Bipolar disorder, like epilepsy and migraine, is episodic in nature. It should not be surprising, then, that anticonvulsants such as carbamazepine and valproate have proven efficacy as mood stabilizers. The newer anticonvulsants—agents like lamotrigine, gabapentin, topiramate, oxcarbazepine, and zonisamide—may also be effective treatments for bipolar disorder. Identifying an anticonvulsant for use in bipolar disorder should take into account not only the pathophysiology of bipolar disorder but also the mechanism of action of the anticonvulsant. This article will explore the mechanisms of action of the newer anticonvulsants and their relationship to the pathophysiology of bipolar disorder in an attempt to determine which of these agents might make effective mood stabilizers.

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Mechanism of Action of Newer Anticonvulsants

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Bipolar disorder, like epilepsy and migraine, is episodic in nature. It should not be surprising, then, that anticonvulsants such as carbamazepine and valproate have proven efficacy as mood stabilizers. The newer anticonvulsants—agents like lamotrigine, gabapentin, topiramate, oxcarbazepine, and zonisamide—may also be effective treatments for bipolar disorder. Identifying an anticonvulsant for use in bipolar disorder should take into account not only the pathophysiology of bipolar disorder but also the mechanism of action of the anticonvulsant. This article will explore the mechanisms of action of the newer anticonvulsants and their relationship to the pathophysiology of bipolar disorder in an attempt to determine which of these agents might make effective mood stabilizers.

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valproate and carbamazepine and some of the newer drugs, have been shown to be effective in experimental models of kindling as well as in the management of bipolar disorder.4–7 For example, in a study of amygdala-kindled rats, Loscher et al.6 found valproic acid to be effective in the reduction of kindled seizures. Otsuki et al.7 studied lamotrigine and other anticonvulsants in amygdala- and hippocampal-kindled rats and found that lamotrigine and valproate effectively and safely prevented seizures. Valproate is commonly used in the management of bipolar disorder, and several of the newer anticonvulsants are proving to be effective as mood stabilizers as well (see Evins,8 this supplement).

**NEUROTRANSMITTER LEVEL**

The balance among neurotransmitter levels is delicate, and the imbalance within particular brain regions that can precipitate mania and/or lead to depression can be complicated. Depression is generally thought to be due to a reduction in levels of the catecholamines norepinephrine and serotonin. The dysfunction of one of these neurotransmitter systems can have an impact on the other two; for example, abnormally decreased serotonin levels can disrupt the levels of both dopamine and norepinephrine. Drugs aimed at restoring the normal levels of catecholamines, such as the tricyclic antidepressants (TCAs), are often effective in alleviating depression. Unfortunately, the elevation of some of the catecholamines, dopamine in particular, can induce mania.9 Since the TCAs have such a broad range of action, it should not be surprising that TCAs have been found to precipitate mania and/or hypomania in patients with bipolar disorder.10,11

Newer antidepressant drugs, such as the selective serotonin reuptake inhibitors (SSRIs), that target the stimulation of serotonergic activity to relieve depression may also stabilize mood, but they, like the TCAs, might induce mania in a bipolar patient. A recent study12 retrospectively reviewed 533 patients admitted to a psychiatric unit during a 14-month period. Of those patients, 43 (8.1%) were admitted as a result of antidepressant-induced psychosis or mania; 70% of the drugs being taken at admission were SSRIs, and 21% were atypical antidepressants (bupropion, nefazodone, or venlafaxine). Although the SSRIs and other newer antidepressants generally have a safer side effect profile than the TCAs, these agents should be prescribed with caution for patients with bipolar disorder.

\[ \gamma \text{-Aminobutyric acid (GABA)} \] is also dysregulated in bipolar disorder. Low plasma levels of GABA have been found in both depressed and manic patients,13,14 and post-mortem studies of patients with schizophrenia and those with bipolar disorder have shown defective transmission of GABAergic neurotransmitters in both disorders.14 In his review of GABA in mood disorders, Petty13 hypothesized that individuals who have inherent low GABA function may be vulnerable to mood disorders and that normalizing GABA levels with drug treatment may then be associated with remission of mood symptoms. Drugs that increase GABA levels, including some of the newer anticonvulsants, may prove to be effective mood stabilizers in bipolar disorder.

**MOLECULAR LEVEL**

Looking at the pathophysiology of bipolar disorder on the molecular level may help identify which of the newer anticonvulsants may be an effective treatment for bipolar disorder. Changes in the regulation of sodium and calcium channels can modify catecholamine release, which in turn affects levels of dopamine, serotonin, and norepinephrine, all of which are implicated in the affective disorders. A number of experiments have suggested that alterations in either the gating kinetics or the activation of sodium and calcium channels can lead to abnormal balance between intracellular and extracellular levels of neurotransmitters. As such, modulation of voltage-sensitive sodium and calcium channels can lead to a correction in neurotransmitter release.5,15,16 In this regard, voltage-gated ion channels, including voltage-sensitive sodium and calcium channels, contribute to neurotransmitter regulation and, therefore, mood; seeing the voltage-gated ion channels as a target for action may clarify which anticonvulsants could also be effective as mood stabilizers. In general, the drugs that modify voltage-sensitive sodium and calcium channels would be expected to decrease the release of catecholamines during an acute manic episode and thereby normalize neurotransmitter levels, which would be expected to reduce mania. These same mechanisms may also prevent depressive episodes by stabilizing neurotransmitter release to avoid neurotransmitter depletion.

**Action of the Newer Anticonvulsants**

Table 1 summarizes the effect of some of the newer anticonvulsants on voltage-sensitive sodium and calcium chan-
nals, GABA receptor modulation, kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid) receptors, and carbonic anhydrase. Some kainate/AMPA receptors are specifically calcium permeable; blocking these receptors could have an impact on calcium levels, which can affect neurotransmitter levels. Carbonic anhydrase is an enzyme found in the brain and in erythrocytes and is involved in pH regulation. By modifying intracellular and extracellular pH through carbonic anhydrase inhibition, a drug could affect neurotransmitter systems that are pH dependent.

As shown in Table 1, nearly all of the newer anticonvulsants under discussion have effects at voltage-sensitive sodium channels and calcium channels. Gabapentin is the exception. This drug decreases sustained repetitive firing, which is usually attributed to an effect at voltage-sensitive sodium channels, but it has not been shown that gabapentin has a direct effect on a voltage-sensitive sodium channel. Gabapentin binds to a particular subunit of voltage-sensitive calcium channels, the α2δ subunit. Although the precise mechanism of action is unknown, it has been hypothesized that this particular subunit is involved in neurotransmitter release. Since all these drugs affect voltage-sensitive sodium and calcium channels to some degree, it seems reasonable to suggest that they may all be effective, some more than others, in the treatment of bipolar disorder.

Gabapentin, topiramate, and zonisamide act on GABA in one way or another. Topiramate enhances GABA_A receptor function in a unique manner, and zonisamide binds to the GABA_A receptor, and gabapentin and topiramate increase brain GABA levels.

Among the drugs discussed here, topiramate and zonisamide have additional actions that contribute to their effects in epilepsy and may contribute to efficacy in bipolar disorder as well. Topiramate is a pharmacologically rich anticonvulsant with a broad spectrum of activity. It appears to be selective for the calcium-permeable kainate and AMPA receptors, and it has a unique ability to modulate non-NMDA (N-methyl-D-aspartate) glutamate receptors. Both topiramate and zonisamide inhibit carbonic anhydrase, which indirectly affects both excitatory and inhibitory pH-dependent neurotransmitter systems.

All of these molecular actions affect neuronal trafficking and the release of neurotransmitters. Drugs that modify the voltage-sensitive sodium and calcium channels would be expected to decrease the release of catecholamines during an acute manic situation and normalize catecholamine levels, thereby reducing mania. By normalizing catecholamine levels, these agents may also be effective in preventing the depletion of catecholamines that causes depression.

**CONCLUSION**

Ongoing investigations into the molecular mechanism of action of drugs and the pathophysiology of bipolar disorder will provide much-needed information concerning the role of the various etiologies that have been associated with bipolar disorder. Unfortunately, at the present time, it is not possible to make a clear association between molecular activity and clinical efficacy. The newer anticonvulsants may be well studied in epilepsy, but more studies are needed in bipolar disorder to help us learn how their mechanisms are, or are not, related to mood-stabilizing properties. Once we understand how particular agents work in terms of the pathophysiology of bipolar disorder, then understanding the mechanism of action of a particular drug can lead to the rational selection of a particular therapy when it becomes necessary to modify the treatment regimen of a patient with bipolar disorder.

**Drug names:** bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), gabapentin (Neurontin), lamotrigine (Lamictal), nefazodone (Serzone), oxcapaxepine (Trileptal), topiramate (Topamax), valproic acid (Depakene and others), venlafaxine (Effexor), zonisamide (Zonegran).

**Disclosure of off-label usage:** The author of this article has determined that, to the best of his knowledge, gabapentin, lamotrigine, 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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