

Psychiatric and nonpsychiatric indications for mood stabilizers and select antiepileptics

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Mr. B, age 64, is being treated in the psychiatric clinic for generalized anxiety disorder. He also has a history of type 2 diabetes mellitus and osteoarthritis. His present medications include metformin 500 mg twice daily, escitalopram 20 mg/d, and a multivitamin.

Three months after a shingles outbreak on his left trunk, Mr. B develops a sharp, burning pain and hypersensitivity to light in the same area as the shingles flare-up. He is diagnosed with postherpetic neuralgia. Despite a 12-week trial of cognitive-behavioral therapy, Mr. B continues to report excessive worry, irritability, poor concentration, psychomotor restlessness, and poor sleep.

Contrasting with the serendipitous discovery of iproniazid and chlorpromazine leading to the development of the current spectrum of antidepressant and antipsychotic agents, discovery of the benefits various antiepileptic agents have in bipolar disorder has not led to a similar proliferation of medication development for bipolar mania or depression.¹⁻³ Divalproex, one of the most commonly used antiepileptic drugs (AEDs) in psychiatry, was thought

to be an inactive organic solvent until it was used in 1962 to test the anticonvulsant activity of other compounds. This led to the discovery and subsequent use of divalproex in patients with epilepsy, followed by FDA approval in bipolar disorder.^{4,5} Off-label use of many AEDs as mood-stabilizing agents in bipolar disorder led to the emergence of carbamazepine, divalproex, and lamotrigine, which joined lithium as classic mood-stabilizing agents.^{4,6-8} Amid varying definitions of “mood stabilizer,” many AEDs have failed to demonstrate mood-stabilizing effects in bipolar disorder and therefore should not all be considered mood stabilizers.⁹ Nonetheless, the dual use of a single AED for both psychiatric and nonpsychiatric indications can decrease polypharmacy and increase acceptability of medications in patients who have low insight into their illness.^{10,11}

Practice Points

- The use of individual antiepileptic drugs (AEDs) for dual indications—psychiatric and nonpsychiatric—can decrease polypharmacy and increase acceptability of medications in situations where patient insight into their illness may be low.
- Dual use of AEDs for psychiatric and nonpsychiatric indications requires appreciation and consideration of indication-specific dosing.
- Limitations, such as drug-drug interactions and the propensity for AEDs to cause suicidality, should be considered when prescribing AEDs for both psychiatric and nonpsychiatric indications.

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Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0230

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Table

Mood stabilizers and select antiepileptics with common psychiatric and nonpsychiatric indications

Medication	Psychiatric indication(s)	Nonpsychiatric indication(s)
Carbamazepine	<i>FDA-approved:</i> Bipolar disorder ⁶ <i>Off-label:</i> Bipolar depression, ^{9,17} maintenance treatment for bipolar disorder ^{9,18,19}	<i>FDA-approved:</i> Focal onset seizures, ⁶ generalized onset seizures ⁶ <i>Off-label:</i> None
Divalproex	<i>FDA-approved:</i> Acute manic/mixed episodes of bipolar disorder ⁴ <i>Off-label:</i> Bipolar depression, ^{9,20} bipolar maintenance ²¹	<i>FDA-approved:</i> Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures, adjunctive therapy in patients with multiple seizure types that include absence seizures, ⁴ migraine prophylaxis ⁴ <i>Off-label:</i> Status epilepticus, ²² seizure prophylaxis after brain injury ²³
Gabapentin	<i>Off-label:</i> Alcohol use disorder, ^{24,25} alcohol withdrawal, ²⁵⁻²⁷ social anxiety disorder ²⁸	<i>FDA-approved:</i> Postherpetic neuralgia, ¹² focal seizures ¹² <i>Off-label:</i> Cough (chronic, refractory), ^{29,30} fibromyalgia, ³¹ hiccups, ^{32,33} neuropathic pain, ³⁴⁻³⁶ chronic and uremic pruritus (neuropathic or malignancy-related), ³⁷ RLS, ³⁸ vasomotor symptoms associated with menopause ³⁹
Lamotrigine	<i>FDA-approved:</i> Bipolar disorder ⁷ <i>Off-label:</i> Bipolar depression, ⁹ rapid-cycling bipolar disorder prophylaxis ⁴⁰	<i>FDA-approved:</i> Focal onset seizures, ⁷ generalized onset seizures ⁷ <i>Off-label:</i> Prophylaxis of unilateral neuralgiform headaches ⁴¹
Lithium	<i>FDA-approved:</i> Acute manic episodes of bipolar disorder, ⁸ maintenance treatment in bipolar disorder ⁸ <i>Off-label:</i> Acute hypomania, ⁹ acute depressive episodes of bipolar disorder, ⁹ adjunct MDD, ⁴² aggressive behavior, ⁴³ suicidality ⁴⁴	<i>Off-label:</i> Thyrotoxicosis ^{45,46}
Pregabalin	<i>FDA-approved:</i> Fibromyalgia ⁴⁷ <i>Off-label:</i> Generalized anxiety disorder, ⁴⁸ social anxiety disorder ⁴⁹	<i>FDA-approved:</i> Diabetic peripheral neuropathy, postherpetic neuralgia, ⁴⁷ neuropathic pain associated with spinal cord injury, ⁴⁷ adjunct therapy for partial-onset seizures ⁴⁷ <i>Off-label:</i> Chronic refractory cough, ⁵⁰ chronic pruritus, ⁵¹ RLS, ⁵² vasomotor symptoms of menopause ⁵³
Tiagabine	<i>Off-label:</i> Social anxiety disorder, ⁵⁴ alcohol use disorder ⁵⁵	<i>FDA-approved:</i> Focal seizures ⁵⁶ <i>Off-label:</i> None
Topiramate	<i>Off-label:</i> Binge eating disorder, ¹⁶ alcohol dependence ⁵⁷	<i>FDA-approved:</i> Migraine prophylaxis, ^{13,58} partial onset seizures, ¹³ generalized tonic-clonic seizures, ¹³ Lennox-Gastaut syndrome ¹³ <i>Off-label:</i> Cluster headache prevention, ⁵⁹ essential tremor, ⁶⁰ antipsychotic-induced weight gain, ⁶¹ obesity ^{62,63}
Zonisamide	<i>Off-label:</i> Binge eating disorder ⁶⁴	<i>FDA-approved:</i> Partial onset seizures ⁶⁵ <i>Off-label:</i> Refractory migraine prophylaxis, ⁶⁶ adjunctive Parkinson disease, ⁶⁷ obesity ⁶⁸

MDD: major depressive disorder; RLS: restless leg syndrome

Clinical Point

AEDs as a class have broad pharmacologic actions, but are generally CNS depressants



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Clinical Point

Patients with comorbid psychiatric and neurologic disorders are ideal candidates for dually indicated AEDs

Related Resources

- Koch J. Mood stabilizers: balancing tolerability, serum levels, and dosage. *Current Psychiatry*. 2021;20(7):37-40. doi:10.12788/cp.0147
- Samel S, Stummer L, Karas A, et al. Nonpsychiatric indications for antidepressants and antipsychotics. *Current Psychiatry*. 2022;21(3):34-42. doi:10.12788/cp.0222

Drug Brand Names

Carbamazepine • Tegretol, Equetro	Levetiracetam • Keppra
Chlorpromazine • Thorazine	Lithium • Eskalith, Lithobid
Divalproex • Depakote	Metformin • Fortamet, Glucophage
Duloxetine • Cymbalta	Pregabalin • Lyrica
Escitalopram • Lexapro	Tiagabine • Gabitril
Gabapentin • Neurontin	Topiramate • Topamax
Lamotrigine • Lamictal	Zonisamide • Zonegran

Because AEDs were originally purposed to treat neurologic disease, psychiatric indications must first be established before considering other indications. AEDs as a class have broad pharmacologic actions, but are generally CNS depressants, decreasing brain signaling through mechanisms such as ion channel antagonism (carbamazepine, gabapentin) or alterations to gamma-aminobutyric acid/glutamate signaling (divalproex, topiramate).^{4,6,12,13} Compared to antidepressants and antipsychotics, whose primary use for psychiatric conditions is firmly rooted in evidence, rational use of AEDs for psychiatric conditions and symptoms depends on the agent-specific efficacy. Patients with comorbid psychiatric and neurologic disorders are ideal candidates for dually indicated AEDs due to these agents' class effects rooted in epilepsy. Due to the history of positive psychiatric benefits with AEDs, newer agents may be psychiatrically beneficial but will likely follow the discovery of these benefits in patients for whom epilepsy is the primary diagnosis.

Consider the limitations

Using AEDs to reduce polypharmacy should be done judiciously from a drug-drug interaction perspective, because certain AEDs (eg, carbamazepine, divalproex) can greatly influence the metabolism of

other medications, which may defeat the best intentions of the original intervention.^{4,6}

Several other limitations should be considered. This article does not include all AEDs, only those commonly used for psychiatric indications with known nonpsychiatric benefits. Some may worsen psychiatric conditions (such as rage and irritability in the case of levetiracetam), and all AEDs have an FDA warning regarding suicidal behaviors and ideation.^{14,15} Another important limitation is the potential for differential dosing across indications; tolerability concerns may limit adequate dosing across multiple uses. For example, topiramate's migraine prophylaxis effect can be achieved at much lower doses than the patient-specific efficacy dosing seen in binge eating disorder, with higher doses increasing the propensity for adverse effects.^{13,16}

Dual-use AEDs should be considered wherever possible, but judicious review of evidence is necessary to appropriately adjudicate a specific patient's risk vs benefit. The *Table*^{4,6-9,12,13,16-68} (page 35) provides information on select AEDs with both psychiatric and nonpsychiatric indications, including both FDA-approved and common off-label uses. These indications are limited to adult use only.

CASE CONTINUED

After reviewing Mr. B's medical history, the treating medical team decides to cross-taper escitalopram to duloxetine 30 mg twice daily. Though his pain lessens after several weeks, it persists enough to interfere with Mr. B's daily life. In addition to duloxetine, he is started on pregabalin 50 mg 3 times a day. Mr. B's pain decreases to a tolerable level, and he reports decreased worrying and restlessness, and improvements in concentration and sleep.

References

1. Meyer JM. A concise guide to monoamine oxidase inhibitors. *Current Psychiatry*. 2017;16(12):14-16,18-23,47,A.
2. Ban TA. Fifty years chlorpromazine: a historical perspective. *Neuropsychiatr Dis Treat*. 2007;3(4):495-500.
3. López-Muñoz F, Shen WW, D'Ocon P, et al. A history of the pharmacologic treatment of bipolar disorder. *Int J Mol Sci*. 2018;19(7):2143.
4. Depakote [package insert]. North Chicago, IL: AbbVie, Inc; 2021.

5. Henry TR. The history of valproate in clinical neuroscience. *Psychopharmacol Bull.* 2003;37 Suppl 2:5-16.
6. Tegretol and Tegretol-XR [package insert]. East Hanover, NJ: Pharmaceuticals Co.; 2020.
7. Lamictal [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
8. Lithobid [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc; 2009.
9. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20(2):97-170.
10. National Alliance on Mental Illness. Anosognosia. Common with mental illness. Accessed March 3, 2022. <https://www.nami.org/About-Mental-Illness/Common-with-Mental-Illness/Anosognosia>
11. Hales CM, Servais J, Martin CB, et al. Prescription drug use among adults aged 40-79 in the United States and Canada. *NCHS Data Brief.* 2019(347):1-8.
12. Neurontin [package insert]. New York, NY: Pfizer; 2017.
13. Topamax [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2009.
14. Molokwu OA, Ezeala-Adikaibe BA, Onwuekwe IO. Levetiracetam-induced rage and suicidality: two case reports and review of literature. *Epilepsy Behav Case Rep.* 2015;4:79-81.
15. U.S. Food & Drug Administration. FDA Statistical Review and Evaluation. Antiepileptic Drugs and Suicidality. 2008. Accessed March 3, 2022. <https://www.fda.gov/files/drugs/published/Statistical-Review-and-Evaluation--Antiepileptic-Drugs-and-Suicidality.pdf>
16. McElroy SL, Hudson JI, Capece JA, et al. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry.* 2007;61(9):1039-1048.
17. Zhang ZJ, Kang WH, Tan QR, et al. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. *J Psychiatr Res.* 2007;41(3-4):360-369.
18. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology.* 2000;42 Suppl 1:2-10.
19. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol.* 2016;30(6):495-553.
20. Davis LL, Bartolucci A, Petty F. Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord.* 2005;85(3):259-266.
21. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology.* 2003;28(7):1374-1382.
22. Limdi NA, Shimpi AV, Faught E, et al. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology.* 2005;64(2):353-355.
23. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. *J Neurosurg.* 1999;91(4):593-600.
24. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry.* 2018;175(1):86-90.
25. US Dept of Veterans Affairs, US Dept of Defense, The Management of Substance Use Disorders Work Group. VA/DoD clinical practice guideline for the management of substance use disorders. US Dept of Veterans Affairs/ Dept of Defense; 2015. Accessed March 3, 2022. <http://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised2216.pdf>
26. Myrick H, Malcolm R, Randall PK, et al. A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. *Alcohol Clin Exp Res.* 2009;33(9):1582-1588.
27. Ahmed S, Stanciu CN, Kotapati PV, et al. Effectiveness of gabapentin in reducing cravings and withdrawal in alcohol use disorder: a meta-analytic review. *Prim Care Companion CNS Disord.* 2019;21(4):19r02465.
28. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol.* 1999;19(4):341-348.
29. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomized, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9853):1583-1589.
30. Gibson P, Wang G, McGarvey L, et al. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest.* 2016;149(1):27-44.
31. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-1344.
32. Alonso-Navarro H, Rubio L, Jiménez-Jiménez FJ. Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol.* 2007;30(3):186-187.
33. Jatzko A, Stegmeier-Petroianu A, Petroianu GA. Alpha-2-delta ligands for singultus (hiccup) treatment: three case reports. *J Pain Symptom Manage.* 2007;33(6):756-760.
34. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173.
35. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2014;2014(4):CD007938.
36. Yuan M, Zhou HY, Xiao ZL, et al. Efficacy and safety of gabapentin vs. carbamazepine in the treatment of trigeminal neuralgia: a meta-analysis. *Pain Pract.* 2016;16(8):1083-1091.
37. Weishaar E, Szepletowski JC, Darsow U, et al. European guideline on chronic pruritus. *Acta Derm Venereol.* 2012;92(5):563-581.
38. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-Foundation. *Sleep Med.* 2016;21:1-11.
39. Cobin RH, Goodman NF; AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause—2017 update [published correction appears in *Endocr Pract.* 2017;23(12):1488]. *Endocr Pract.* 2017;23(7):869-880.
40. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder: Lamictal 614 Study Group. *J Clin Psychiatry.* 2000;60(11):841-850.
41. May A, Leone M, Afra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol.* 2006;13(10):1066-1077.
42. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *Br J Psychiatry.* 1993;162:634-640.
43. Craft M, Ismail IA, Krishnamurti D, et al. Lithium in the treatment of aggression in mentally handicapped patients: a double-blind trial. *Br J Psychiatry.* 1987;150:685-689.
44. Cipriani A, Pretty H, Hawton K, et al. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry.* 2005;162(10):1805-1819.
45. Dickstein G, Shechner C, Adawi F, et al. Lithium treatment in amiodarone-induced thyrotoxicosis. *Am J Med.* 1997;102(5):454-458.
46. Bogazzi F, Bartalena L, Brogioni S, et al. Comparison of radioiodine with radioiodine plus lithium in the treatment of Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 1999;84(2):499-503.
47. Lyrica [package insert]. New York, NY: Parke-Davis, Division of Pfizer Inc; 2020.
48. Lydiard RB, Rickels K, Herman B, et al. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. *Int J Neuropsychopharmacol.* 2010;13(2):229-241.
49. Pande AC, Feltner DE, Jefferson JW, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-

Clinical Point

Keep in mind that certain AEDs (eg, carbamazepine, divalproex) can greatly influence the metabolism of other medications

Clinical Point

Tolerability concerns may limit adequate dosing across multiple uses

- controlled, multicenter study. *J Clin Psychopharmacol.* 2004;24(2):141-149.
50. Vertigan AE, Kapela SL, Ryan NM, et al. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. *Chest.* 2016;149(3):639-648.
 51. Matsuda KM, Sharma D, Schonfeld AR, et al. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol.* 2016;75(3):619-625.e6.
 52. Allen R, Chen C, Soaita A, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. *Sleep Med.* 2010;11(6):512-519.
 53. Loprinzi CL, Qin R, Balcueva EP, et al. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1 [published correction appears in *J Clin Oncol.* 2010;28(10):1808]. *J Clin Oncol.* 2010;28(4):641-647.
 54. Dunlop BW, Papp L, Garlow SJ, et al. Tiagabine for social anxiety disorder. *Hum Psychopharmacol.* 2007;22(4):241-244.
 55. Paparrigopoulos T, Tzavellas E, Karaiskos D, et al. An open pilot study of tiagabine in alcohol dependence: tolerability and clinical effects. *J Psychopharmacol.* 2010;24(9):1375-1380.
 56. Gabitril [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2015.
 57. Johnson BA, Ait-Daoud N, Bowden C, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet.* 2003;361(9370):1677-1685.
 58. Linde M, Mulleners WM, Chronicle EP, et al. Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev.* 2013;2013(6):CD010610.
 59. Pascual J, Láinez MJ, Dodick D, et al. Antiepileptic drugs for the treatment of chronic and episodic cluster headache: a review. *Headache.* 2007;47(1):81-89.
 60. Ondo WG, Jankovic J, Connor GS, et al. Topiramate in essential tremor: a double-blind, placebo-controlled trial. *Neurology.* 2006;66(5):672-677.
 61. Ko YH, Joe SH, Jung IK, et al. Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. *Clin Neuropharmacol.* 2005;28(4):169-175.
 62. Wilding J, Van Gaal L, Rissanen A, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. *Int J Obes Relat Metab Disord.* 2004;28(11):1399-1410.
 63. Rosenstock J, Hollander P, Gadde KM, et al. A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care.* 2007;30(6):1480-1486.
 64. McElroy SL, Kotwal R, Guerdjikova AI, et al. Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial. *J Clin Psychiatry.* 2006;67(12):1897-1906.
 65. Zonegran [package insert]. Teaneck, NJ: Eisai Inc; 2006.
 66. Drake ME Jr, Greathouse NI, Renner JB, et al. Open-label zonisamide for refractory migraine. *Clin Neuropharmacol.* 2004;27(6):278-280.
 67. Matsunaga S, Kishi T, Iwata N. Combination therapy with zonisamide and antiparkinson drugs for Parkinson's disease: a meta-analysis. *J Alzheimers Dis.* 2017;56(4):1229-1239.
 68. Gadde KM, Kopping MF, Wagner HR 2nd, et al. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med.* 2012;172(20):1557-1564.