, they may represent early manifestations of Stevens–Johnson syndrome or toxic epidermal necrolysis. Nevertheless, even if lamotrigine is discontinued immediately upon development of rash or other signs of hypersensitivity reaction, such as fever and lymphadenopathy, this may not prevent subsequent development of a life-threatening rash or permanent disfiguration. Estimates of the rate of serious rash vary, depending on the source of the data. In some studies, the incidence of serious rashes was 0.08 percent in adult patients receiving lamotrigine as initial monotherapy and 0.13 percent in adult patients receiving lamotrigine as adjunctive therapy. German registry data,

based on clinical practice, suggest that the risk of rash may be as low as 1 in 5,000 patients. The appearance of any type of rash necessitates immediate discontinuation of drug administration. It is known that the likelihood of a rash increases if the recommended starting dose and speed of dose increase exceed what is recommended. Concomitant administration of valproic acid also increases risk and should be avoided if possible. If valproate is used, a more conservative dosing regimen is followed. Children and adolescents younger than age 16 years appear to be more susceptible to rash with lamotrigine. If patients miss more than four consecutive days of lamotrigine treatment, they need to restart therapy at the initial starting dose and titrate upward as if they had not already been on the medication.

LABORATORY TESTING There is no proven correlation between lamotrigine blood concentrations and either antiseizure effects or efficacy in bipolar disorders. Laboratory tests are not useful in predicting the occurrence of adverse events. DRUG INTERACTIONS Lamotrigine has significant, well-characterized drug interactions involving other anticonvulsants. The most potentially serious lamotrigine drug interaction involves concurrent use of valproic acid, which doubles serum lamotrigine concentrations. Lamotrigine decreases the plasma concentration of valproic acid by 25 percent. Sertraline (Zoloft) also increases plasma lamotrigine concentrations, but to a lesser extent than does valproic acid. Lamotrigine concentrations are decreased by 40 to 50 percent, with concomitant administration of carbamazepine, phenytoin, or phenobarbital. Combinations of lamotrigine and other anticonvulsants have complex effects on the time of peak plasma concentration and the plasma half-life of lamotrigine. LABORATORY INTERFERENCES Lamotrigine and topiramate do not interfere with any laboratory tests. DOSAGE AND ADMINISTRATION In the clinical trials leading to the approval of lamotrigine as a treatment for bipolar disorder, no consistent increase in efficacy was associated with doses above 200 mg per day. Most patients should take between 100 and 200 mg a day. In epilepsy, the drug is administered twice daily, but in bipolar disorder, the total dose can be taken once a day, either in the morning or night, depending on whether the patient finds the drug activating or sedating. Lamotrigine is available as unscored 25, 100, 150, and 200 mg tablets. The major determinant of lamotrigine dosing is minimization of the risk of rash. Lamotrigine should not be taken by anyone younger than 16 years of age. Because valproic acid markedly slows the elimination of lamotrigine, concomitant administration of these two drugs necessitates a much slower titration (Table 29.18-1). People with renal insufficiency should aim for a lower maintenance dosage. Appearance of any type of rash necessitates immediate discontinuation of lamotrigine administration. Lamotrigine should usually be discontinued gradually over 2 weeks unless a rash emerges, in which case it should be discontinued over 1 to 2 days. Table 29.18-1 Lamotrigine Dosing (mg/day)

Lamotrigine orally disintegrating tablets (Lamictal ODT) are available for patients who have difficulty swallowing. It is the only antiepileptic treatment that is available in an orally disintegrating formulation. It is available in 25, 50, 100, and 200 mg strengths and matches the dose of lamotrigine tablets. Chewable dispersible tablets of 2, 5, and 25 mg are also available. REFERENCES Calabrese JR, Huffman RF, White RL. Lamotrigine in the acute treatment of bipolar depression: Results of five doubleblind, placebo-controlled clinical trials. Bipolar Disord. 2008;10:323. Delvendahl I, Lindemann H, Heidegger T, Normann C, Ziemann U, Mall V. Effects of lamotrigine on human motor cortex plasticity. Clin Neurophysiol. 2013;124(1):148–153. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry. 2009;194:4. Goldberg JF, Bowden CL, Calabrese JR. Six-month prospective life charting of mood

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Revision #1
Created 2026-01-04 19:51:47 UTC by Omar Ayman
Updated 2026-01-04 19:51:47 UTC by Omar Ayman