Mechanism of Action of Newer Anticonvulsants

H. Steve White, Ph.D.

Bipolar disorder, like epilepsy, 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.

(J Clin Psychiatry 2003;64[suppl 8]:5–8)

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, such as 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; a greater understanding of both may enable the clinician to identify which anticonvulsant will be the most effective treatment. Several hypotheses concerning the etiology of bipolar disorder exist. They can be very general or very specific in nature, and this article will explore the pathophysiology of bipolar disorder and the mechanism of action of the newer anticonvulsants on 3 levels—systems, neurotransmitter, and molecular—in an attempt to determine which agents might make effective mood stabilizers (Figure 1).

SYSTEMS-LEVEL HYPOTHESIS: THE KINDLING AND SENSITIZATION MODEL

On a general level, one hypothesis about the etiology of bipolar disorder uses the analogy of kindling and sensitization phenomena.[1–3] In animal displays, amygdala-kindled seizures are repeatedly induced with a stimulation current; eventually, the animal displays spontaneous epileptic-type seizures, i.e., with no outside stimulation. Studies in stimulant-induced sensitization show that after an initial exposure to a high dose of a stimulant such as cocaine, an animal is likely to have a strong and robust reaction to lower doses of the same stimulant. In other words, the animal is more sensitive to the stimulant, and lower doses induce the same reaction as the high dose.[4]

The kindling and sensitization model in bipolar disorder postulates that stress, when presented to a susceptible individual, alters the structure and function of various brain networks and ultimately results in bipolar symptoms. Structural and functional changes are presumed to make the individual more sensitive to psychosocial stressors, resulting in frequent manic or depressive episodes that could cause further functional and structural changes. Eventually, manic or depressive episodes could occur spontaneously, without provocation from an outside stressor. This cycle of stress, changes in structure and function, and symptoms that lead to more stress may account for the increasingly severe progressive nature of the disease.

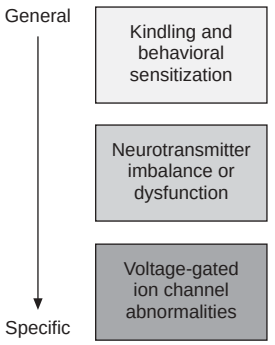
Stimulant-induced highs have characteristics similar to those of manic episodes; stimulant sensitization can therefore provide a clear and homologous analogy for manic episodes. The physiologic process involved in the transition from induced to spontaneous amygdala-kindled seizures in epilepsy research is no doubt different from that involved in the transition from manic or depressive episodes induced by a clearly stressful event or situation to episodes that seem to occur without an outside psychosocial stressor. In this regard, the kindling model may represent a useful model for understanding the progressive nature of bipolar disorder. Many anticonvulsants, including

From the Department of Pharmacology and Toxicology, University of Utah, Salt Lake City.

From the teleconference "Using the Newer Anticonvulsants as Mood Stabilizers in Affective Disorders," which was held July 16, 2001, and supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

Corresponding author and reprints: H. Steve White, Ph.D., Department of Pharmacology and Toxicology, 30 S2030 East, Room 112, University of Utah, Salt Lake City, UT 84112 (e-mail: swhite@hsc.utah.edu).

Figure 1. Tracing the Etiology of Bipolar Disorder



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 study[12] 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.

γ-Aminobutyric acid (GABA) is also dysregulated in bipolar disorder. Low plasma levels of GABA have been found in both depressed and manic patients,[13] and postmortem 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, Petty[13] 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-

Table 1. Possible Mechanisms of Action of the Newer Anticonvulsants[a]

Drug	Voltage-Sensitive Ion Channel Blockade: Sodium	Voltage-Sensitive Ion Channel Blockade: Calcium	$GABA_A$ Receptor Modulator	Increase GABA Levels	Kainate/AMPA Receptor Blockade	Carbonic Anhydrase Inhibition
Lamotrigine[b]	✓	✓	...	...	...	...
Gabapentin[c]	?	✓	...	✓	...	...
Topiramate[d]	✓	✓	✓	✓	✓	✓
Oxcarbazepine[e]	✓	✓	...	...	...	...
Zonisamide[f]	✓	✓	✓	...	...	✓

[a]Abbreviations: AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid, GABA = γ-aminobutyric acid. Symbols: ... = no action or data not known, ? = no direct effect has been demonstrated.
[b]See Grunze et al.[17] and Xie and Hagan[18] for review and references.
[c]See White[19] and Stefani et al.[20] for review and references. Direct effect on voltage-sensitive sodium channels has not been demonstrated; binds to the α2δ subunit of voltage-sensitive calcium channels.
[d]See White[19] Zhang et al.,[21] Perucca and Bialer,[22] Kuzniecky et al.,[23] and Petroff et al.[24] for review and references.
[e]See White[19] for review and references.
[f]See White[19] and Perucca and Bialer[22] for review and references. Zonisamide binds to the $GABA_A$ receptors.

nels, 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 effect 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.[19] 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,[19] zonisamide binds to the $GABA_A$ receptor,[19] and gabapentin[19] and topiramate[23,24] 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,[19] and it has a unique ability to modulate non-NMDA (*N*-methyl-D-aspartate) glutamate receptors.[25] 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), oxcarbazepine (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.

REFERENCES

1. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010
2. Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitization in the longitudinal course of affective illness. Br J Psychiatry 1986;149:191–201
3. Post RM, Rubinow DR, Ballenger JC. Conditioning, sensitization, and kindling: implications for the course of affective illness. In: Post RM, Ballenger JC, eds. Neurobiology of Mood Disorders. Baltimore, Md: Williams & Wilkins; 1984
4. Post RM, Weiss SRB. Sensitization, kindling, and anticonvulsants in mania. J Clin Psychiatry 1989;50(12, suppl):23–30
5. Stoll AL, Severus WE. Mood stabilizers: shared mechanisms of action at postsynaptic signal-transduction and kindling processes. Harv Rev Psychiatry 1996;4:77–89
6. Loscher W, Fisher JE, Nau H, et al. Valproic acid in amygdala-kindled rats: alterations in anticonvulsant efficacy, adverse effects and drug and metabolite levels in various brain regions during chronic treatment. J Pharmacol Exp Ther 1989;250:1067–1078
7. Otsuki K, Morimoto K, Sato K, et al. Effects of lamotrigine and conventional antiepileptic drugs on amygdala- and hippocampal-kindled seizures in rats. Epilepsy Res 1998;31:101–112
8. Evins AE. Efficacy of newer anticonvulsant medications in bipolar spectrum mood disorders. J Clin Psychiatry 2003;64(suppl 8):9–14
9. Diehl DJ, Gershon S. The role of dopamine in mood disorders. Compr Psychiatry 1992;33:115–120
10. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? Am J Psychiatry 1987;144:1403–1411
11. Nolen WA, Bloemkolk D. Treatment of bipolar depression: a review of the literature and a suggestion for an algorithm. Neuropsychobiology 2000; 42(suppl 1):11–17
12. Preda A, MacLean RW, Mazure CM, et al. Antidepressant-associated mania and psychosis resulting in psychiatric admissions. J Clin Psychiatry 2001;62:30–33
13. Petty F. GABA and mood disorders: a brief review and hypothesis. J Affect Disord 1995;34:275–281
14. Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 2001;25:1–27
15. Catterall WA. Molecular properties of brain sodium channels: an important target for anticonvulsant drugs. Adv Neurol 1999;79:441–456
16. Taylor CP, Narasimhan LS. Sodium channels and therapy of central nervous system diseases. Adv Pharmacol 1997;39:47–98
17. Grunze H, von Wegerer J, Greene RW, et al. Modulation of calcium and potassium currents by lamotrigine. Neuropsychobiology 1998;38:131–138
18. Xie X, Hagan RM. Cellular and molecular actions of lamotrigine: possible mechanisms of efficacy in bipolar disorder. Neuropsychobiology 1998;38: 119–138
19. White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia 1999;40(suppl 5): S2–S10
20. Stefani A, Spadoni F, Giacomini P, et al. The effects of gabapentin on different ligand- and voltage-gated currents in isolated cortical neurons. Epilepsy Res 2001;43:239–248
21. Zhang X, Velumian AA, Jones OT, et al. Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 2000;41(suppl 1):S52–S60
22. Perucca E, Bialer M. The clinical pharmacokinetics of the newer antiepileptic drugs: focus on topiramate, zonisamide, and tiagabine. Clin Pharmacokinet 1996;31:29–46
23. Kuzniecky R, Hetherington H, Ho S, et al. Topiramate increases cerebral GABA in healthy humans. Neurology 1998;51:627–629
24. Petroff OA, Hyder F, Rothman DL, et al. Topiramate rapidly raises brain GABA in epilepsy patients. Epilepsia 2001;42:543–548
25. Skradski S, White HS. Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia 2000;41(suppl 1):S45–S47