# Cognitive Side Effects of Anticonvulsants

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The increasing use of anticonvulsant drugs in psychiatry has prompted greater awareness of their effects on a range of psychiatric domains, including cognition. Older versus newer antiepileptic drugs have been reported to either worsen or enhance cognitive performance in clinical populations, and the extent to which cognitive disturbances may reflect iatrogenic factors versus psychopathology is subject to debate. We review current information about the role of anticonvulsants in cognition, with particular emphasis on newer compounds (such as lamotrigine, gabapentin, and topiramate), the cognitive dimensions of affective illness, and the clinical approach to evaluating cognition in psychiatric patients taking anticonvulsant drugs over time. *(J Clin Psychiatry 2001;62[suppl 14]:27–33)*



Impaired cognition has been described as a commonly observed feature in severe affective disorders.[1–3] However, clinicians frequently may be unable to discern when subjective or objective cognitive complaints derive from unipolar or bipolar illness, or from the use of antidepressant or thymoleptic pharmacotherapies. Older mood stabilizers (such as lithium) or antidepressants (such as tricyclics) have historically been associated with a high potential to interfere with attention, memory, concentration, and related executive functions, as well as motor speed and coordination. As newer antimanic and antidepressant compounds gain wider use in affective disorders, the relative degree to which they dull or enhance cognition becomes an important aspect of evaluating their effectiveness, tolerability, and likelihood for patient adherence. This article will focus on the extent to which newer anticonvulsant agents have been shown to influence cognition in both epileptic and clinical/neuropsychiatric patient populations and strategies for clinicians in the evaluation and management of cognitive complaints that may arise during pharmacotherapy.

## COGNITION IN MOOD DISORDERS

Until fairly recently, it was widely accepted that bipolar patients who recover from acute manic or depressive episodes seldom show residual or subsyndromal symptoms, yet growing evidence from modern studies now suggests that many, if not most, bipolar patients show persistent low-grade forms of psychopathology between full affective episodes.[4–6] Diffuse cognitive deficits have been reported among patients during either manic or depressive episodes, but very few studies have systematically investigated neuropsychological functioning during periods of wellness. Unfortunately, this methodology does not allow for investigating trait-related deficits that may persist during affectively intermorbid periods of bipolar illness. It has recently been noted that more obvious cognitive deficits remit during periods of euthymia, but some subtler deficits may persist in about one third of bipolar patients following clinical recovery.[7] Current data suggest that cognitive dysfunction may be associated with severity and chronicity of illness and that lifetime duration of bipolar disorder has a negative impact on executive functions and memory.[7]

Further evidence that a cognitive deficit may be intrinsic to bipolar illness derives from genetic studies involving discordant monozygotic twin pairs. Cognitive deficits that persist after the resolution of an affective episode may be a residual illness component or a stable trait marker. A recent report by Gourovitch et al.[8] studied 7 monozygotic twin pairs discordant for bipolar disorder, evaluating neuropsychological deficits in affected and unaffected individuals. The findings suggest specific deficits in select visual processing measures and short- and long-term verbal memory in affected probands as compared with their unaffected cotwins and a group of normal monozygotic twins. In addition, unaffected twins showed significantly poorer short-term and overall memory as compared with normal control twins. The memory deficit found in the unaffected twin group was not as pervasive as that demonstrated by the affected cotwins. Affected twins demonstrated deficits on recognition memory, whereas unaffected twins did not.

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This may suggest that while the affected twins show both learning and memory problems for verbal material, the deficits seen in the unaffected twins are restricted to a dysfunction in retrieval of information, but not memory consolidation. Because both members of the twin pairs demonstrated mild impairments in this study, the impairments may be related to a genetic risk factor for bipolar disorder rather than the symptoms of the illness.

A number of clinical factors may bear on the cognitive profile of bipolar patients, including diagnostic subtype (i.e., bipolar I vs. II), rapid cycling, chronicity, number of episodes, duration of remissions, and comorbid conditions, including substance use disorders. Notably, a recent study by van Gorp et al.[9] investigated neuropsychological functioning in euthymic bipolar patients with and without prior alcohol dependence. Because half or more of bipolar patients meet lifetime diagnostic criteria for comorbid alcohol or other psychoactive substance abuse or dependence,[10] the differentiation of cognitive effects potentially attributable to alcohol use versus bipolar illness per se becomes an important clinical distinction. Van Gorp et al.[9] found that currently euthymic bipolar patients *without* prior alcohol dependence had select neurocognitive impairment in verbal memory. However, patients *with* histories of comorbid alcohol dependence also demonstrated verbal memory deficits, with additional frontal executive impairment. Furthermore, the total number of months of mania and depression during the course of the illness was negatively correlated with cognitive performance, but only in the group of bipolar patients *without* alcohol dependence. These findings suggest possible progressive frontal lobe and hippocampal damage or disruption of frontal or subcortical circuits or frontal mesocortical circuits in patients with bipolar disorder. The fact that patients with a history of alcohol dependence did not exhibit this relationship may be due to the overshadowing effects of chronic alcohol use on cognitive functioning. The significant correlation of age at onset of alcohol use and several measures of neuropsychological functioning in the bipolar group with prior alcohol dependence supports this conclusion.

Similarly, Denicoff et al.[11] found that neuropsychological deficits in bipolar patients were associated with a longer duration and more severe prior course of illness, as reflected by number of hospitalizations and number of episodes of mania and depression. Specifically, an increased number of episodes were significantly correlated with impairment in memory and abstraction tasks, whereas increased number of hospitalizations and longer duration of illness were associated with select deficits in attention and concentration measures.

Functional neuroimaging studies provide further evidence of persistent neuropsychiatric deficits in bipolar illness. Previous research suggests that neuropsychological deficits are correlated with neuroanatomic abnormalities. While distinct structural abnormalities are not currently well established, some investigators have reported left temporal lobe enlargement,[12] whereas others have found either decreased left temporal lobe volume or no significant differences from normal control subjects.[13] Hippocampal volume has been reported as either increased[14] or decreased or unchanged[13] in bipolar patients. Lateral ventricular enlargement has been a common and consistent finding, especially in male and older bipolar patients, supporting the possibility of a progressive loss of tissue with increased duration of illness.[15]

A recent study[16] investigating the relation of neuropsychological performance to neuroanatomic structures found that deficits in verbal working memory, verbal fluency, and sustained attention were associated with enlargement of the right hippocampus in euthymic patients with bipolar disorder. This finding is controversial and not fully understood. It is unclear whether the enlargement of neuroanatomical structures is due to an abnormality in the developmental process of synaptic pruning or the result of a compensatory synaptic increase, associated with decreased cortical input from frontal and temporal structures.[16]

Functional neuroimaging studies have reported changes in brain areas relative to clinical symptoms and cognitive deficits. Dolan et al.[17] investigated the prominent feature of psychomotor slowing using positron emission tomography and found decreased activity in the dorsolateral prefrontal cortex in both bipolar and schizophrenic patients who were experiencing psychomotor deficits. Abnormalities in regional brain metabolism have been found in bipolar patients despite clinical improvement. Specifically, hypometabolism and hypoperfusion are present in the prefrontal cortex, anterior cingulate, and basal ganglia.[18,19]

## ANTICONVULSANT PHARMACOTHERAPY AND COGNITION

While cognitive impairment may play an intrinsic role in severe affective disorders, it is often difficult for clinicians to confidently attribute cognitive dysfunction to illness-specific versus treatment-related factors. Moreover, the effects of disease chronicity, comorbid illnesses, normal aging, drug dose dependency, and multiple medications often further obscure the likely etiologies of cognitive deficits observed in the course of mood disorders. Studies that focus on epileptic versus psychiatric versus normal control populations also lead to variability in outcomes, as does the use of heterogeneous measures of neuropsychological or other cognitive functioning. Nonetheless, existing studies provide data to suggest that cognitive impairment may be less frequently encountered with newer than older classes of anticonvulsants. In fact, subjective reports of enhanced well-being and cognitive enhancement have been described among epileptic populations for whom some newer anticonvulsant agents are

**Table 1. Neurocognitive Dysfunction With Newer Anticonvulsants[a]**

| Drug | Cognitive Domain: Attention and Concentration | Memory | Motor Speed | Visuospatial Processing | Comments |
|---|---|---|---|---|---|
| Valproate | Subtle attentional deficits by formal testing; not typically reported by patient as problematic. Alleviated by drug cessation | Reports of mild memory deficits correlated with serum levels of drug, alleviated by drug cessation | Slightly lengthened decision time in normal controls<br>Psychomotor and attentional problems especially when used in combination with drugs such as clonazepam, phenytoin, and carbamazepine | No reported deficits | Subtle dose-related cognitive deficits, worse with drug combinations<br>Lithium to valproate crossover may ameliorate cognitive dulling<br>Overall, deficits are subtle, especially in the standard therapeutic range |
| Carbamazepine | Subtle learning deficits, as seen in lack of practice effects upon repeated testing | Mild changes in visual memory reported during event-related potential study | No reported deficits | Prolonged stimulus evaluation time as seen in delayed P300 response in event-related potentials | Subtle dose-related cognitive deficits<br>Mild impairment in new learning |
| Lamotrigine | Better sustained attention and concentration as compared with control subjects taking topiramate | Better verbal memory performance as compared with topiramate, though less robust than with gabapentin | No reported deficits | Better visuomotor processing speed as compared with control subjects taking topiramate | May subjectively enhance cognition; possible neuroprotective effects in preclinical studies |
| Gabapentin | Better sustained attention and concentration as compared with control subjects taking topiramate | Better verbal memory performance as compared with topiramate and lamotrigine | No reported deficits | Better visuomotor processing speed as compared with control subjects taking topiramate | Very few cognitive deficits reported when compared with other new anticonvulsants<br>Cognitive profile is very promising |
| Topiramate | Deficits on measures of attention in normal control subjects as compared with lamotrigine and gabapentin | Verbal memory problems in normal control subjects as compared with lamotrigine and gabapentin<br>Word-finding complaints among epileptic patients | Psychomotor slowing in normal control subjects > than with lamotrigine and gabapentin | No reported deficits | More negative cognitive profile than other anticonvulsants, partially due to rapid dose escalation or concomitant drugs<br>Neuroprotective effect in preclinical studies |

[a]Based on references 20–43.



substituted for older drug regimens. Available information regarding the cognitive aspects of newer anticonvulsants, summarized in Table 1, are described more fully in the following section.

### Valproate and Carbamazepine

Valproate is an antiepileptic drug that generally is considered to have fewer cognitive side effects than older antiepileptic drugs such as phenytoin or phenobarbital. However, few studies have formally evaluated the neuropsychological functioning of epileptic or normal control subjects receiving valproate. Gallassi and colleagues[20] studied 20 epileptic patients who had been seizure-free for at least 2 years while taking fixed-dose valproate monotherapy on a long-term basis; psychomotor modifications were then evaluated when valproate was withdrawn under controlled conditions. Some adverse effects were noted among patients taking valproate as compared with normal control subjects with regard to attention, visuomotor processing, and global level of performance. Deficits were found to be subtle, and patients did not complain of such disturbances, suggesting that formal neuropsychological testing is sensitive enough to detect subclinical changes. Dosage reductions of valproate by half did not alleviate these deficits, but drug discontinuation led to progressive improvement over 1 year. After 1 year off of treatment with valproate, patients were not significantly different from control subjects on any of the neuropsychological measures.[20]

Studies utilizing normal control subjects alleviate some of the methodological problems of intrinsic deficits of varying disease states, including epilepsy and mood disorders. Trimble and Thompson[21] used a crossover design in normal controls in which subjects were administered valproate or placebo for a 2-week period, followed by a washout of 1 week and then crossover. Dosing was titrated up

to 1000 mg/day and administered 3 times a day. Psychological testing occurred before treatment and after each of the 2 treatment periods. Effects of valproate were minimal, resulting in slightly longer decision time on tasks of both simple and difficult questions after administration.

Among children and adolescents, plasma valproic acid concentrations have been shown to correlate weakly with neuropsychological test performance, particularly with regard to memory.[22] Withdrawal of valproate or of carbamazepine has been found to alleviate subtle cognitive deficits that were evident during long-term antiepileptic treatment.[22]

It has been suggested that valproate taken in combination with other antiepileptic drugs may produce different cognitive side effects as compared with valproate monotherapy. Sommerbeck et al.[23] found a significantly greater decrement in performance on tasks associated with psychomotor function and attention among patients taking clonazepam plus valproate, raising the possibility of a cumulative effect or pharmacologic interaction. A more recent study compared epileptic patients taking long-term valproate monotherapy with patients taking a combination of valproate plus either carbamazepine or phenytoin. Patients on polypharmacotherapy had significantly poorer performance on several neuropsychological measures of psychomotor and visual attention as compared with those taking valproate alone. Furthermore, when compared with untreated epileptic patients and nonepileptic control subjects, patients taking valproate monotherapy showed no significant cognitive deficits on any of the tasks administered.[24]

Early crossover studies in epilepsy found that seizure patients who were switched from phenobarbital to valproate showed improved overall cognitive functioning.[25] However, other reports noted minimal psychomotor deficits among epileptic patients taking high doses of valproate as compared with low doses, suggesting that deficits may emerge related to serum levels of drug (e.g., 487.9 and 183.6 μg/mL, respectively).[21] Craig and Tallis[26] also observed greater cognitive impairment among epileptic patients taking valproate than phenytoin initially, although these differences did not persist after 1 year of treatment. Among bipolar patients, Stoll and colleagues[27] reported an open case series in which lithium-associated subjective cognitive dulling and loss of creativity were reversed by changing from lithium to valproate.

Studies that have compared valproate with carbamazepine have reported inconsistent findings. Gallassi et al.[20] found significantly more pronounced verbal memory deficits among epileptic patients taking valproate than those taking carbamazepine, although Forsythe et al.[28] reported better performance by epileptic patients taking valproate than those taking carbamazepine on tests of attention and memory. Interpreting these divergent results is not a straightforward task, since studies vary in their duration and the extent to which they statistically account for blood levels of anticonvulsant, habituation to a medication, and tolerability over time. Adverse cognitive effects from carbamazepine have been described as relatively minimal as compared with placebo, apart from subtle learning deficits as reflected by lack of improvement from practice effects during learning tasks. Such mild deficits appear comparable with both carbamazepine and valproate.[29] In children newly diagnosed with epilepsy, transient initial cognitive deficits have been reported with both carbamazepine and valproate.[30]

A comparative study[31] of carbamazepine, valproate, and other anticonvulsant monotherapies in healthy adult volunteers found changes in sensory memory and prolonged stimulus evaluation time with carbamazepine during testing by event-related potentials. Valproate, in contrast, did not significantly affect any event-related potential components.

Overall, data from epilepsy trials suggest that relatively little cognitive impairment results from treatment with valproate or carbamazepine when blood levels of drug are maintained within a usual therapeutic range.

### Lamotrigine and Gabapentin

Lamotrigine, a phenyltriazine compound thought to act via blocking low-voltage sodium channels and enhancing γ-aminobutyric acid (GABA) transmission, has been the focus of several studies in both unipolar and bipolar disorder, as well as epilepsy and Lennox-Gastaut syndrome. Gabapentin, a novel anticonvulsant that increases whole-brain GABA levels, has also begun to receive attention beyond epilepsy for its possible efficacy in affective and anxiety disorders, as well as in neuropathic pain syndromes. Studies in healthy volunteers found no significant increases from baseline testing with lamotrigine in a range of central nervous system measures, including adaptive tracking, smooth-pursuit eye movements, and body sway.[32,33] A single-blind, parallel-group comparison of lamotrigine (3.5 mg/kg/day, N = 12), gabapentin (17 mg/kg/day, N = 6), and topiramate (2.8 mg/kg/day, N = 6) in healthy volunteers found significantly better performance with either lamotrigine or gabapentin as compared with topiramate during acute treatment on performance tests of verbal fluency and sustained attention and concentration.[34] At 2- and 4-week assessments, subjects taking lamotrigine (escalated to a target dose of 7.1 mg/kg/day) or gabapentin (target dose of 35 mg/kg/day) again showed better sustained attention and concentration as well as better complex visuomotor processing speed and ability than did individuals taking topiramate (targeted at 5.7 mg/kg/day). Subjects taking lamotrigine had superior scores on the selective reminding test of verbal learning and memory as compared with those taking topiramate, but those taking gabapentin tended to have even better performance.[34]

When compared with carbamazepine in healthy subjects, gabapentin produced significantly fewer cognitive side effects across a spectrum of neuropsychological constructs including attention, processing speed, and memory. Additionally, gabapentin was superior to placebo on 1 measure of memory.[35]

Possible neuroprotective effects of lamotrigine have been hypothesized on the basis of preclinical studies showing protection against hippocampal CA3-layer cell loss and reduced surrounding cell damage,[36] as well as better recovery in behavioral testing, after induced cerebral ischemia in rodents[37] with lamotrigine pretreatment versus saline pretreatment. The possible clinical significance of these observations for humans remains unknown.

### Topiramate

Recent studies have suggested that topiramate may have a more negative cognitive profile than other newer anticonvulsant drugs. As noted earlier, Martin et al.[34] found that healthy control subjects taking topiramate performed significantly more poorly than subjects taking either gabapentin or lamotrigine. Performance on tests of attention, psychomotor skills, verbal memory, and verbal fluency declined significantly in subjects taking topiramate as compared with predrug baseline scores. In addition, subjects taking topiramate performed significantly worse than subjects taking gabapentin, lamotrigine, or placebo in both acute dosing (3 hours after administration of the drug) and chronic dosing conditions (2-week and 4-week interval testing sessions). In an epilepsy clinic population of 94 patients, 31% were found to have slowed thinking and word-finding difficulties.[38] Among epileptic children, cognitive and behavioral abnormalities associated with topiramate use appear unrelated to dose escalation frequency and have been suggested to arise more often in those with a previous history of psychiatric disturbances.[39] In adults, acute mental status changes have been described when topiramate is used in the long term in combination with other antiepileptic drugs, with reversibility evident within 48 hours of topiramate discontinuation.[40] When combined with valproate, topiramate has been associated with hyperammonemic encephalopathy that has been hypothesized to arise owing to carbonic anhydrase inhibition by topiramate as well as its effects on cerebral glutamine synthetase.[41] Such mental status changes appear fully reversible after the discontinuation of either drug.

In similar fashion to lamotrigine, neuroprotective effects have been associated with topiramate (diminished hippocampal damage after global ischemia in rodent models and reduced neuronal injury after status epilepticus), although the possible clinical bearing of this observation with regard to cognitive function and memory in humans remains uncertain.[42,43]

### Other Anticonvulsants: Levetiracetam, Zonisamide, Oxcarbazepine

Several newer anticonvulsant drugs have become available in the United States in the past year, including levetiracetam, zonisamide, and oxcarbazepine. While the current principal indication for the use of these agents is seizure disorders, they each offer potential applications for use in psychiatry and mood disorders based on their shared mechanisms of action with other anticonvulsant drugs.

Limited information is available about these compounds with regard to their cognitive effects in humans. Oxcarbazepine, the keto-derivative of carbamazepine, has been studied in Europe for acute mania and shown to have efficacy comparable with lithium.[44] Because it requires neither hematologic nor hepatic monitoring, in contrast to carbamazepine, it has begun to receive increasing interest for its possible off-label utility in affective disorders. In an open trial of oxcarbazepine monotherapy in 14 epilepsy patients, cognitive performance (as measured by memory, attention, and simple psychomotor speed) was comparable with that seen in a comparison sample of 15 patients treated with phenytoin monotherapy, at both 6- and 12-month assessments.[45]

Levetiracetam represents another anticonvulsant recently approved by the U.S. Food and Drug Administration that may have relevance to the treatment of mood disorders. Findings from the N132 Study Group for Levetiracetam indicate that cognitive functioning domains as well as overall quality of life both show significant improvement from baseline in epilepsy patients taking doses of either 1000 mg/day or 3000 mg/day.[46] In another single-blind add-on trial, the addition of levetiracetam to existing antiepilepsy drugs was not associated with a worsening of baseline cognitive performance.[47]

A double-blind trial of zonisamide, carbamazepine, phenytoin, and valproate in 48 healthy volunteers demonstrated reduced attention and information processing with zonisamide, associated with an augmented P3 amplitude during event-related potential testing.[31] In another study[48] of 9 patients with refractory partial seizures, zonisamide was found to impair specific cognitive functions, including the acquisition and consolidation of new information; although verbal learning was adversely affected, visual-perceptual learning was unimpaired. A significant association was also observed in this study between the degree of observed cognitive impairment and plasma zonisamide levels, although tolerance to cognitive side effects was observed over time.

## THE CLINICAL ASSESSMENT AND MANAGEMENT OF COGNITIVE DYSFUNCTION

Efforts by clinicians to characterize the nature of cognitive deficits and identify their likely etiologies often pose a

challenge in patients for whom complex psychiatric symptoms, detailed medication regimens, and potential medical comorbidities may be present. Determining when cognitive complaints reflect a possible medication side effect versus an intrinsic component of a psychopathologic condition often requires longitudinal assessment with corroborative history from observers other than the patient. Subjective memory complaints also have been shown to correlate more strongly with emotional distress than with objective longitudinal memory change (as might be related to the cognitive dysfunction seen in dementias or structural brain diseases[49]), highlighting the importance of careful assessment for patients who report cognitive disturbances. The following systematic approach may be of value in this process:

1. Administer baseline cognitive assessments prior to starting agents with the potential to interfere with cognitive function. Standard office-based assessments of higher integrative functioning (e.g., serial calculations, digit span) will likely provide a more-than-adequate measure. Self-administered cognitive screening tools such as the Cognitive Difficulties Scale[50] may help to catalog subjective complaints while providing a benchmark for the monitoring of potential future changes.
2. In patients taking psychotropic drugs, including anticonvulsants, delineate the aspects of cognitive and psychomotor functioning that may be impaired or intact. Subjective complaints about attention, memory, concentration, and motor function should be obtained by history and then compared with the objective assessment of the complaints by mental status examination. When reviewing the history, particular attention should be focused on abrupt changes from baseline states, age-appropriate functioning, recent medication changes or medical conditions, and functional disability or corollaries in the activities of daily living. The presence of depression, anxiety, psychosis, substance abuse, or other psychiatric conditions known to impair mentation warrant thorough assessment. When assessing higher integrative functioning, the testing of specific neuropsychologic functions (e.g., visuospatial configurations, perseverative tasks associated with frontal lobe function, and psychomotor abilities reflecting parietal lobe function) may be indicated. Formal neuropsychological testing may be warranted when there is an abrupt change that does not correlate with changes in medication regimen or psychiatric diagnosis, or when a patient demonstrates a steady decline in cognitive performance, as assessed by periodic screening procedures, especially among individuals above the age of 65 years.
3. Attempt to characterize the timing and onset of reported cognitive disturbances. Gradual versus abrupt changes and associated features may provide useful information about likely etiologies.
4. Identify other medical or medication-related factors that may contribute to the current clinical picture. For example, cognitive effects may be attributable to the use of anticholinergic medications or sedative-hypnotics, alcohol, or other psychoactive substances, as well as an array of medical conditions.
5. Assess other potential signs of neurotoxicity that may be associated with anticonvulsants or other medications, such as ataxia or tremor.
6. When cognitive dysfunction is attributable to anticonvulsant (or other psychotropic) medications, check serum levels of drug if a standardized dosing range is available and consider dosage reductions when feasible. Remember pharmacokinetic interactions such as lamotrigine with valproate or carbamazepine. Also consider the potential for additive neurotoxic effects with 2 or more agents.
7. Consider the advantages and disadvantages of changing to alternative medications if side effects outweigh beneficial effects and if alternative compounds are available for the primary therapeutic targets.

## SUMMARY

An increasing number of anticonvulsant drugs have begun to enter wider use in psychiatry for a variety of psychopathologic conditions. As their likely spectrum of activity for depression, mania, and anxiety states continues to broaden, their potential benefits versus shortcomings with regard to cognitive function warrant careful clinical assessment. Many of the newer antiepileptic drugs, particularly lamotrigine and gabapentin, show fewer adverse cognitive effects than older anticonvulsants and in some instances may even enhance cognition, although much of the evidence in support of this remains anecdotal. The evaluation of cognitive functioning should become a routine aspect of clinical assessment in patients taking agents known to affect cognition and may provide useful data to the clinician in determining when further assessment or changes in a medication regimen are indicated.

*Drug names:* carbamazepine (Tegretol and others), clonazepam (Klonopin and others), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), topiramate (Topamax), zonisamide (Zonegran).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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