The Emerging Differential Roles of GABAergic and Antiglutamatergic Agents in Bipolar Disorders

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Treatment options to relieve the diverse symptoms encountered in patients with bipolar disorders include not only mood stabilizers, but also anxiolytics, new anticonvulsants, antidepressants, and antipsychotics. These agents have widely varying mechanisms of action, which could contribute to the heterogeneity of clinical effects seen in practice. Several of these medications, especially those with anticonvulsant effects, enhance γ-aminobutyric acid (GABA) inhibitory neurotransmission and/or attenuate glutamate excitatory neurotransmission. We review the efficacy and tolerability of these diverse treatment options in bipolar disorders and explore possible relationships between clinical effects and GABAergic and antiglutamatergic mechanisms of action.

(J Clin Psychiatry 2003;64[suppl 3]:15–20)

Agents with diverse mechanisms are commonly used in the treatment of the varying symptoms encountered in patients with bipolar disorders, in part because monotherapy with any individual agent often yields suboptimal outcomes. By some estimates, two thirds of patients with bipolar disorder are taking more than 1 medication.[1] Two complementary amino acid neurotransmitter–related mechanisms are receiving increasing attention in relationship to bipolar disorder. The role of γ-aminobutyric acid (GABA) as an inhibitory neurotransmitter began to emerge in the mid-1960s, and by 1980, it was postulated that GABA may play an important role in mood disorders. Many agents used in the treatment of bipolar disorder have either direct or indirect GABAergic effects, including mood stabilizers, anxiolytics, some newer anticonvulsants, antidepressants, and antipsychotics. In contrast, glutamate is an excitatory amino acid neurotransmitter structurally related to GABA. Some newer anticonvulsants have antiglutamatergic effects. Below we review the emerging differential roles of GABAergic and antiglutamatergic agents in the management of bipolar disorder.

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This article is derived from the teleconference "The Role of GABA in Neuropsychiatric Disorders: A Review of GABA Agents," which was held April 3, 2002, and supported by an unrestricted educational grant from Cephalon, Inc.

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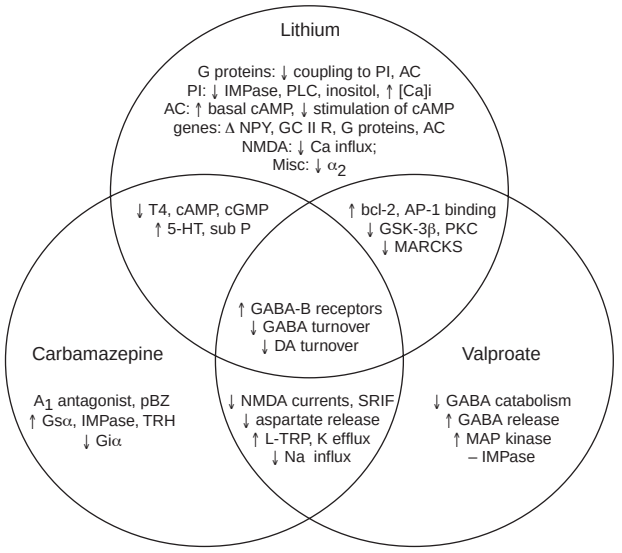
MOOD STABILIZERS

The classic mood stabilizers—lithium, carbamazepine, and valproate—have few mechanistic commonalities (Figure 1). A decrease in GABA turnover in animal models is one shared mechanism, and with chronic administration, these agents all tend to increase limbic $GABA_B$ receptors. All 3 agents also decrease dopamine turnover. However, these drugs have multiple actions with 2-way commonalities and still other actions that differ from one another. The anticonvulsants carbamazepine and valproate both attenuate glutamatergic neurotransmission, decreasing *N*-methyl-D-aspartate (NMDA) currents and aspartate release. Valproate has multiple additional GABAergic actions, including decreasing GABA catabolism and increasing GABA release, while carbamazepine has effects at peripheral-type benzodiazepine receptors. Lithium also effects glutamate neurotransmission and has diverse effects on intracellular signaling.

However, medications with GABAergic actions do not uniformly yield benefit in bipolar disorder. For example, double-blind administration of 10 to 50 mg/day of the $GABA_B$ agonist L-baclofen in 3 of 5 patients with treatment-resistant—primarily rapid-cycling bipolar II—bipolar disorder yielded deterioration, with improvement in excess of baseline upon withdrawal.[2] This outcome suggests that in searching for new GABAergic treatments, $GABA_B$ receptor antagonists could be of considerable interest. While there has been some development in this area, new drugs with this specific mechanism have yet to come to market.

Figure 1. Mechanisms of Action of the Mood Stabilizers Lithium, Carbamazepine, and Valproate[a]



[a]Abbreviations: 5-HT = serotonin; A_1 = adenosine A_1 receptors; α_2 = alpha-2 adrenergic neurotransmission; AC = adenylate cyclase; AP-1 = AP-1 transcription factor binding; bcl-2 = cytoprotective protein; Ca = calcium, [Ca]i = intracellular calcium; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DA = dopamine; GABA = γ-aminobutyric acid; GC II R = glucocorticoid type II receptors; Giα = G protein inhibitory alpha subunits; Gsα = G protein stimulating alpha subunits; GSK-3β = glycogen synthase kinase-3beta; IMPase = inositol monophosphatase; K = potassium; L-TRP = L-tryptophan; MAP = microtubule-associated protein; MARCKS = myristoylated alanine-rich C kinase substrate; Na = sodium; NMDA = *N*-methyl-D-aspartate; NPY = neuropeptide Y; pBZ = peripheral-type benzodiazepine receptors; PI = phosphatidyl inositol; PKC = protein kinase C; PLC = phospholipase C; SRIF = somatostatin-like immunoreactivity; sub P = substance P; T_4 = levothyroxine; TRH = thyrotropin-releasing hormone. Symbols: ↓ = decrease; ↑ = increase; – = no change.

ANXIOLYTICS

Benzodiazepines increase GABAergic neurotransmission and are potent anxiolytics. Up to 20% of patients with bipolar disorder may also have panic disorder,[3–5] and consequently, anxiolytics are common adjuncts to treat anxiety in bipolar disorder. However, the utility of these agents is limited by their abuse potential, particularly in patients with histories of substance abuse, and the risk of disinhibition, particularly in children and adolescents and patients with Cluster B personality disorders.

The desire to decrease exposure to drugs with more problematic side effects has led clinicians to employ the sedative effects of adjunctive benzodiazepines in efforts to limit use of older typical antipsychotics in the treatment of acute mania. Early reports suggested clonazepam tended to offer benefits in mania[6] comparable to or even better than lithium for overactivity and logorrhea. However, in a 2-week, double-blind, controlled study[7] of 24 patients with acute mania, clonazepam yielded an 18% response rate and a 0% remission rate, whereas lorazepam yielded a 61% response rate and a 39% remission rate.

Thus, benzodiazepines may be useful adjuncts, but are not typically used as monotherapy for acute mania. For example, in studies[8–13] conducted to obtain U.S. Food and Drug Administration (FDA) approval for new drugs for acute mania, benzodiazepines are commonly allowed as needed as rescue medications, because they offer some benefit but seldom seem to interfere greatly with detecting differences in antimanic effects between investigational agents and placebo. Typically, adjunctive benzodiazepines are allowed as needed during the first few days, with the maximum allowable daily dose gradually decreased to 0 mg over about a week. In such trials, patients taking placebo drop out more often for inefficacy after tapering off benzodiazepine rescue medication than patients taking active investigational antimanic medication. This suggests an adjunctive role for benzodiazepines, but it also highlights the, at most, modest efficacy of benzodiazepines as primary treatments for acute mania.

NEWER ANTICONVULSANTS

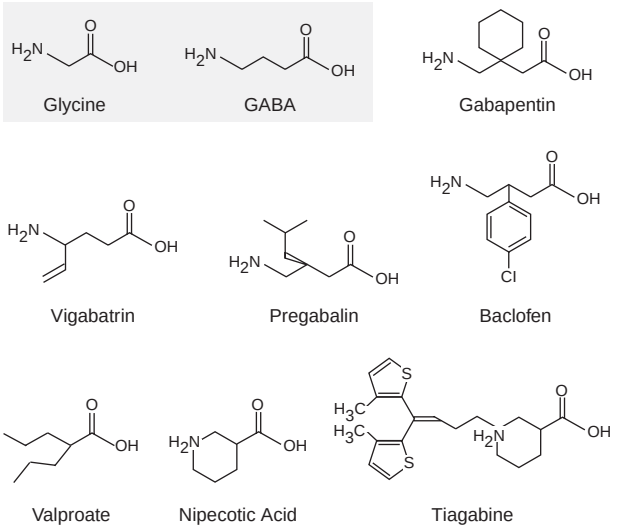
Several newer anticonvulsants have been approved since 1993, and are being evaluated for their potential roles in the treatment of various symptoms of bipolar disorder. One of the challenges in researching treatments for bipolar disorder is to characterize such diverse agents in terms of their heterogeneous psychotropic profiles. It is overly simplistic to merely anticipate profiles similar to either mood stabilizers or anxiolytics, because some newer anticonvulsants have novel profiles not anticipated based on the clinical actions of older agents.

Many newer, like some older, anticonvulsants increase GABAergic inhibitory neurotransmission (Figure 2), but several newer agents attenuate glutamate excitatory neurotransmission (Figure 3). GABAergic, compared with antiglutamatergic, medications may tend to have more sedating profiles. This property is consistent with $GABA_A$ receptor F1 subunit effects of benzodiazepines and with limitations of some older anticonvulsants. However, sedation can be a beneficial effect in patients with mania, anxiety, agitation, and insomnia. Antiglutamatergic, compared with GABAergic, agents may be more stimulating and may even cause anxiety and weight loss in some circumstances. Some newer anticonvulsants with both GABAergic and antiglutamatergic actions yield the uncommon combination of both sedation and weight loss. For example, topiramate yields sedation and weight loss, possibly because of its GABAergic and antiglutamatergic actions, respectively.

Felbamate

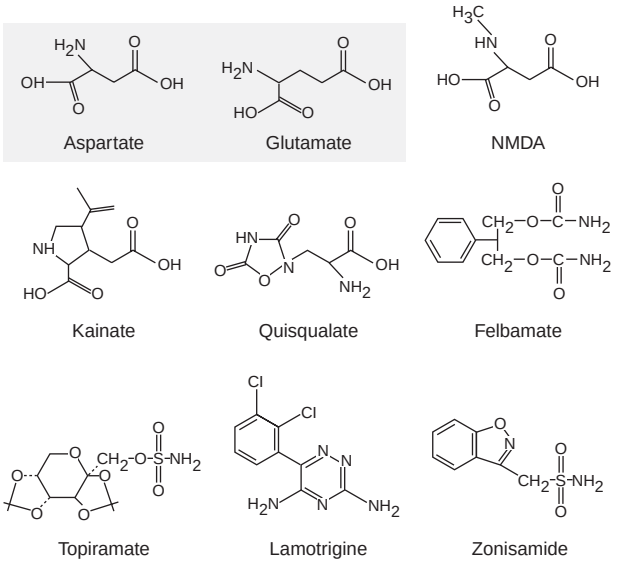
Felbamate has 2 carbamyl groups linked to a phenyl ring and is thus structurally similar to meprobamate, which

Figure 2. Inhibitory Amino Acid Neurotransmitters and Related Compounds[a]



[a]Abbreviation: GABA = γ-aminobutyric acid.

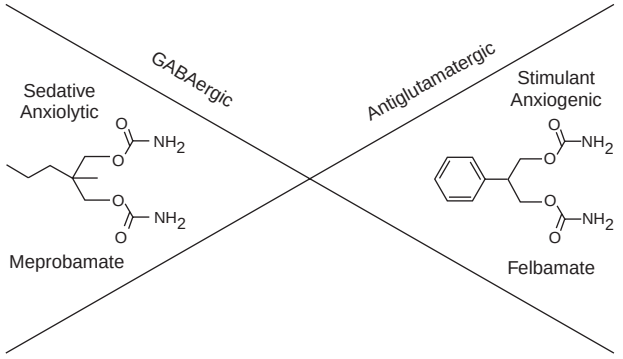
Figure 3. Excitatory Amino Acid Neurotransmitters and Related Compounds[a]



[a]Abbreviation: NMDA = *N*-methyl-D-aspartate.

has 2 such groups linked to an aryl chain (Figure 4). However, this relatively minor structural difference translates into major functional differences, as felbamate is mechanistically primarily antiglutamatergic and may be clinically stimulant-like,[14] whereas meprobamate is mechanistically primarily GABAergic and clinically anxiolytic. In a controlled epilepsy study,[14] more patients randomly assigned to receive felbamate monotherapy compared with those taking placebo had clinically significant increases in

Figure 4. Contrasting Mechanisms and Clinical Effects of Dicarbamates[a]



[a]Abbreviation: GABA = γ-aminobutyric acid.

anxiety. Also, felbamate can cause robust weight loss. Could this novel stimulant-like or activating profile be related to the primarily antiglutamatergic action rather than GABAergic action of felbamate? Unfortunately, felbamate use is restricted to treatment-resistant epilepsy due to the risks of aplastic anemia and fatal hepatitis.

Gabapentin

Gabapentin, which seems to have indirect GABAergic actions and some sedating effects, appeared promising as an adjunctive agent in early open studies of patients with bipolar disorders.[15] However, in 2 controlled studies[16,17] of specific applications as a primary treatment for bipolar disorder, gabapentin was ineffective. In a double-blind, placebo-controlled study[16] of bipolar patients suffering from mania or hypomania while taking lithium, valproate, or lithium and valproate, placebo tended to lower mania scores better than adjunctive gabapentin. Also, in treatment-resistant—primarily rapid-cycling bipolar—mood disorders, gabapentin was no more effective than placebo,[17] and during this 6-week trial, patients taking gabapentin gained 1.7 kg (3.8 lb). In contrast, lamotrigine was more effective than both gabapentin and placebo and yielded a 1.0-kg (2.2-lb) weight loss.

Our group conducted a study of adjunctive gabapentin[18] in 22 patients with bipolar disorder who were currently taking mood stabilizers but still suffering from depression. Adjunctive open gabapentin had antidepressant effects in patients with mild-to-moderate, but not severe, depression.

Controlled studies found gabapentin has anxiolytic effects in social phobia[19] and panic disorder[20] and analgesic effects in postherpetic neuralgia[21] and diabetic neuropathy,[22] suggesting utility as an adjunct for such symptoms in patients with bipolar disorder. Taken together, the above considerations suggest that the GABAergic agent gabapentin may, like benzodiazepines, be a useful adjunct but not a primary treatment for bipolar disorder.

Lamotrigine

Lamotrigine, which has more antiglutamatergic than GABAergic effects (T.A.K.; R. M. Post, M.D., manuscript submitted), has utility in treating depressive symptoms and rapid cycling in patients with bipolar disorder. Calabrese et al.[23] compared lamotrigine monotherapy at doses of 50 or 200 mg/day with placebo for 7 weeks in patients with bipolar I depression. Lamotrigine at 200 mg/day demonstrated significant antidepressant efficacy compared with placebo. Response rates were 51% for lamotrigine 200 mg/day, 41% for lamotrigine 50 mg/day, and 26% for placebo.

Calabrese et al.[24] studied lamotrigine monotherapy in 182 patients with rapid-cycling bipolar disorder. Patients randomly assigned to 6 months of lamotrigine or placebo did not differ significantly in time to additional pharmacotherapy, which was the primary outcome measure. However, survival in study, which was a secondary outcome measure, favored lamotrigine over placebo, with median survival times of 14 and 8 weeks, respectively.

As mentioned above, a double-blind, placebo-controlled, crossover study[17] of 6 weeks of monotherapy with gabapentin, lamotrigine, and placebo yielded differential efficacy and tolerability profiles for lamotrigine and gabapentin. Among the 31 treatment-resistant—primarily bipolar rapid cycling—mood disorder patients, there were 16 lamotrigine, 8 gabapentin, and 7 placebo responders. Moreover, only 6 weeks of treatment yielded a 2.7-kg (6.0-lb) weight difference between lamotrigine and gabapentin, which have putatively different amino acid neurotransmission effects. These data are consistent with the notion that markedly different clinical profiles may be seen with antiglutamatergic agents, such as lamotrigine, compared with GABAergic agents, such as gabapentin.

Topiramate

Topiramate is a newer anticonvulsant with both GABAergic and antiglutamatergic mechanisms. In a preliminary 3-week, double-blind, randomized, placebo-controlled trial,[10] the efficacy of topiramate at 256 mg/day or 512 mg/day in acute mania was examined. An interim analysis in 36 patients suggested that topiramate monotherapy was effective in mania. However, in an expansion of the study that increased the sample size to 97 patients, topiramate failed to separate from placebo. Subsequent controlled monotherapy trials failed to demonstrate efficacy in acute mania (D. P. van Kammen, M.D., Ph.D., personal communication, Dec. 2002).

In an 8-week, randomized, single-blind study[25] of bipolar depression, adjunctive topiramate 176 mg/day and bupropion sustained release (SR) 250 mg/day appeared to offer similar efficacy, with 56% and 59% response rates, respectively. Patients taking topiramate lost 5.8 kg (12.9 lb), and those taking bupropion SR lost 1.2 kg (2.7 lb). As noted above, topiramate has a novel profile that includes both sedation and weight loss, perhaps related to its GABAergic and antiglutamatergic effects, respectively.

Tiagabine

Tiagabine, a selective GABA reuptake inhibitor, is another interesting newer anticonvulsant. There are not yet controlled data in bipolar disorder, but anecdotal benefits have been reported.[26,27] Kaufman[26] reported on 2 patients with bipolar disorder and 1 patient with schizoaffective disorder, bipolar type, who improved with adjunctive, open, low-dose tiagabine initiated at 4 mg/day and with final doses of 8 to 12 mg/day.

In an open study,[28] 8 of 22 patients with rapid-cycling, mixed, or hypomanic presentations responded to adjunctive tiagabine at 1 to 8 mg/day. In 13 of 14 nonresponders, treatment failure was due to adverse effects.

In another open study,[29] tiagabine was rapidly loaded in 8 acutely manic patients starting at 20 mg/day, which is 5 times greater than the suggested starting dose in the Physicians Desk Reference. Tiagabine was ineffective in treating mania and poorly tolerated when administered in this manner. One patient, who had been taking tiagabine 30 mg/day added to valproate 2500 mg/day, had a seizure on the third day. Although GABA is inhibitory in most brain regions, it may be excitatory in the thalamus, which is the putative generator of absence seizures, and some GABAergic medications can increase absence in seizure disorder patients.

The latter 2 studies emphasize safety concerns, particularly in loading tiagabine and combining it with other potent GABAergic medications, but much remains to be established concerning the potential roles of tiagabine in bipolar disorder. An in vitro study suggested potential for tiagabine to relieve migraine,[30] and tiagabine may have clinical anxiolytic effects.[31–33] Clearly, controlled studies of tiagabine are needed to understand the potential roles of this GABAergic agent in bipolar disorder.

ANTIDEPRESSANTS

Antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs), are used as adjuncts in the treatment of depression and anxiety in bipolar disorder. However, the utility of these agents is limited by the risks of provoking switches into mania or cycle acceleration. While the SSRIs are not directly GABAergic, they may indirectly enhance GABAergic neurotransmission. For example, in unipolar major depressive disorder patients, SSRIs increased occipital GABA concentrations,[34] normalizing a baseline cerebral GABA deficiency.[35] This effect could be related to SSRI-induced increases in brain allopregnanolone, as these agents can increase cerebrospinal fluid allopregnanolone concentrations in depressed patients.[36] Allopregnanolone is a GABAergic neurosteroid that binds with high affinity to various $GABA_A$ receptor

subtypes, potentially facilitating GABAergic actions. Also, GABA modulation of serotonin could contribute to the modest adjunctive benefit of some GABAergic agents in depression.[18] Antidepressants may also influence glutamate neurotransmission. In animals, chronic administration of SSRIs and antidepressants from every major class and electroconvulsive therapy reduce cortical NMDA receptors.[37,38]

Taken together, the above considerations are consistent with the hypotheses that some antidepressants have at least some GABAergic and antiglutamatergic actions and some GABAergic agents are useful adjuncts for depression.

ANTIPSYCHOTICS

Antipsychotics are commonly used in severe, psychotic, and treatment-resistant mood disorders. Older, or typical, antipsychotics offered prominent dopamine D_2 receptor blockade and antimanic effects, but their use in bipolar disorder was limited by concerns about the risks of acute extrapyramidal symptoms, tardive dyskinesia, and worsening of the depressive component of bipolar disorder. Newer, or atypical, antipsychotics block not only dopamine D_2, but also serotonin 5-HT_2 receptors, which could contribute to antimanic and antidepressant effects, respectively. Moreover, newer compared with older antipsychotics appear to carry much less risk of acute extrapyramidal symptoms and tardive dyskinesia. Controlled clinical trials suggest acute antimanic effects of olanzapine,[11,12] ziprasidone,[13] and aripiprazole monotherapy[8]; risperidone adjunctive therapy[39,40]; and a role for adjunctive clozapine[41] in the long-term management of treatment-resistant bipolar disorder.

Our group[42] found that open-label olanzapine offered antimanic, antidepressant, and anxiolytic benefits in a 9-week study of 25 patients with diverse exacerbations of bipolar disorder. Olanzapine has multiple cellular actions, which could differentially contribute to its varying clinical effects. These actions may include GABAergic effects, as demonstrated in a study[43] in which acute olanzapine increased cerebral cortical levels of the potent $GABA_A$ receptor modulator allopregnanolone up to fourfold in rat brain. Also, in rats, administration of olanzapine for 1 month markedly decreased hippocampal and temporal cortical $GABA_A$ receptor density[44] and for 6 months increased glutamic acid decarboxylase expression in the reticular nucleus of the thalamus.[45]

Thus, although atypical antipsychotics have been considered primarily as dopamine D_2 and serotonin 5-HT_2 receptor antagonists, their multiple mechanisms of action may include GABAergic actions that could contribute to their clinical effects. Also, because GABA negatively modulates dopamine, GABAergic agents may have adjunctive roles in psychotic disorders.[46] Similarly, glutamatergic mechanisms have been explored in psychotic disorders, and indirect enhancers of NMDA receptor function may reduce negative symptoms and improve cognition in schizophrenia patients taking typical antipsychotics.[47]

Taken together, the above considerations indicate that some antipsychotics have at least some GABAergic and glutamatergic actions and some agents influencing GABAergic and glutamatergic neurotransmission are useful adjuncts in psychosis.

CONCLUSION

Clinical trials of GABAergic and antiglutamatergic medications are helping us to understand the emerging roles of various new treatment options for bipolar disorder. The classic mood stabilizers have shared GABAergic actions as well as some effects on glutamatergic neurotransmission, and the GABAergic benzodiazepines are useful as adjunctive anxiolytics in bipolar disorder and perhaps as adjuncts in mania.

Of the newer anticonvulsants, adjunctive treatment with the GABAergic agent gabapentin may decrease anxiety and pain, even though it lacks benefit as a primary treatment for mania or rapid cycling. The antiglutamatergic agent lamotrigine is effective in bipolar depression and rapid cycling. The mixed GABAergic and antiglutamatergic agent topiramate yields weight loss, and there are emerging data concerning antimanic and antidepressive effects. While there are intriguing preliminary data for tiagabine, there is a lack of controlled data to help clinicians appreciate its potential roles in the treatment of bipolar disorder. Some antidepressants and antipsychotics may have effects on GABAergic and glutamatergic neurotransmission that could contribute to their clinical effects in bipolar disorder.

New treatment options to better relieve suffering in bipolar disorder will hopefully increasingly emerge with ongoing evaluation of GABAergic and antiglutamatergic agents, whose potential roles in bipolar disorder remain to be established.

Drug names: baclofen (Lioresal and others), bupropion SR (Wellbutrin SR), carbamazepine (Carbatrol, Tegretol, and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), lorazepam (Ativan and others), meprobamate (Miltown, Tranmep, and others), olanzapine (Zyprexa), risperidone (Risperdal), tiagabine (Gabitril), topiramate (Topamax), ziprasidone (Geodon), zonisamide (Zonegran).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, bupropion is not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression; carbamazepine, clonazepam, clozapine, felbamate, lamotrigine, risperidone, tiagabine, ziprasidone, and L-baclofen are not approved for the treatment of bipolar disorder; gabapentin is not approved for the treatment of bipolar disorder, anxiety, and pain disorders; and topiramate is not approved for the treatment of bipolar disorder and weight loss.

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