

Anticonvulsants as Mood Stabilizers and Adjuncts to Antipsychotics: Valproate, Lamotrigine, Carbamazepine, and Oxcarbazepine and Actions at Voltage-Gated Sodium Channels

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Issue: *Actions of certain anticonvulsants upon voltage-gated sodium channels may not only explain why they are effective mood stabilizers but may also explain why they could be useful adjuncts to antipsychotics for resistant psychosis.*

The past several BRAINSTORMS features have discussed 3 major mechanisms of therapeutic action for anticonvulsants: enhancement of the inhibitory neurotransmitter GABA (γ -aminobutyric acid), blockade of voltage-gated calcium channels as $\alpha_2\delta$ ligands, and blockade of voltage-gated sodium channels.¹⁻⁴ Each of these mechanisms is linked to reduction of seizures in seizure disorders.¹ Enhancing GABA may provide anxiolytic actions as well.² The $\alpha_2\delta$ ligands at voltage-gated calcium channels appear to be promising therapeutic agents across the spectrum from anticonvulsants¹ to anxiolytics³ to treatments for chronic pain.⁴ Finally, blockade of voltage-gated sodium channels may

not only provide anticonvulsant actions¹ and treatment for chronic pain,⁴ but as discussed here, may also have mood-stabilizing and even anti-psychotic-enhancing actions.

VOLTAGE-GATED SODIUM CHANNEL BLOCKADE AND MOOD-STABILIZING ACTIONS IN BIPOLAR DISORDER

Anticonvulsants with the best evidence for mood-stabilizing actions include valproate^{5,6} and lamotrigine.^{5,7} Although both agents are thought to have actions on voltage-gated sodium channels, perhaps resulting as well in the enhancement of GABA by valproate and in the reduction of glutamate release by lamotrigine,¹ differences in the manner in which these agents act upon the sodium channels (as well as other differences in their mechanisms of action) could theoretically be linked to observations that valproate and lamotrigine have differing therapeutic profiles in bipolar disorder. Thus, efficacy of valproate is best documented for mania, less well for bipolar maintenance, and least well for bipolar depression, whereas efficacy of lamotrigine is best documented for bipolar maintenance, less well for

bipolar depression, and least well for mania.⁵⁻⁸ Differential actions of valproate and lamotrigine on sodium channels, or upon downstream effects on the neurotransmitters GABA and glutamate, may provide hints about the differences in the biological nature of the manic, depressed, and maintenance phases in bipolar disorder and provide a rationale for combining these agents to achieve optimum symptom relief in bipolar disorder by exploiting their complementary therapeutic profiles.

Other anticonvulsants may also have efficacy in bipolar disorder, especially carbamazepine, another voltage-gated sodium channel inhibitor.^{5,9} A structurally related anticonvulsant with the same mechanism of action of blocking voltage-gated sodium channels is oxcarbazepine, and this agent might also be useful in bipolar disorder.^{9,10} However, several other anticonvulsants do not appear as robust in their actions for the treatment of bipolar disorder, including gabapentin and topiramate, possibly because of differences in their mechanisms of action, although the lack of adequate clinical trials or side effects may also be important considerations.^{5,10}

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VOLTAGE-GATED SODIUM CHANNEL BLOCKADE AND ADJUNCTIVE ANTIPSYCHOTIC ACTIONS IN SCHIZOPHRENIA

In addition to their well-documented efficacies in bipolar disorder, both valproate and lamotrigine may also enhance the antipsychotic actions of atypical antipsychotics in schizophrenia, even though they are apparently not effective as antipsychotics when used as monotherapies. Thus, valproate may both enhance the onset of antipsychotic actions of atypical antipsychotics and boost the efficacy of antipsychotics in schizophrenic patients who have inadequate responses.^{11,12} Early evidence suggests that lamotrigine can also enhance antipsychotic actions in schizophrenia.¹³ These clinical actions of valproate and lamotrigine do not appear to be explained simply by mood stabilization or reduction in impulsivity or aggression in schizophrenia but seem to be due to improvement in core psychotic features of schizophrenia, including positive and negative symptoms. Perhaps actions on voltage-gated sodium channels induced by certain anticonvulsants can contribute desirable therapeutic effects to those therapeutic effects associated with blockade of D₂ and 5-HT_{2A} receptors by atypical antipsychotics.

THERAPEUTIC SYNERGY OF ATYPICAL ANTIPSYCHOTICS AND VOLTAGE-GATED SODIUM CHANNEL INHIBITORS

The possibility of therapeutic synergy between the actions of voltage-gated sodium channel inhibitors and atypical antipsychotics has been widely recognized in bipolar disorder and in schizophrenia.^{8,14} It is well known that many monotherapies exist now for bipolar disorder, including lithium, valproate, and lamotrigine, as well as the atypical antipsy-

chotics.^{8,15} Atypical antipsychotics are the standards as monotherapies for schizophrenia. However, in the real world, patients with bipolar disorder or schizophrenia often have inadequate responses to a monotherapy. Increasingly, therefore, both disorders are being treated with combinations of anticonvulsants and antipsychotics.¹⁶

Several such combinations are proven effective and are rational, but not all such combinations are evidence-based and not all combinations are rational.^{16,17} Specifically, current evidence best supports combining 2 drugs with different mechanisms of action, especially anticonvulsants active at voltage-gated sodium channels with atypical antipsychotics. ♦

Take-Home Points

- ♦ Treatments for schizophrenia and bipolar disorder are now beginning to converge.
- ♦ To optimize symptom relief, both disorders are increasingly being treated concomitantly with atypical antipsychotics and with mood-stabilizing anticonvulsants.
- ♦ Although all atypical antipsychotics have therapeutic actions in schizophrenia and bipolar disorder, only those anticonvulsants that act upon voltage-gated ion channels are convincing treatments for bipolar disorder or for enhancing the action of antipsychotics in schizophrenia.

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