Predictors of Treatment Response in Bipolar Disorders: Evidence From Clinical and Brain Imaging Studies

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The clinical features of bipolar disorders can be correlated with responses to medications. Patients who respond to lithium, for example, often present differently from those who respond to divalproex or carbamazepine, but the correlations are relatively modest. Brain-imaging tools, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), can relate brain function to clinical features and medication responses. For example, in depression, it appears that prefrontal cortical function is decreased while subcortical anterior paralimbic activity is increased. Preliminary evidence suggests that baseline metabolism increases and decreases in the left insula may be associated with carbamazepine and nimodipine responses, respectively, and that cerebral lithium concentrations may correlate with antimanic effects. Although it is not yet a clinical tool for bipolar disorders, brain imaging provides useful research data to understand the fundamental neurobiology of mood disorders and to more effectively target therapeutics.

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The clinical features of bipolar disorders correlate with responses to medication; however, the modest nature of these correlations limits their clinical utility.[1] This article reviews such correlations and presents preliminary data relating medication responses to brain-imaging data. Although it cannot yet be considered a clinical tool, brain imaging is a powerful research tool to increase our understanding of the neurobiology of mood and its disorders.[2]

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CLINICAL MARKERS OF RESPONSE TO MEDICATION

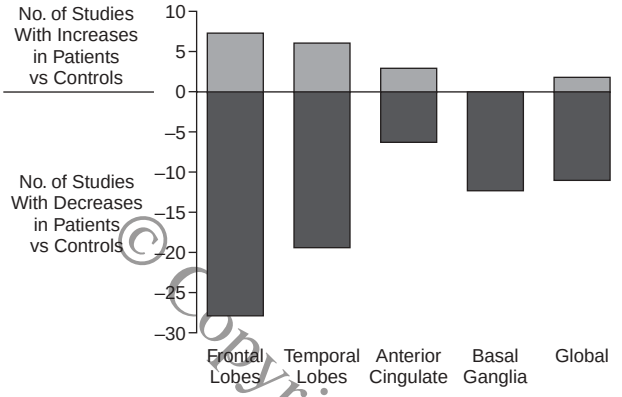
Lithium

Clinical markers of lithium responsiveness have been extensively explored. Lithium responsiveness has been associated with euphoric mania,[3–6] a classic pattern of mania followed by depression,[7,8] fewer prior episodes,[9,10] complete recovery between episodes,[11] a personal history of lithium response,[3,12] and a family history of bipolar disorder or lithium response.[13,14] In contrast, rapid cycling,[15–18] dysphoric[19] or mixed-manic episodes,[3–6] a history of at least 3 prior episodes,[9,10] a pattern of depression followed by mania,[7] severe mania,[20,21] and secondary mania[22–25] portend poorer responses to lithium. Adolescents,[26,27] patients with comorbid substance abuse,[28,29] or patients with a personal history of nonresponse to lithium[3] are also less likely to do well on lithium therapy. Finally, occasionally patients stabilized on lithium for extended periods of time may become lithium-resistant after discontinuing the agent and then suffer a relapse.[30,31]

Divalproex

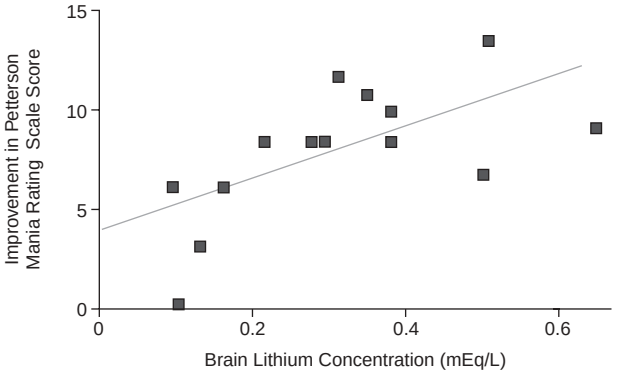
Many patients with poor response to lithium may respond to divalproex, which is effective in pure,[3] mixed,[3,32] or dysphoric mania.[19,33] Moreover, adolescents,[34] patients with rapid-cycling[3,32] or secondary[23–25]

Figure 1. Cerebral Blood Flow and Metabolism in Mood Disorders: Findings of 36 Controlled Studies[a]



[a]Reprinted with permission from Ketter et al.[44]

Figure 2. Cerebral Lithium Concentrations Correlate With Antimanic Responses[a]



[a]Reprinted with permission from Kato et al.[47] r = 64, p < .05.

bipolar disorder or bipolar disorder combined with concurrent substance abuse,[35] and patients unresponsive to lithium or those who cannot tolerate lithium[3,4] often respond to divalproex.

Previous treatment with antidepressants or stimulants may increase the risk of nonresponse to divalproex. In an open trial by Winsberg et al.,[36] medication-naive patients had an 82% (9/11) response rate to divalproex, while the response rate among patients who had been treated in the past with antidepressants or stimulants was only 38% (3/8). If these results are borne out, they may indicate that early treatment with mood stabilizers is preferable to early exposure to antidepressants or stimulants.

Carbamazepine

Clinical markers of response to carbamazepine are similar in some respects to those for response to divalproex, i.e., nonclassical,[8] secondary,[22] lithium-unresponsive, or intolerant patients[37,38] may respond to carbamazepine. However, findings have been less consistent with regard to the predictive value of a rapid-cycling pattern,[18,38–40] dysphoric mania,[41,42] and severe mania.[38,43]

CAN CLINICAL FEATURES BE CORRELATED WITH BRAIN-IMAGING DATA?

Brain functions, such as cerebral blood flow (CBF) and glucose metabolism (CRMglu), can be measured with tools such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Cerebral biochemistry can be assessed using PET with specific radioligands and using magnetic resonance spectroscopy (MRS).

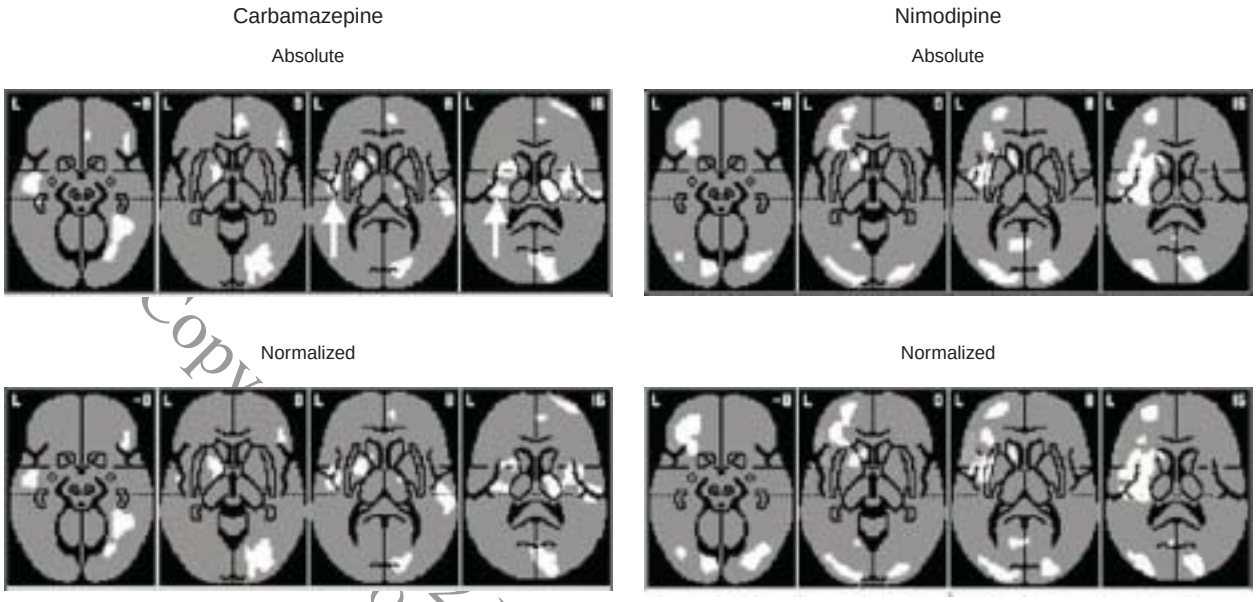
Many studies have found that depressed patients have decreased frontal lobe function[44] (see Figure 1). In a recent study,[45] whole brain glucose metabolism was decreased 7.7% in bipolar patients with moderate-to-severe depression, but was not significantly altered in mildly depressed or euthymic bipolar patients. Decreased prefrontal cortical blood flow is also found in depressions secondary to diverse conditions, such as Huntington's chorea, Parkinson's disease, and epilepsy. Hence, decreased prefrontal function may be a final common pathway to depression. Conversely, cerebral activity appears to be increased in the amygdala and other subcortical anterior paralimbic structures in primary depression, and this corticolimbic dysregulation (increased subcortical and decreased prefrontal activity) is consistent with the notion that in depression, affective compared with cognitive processing has increased influence.[46]

CAN TREATMENT RESPONSES BE CORRELATED WITH BRAIN-IMAGING DATA?

Because lithium has an odd number of electrons, its concentration in the brain can be measured using MRS. Brain lithium concentrations ≥ 0.2 mEq/L (which roughly correspond to serum concentrations ≥ 0.4 mEq/L) correlated with clinical antimanic responses as measured using the Petterson Mania Rating Scale (PMRS) (r = .64; p < .05; see Figure 2); the correlation was much weaker between antimanic responses and plasma lithium levels (r = .33).[47] Measurements of red blood cell lithium levels correlated poorly with clinical responses and, therefore, appear less useful than measurements of plasma and brain lithium levels.

One recent study[48] found that, compared with healthy control subjects and nonresponders, carbamazepine responders had higher pretreatment whole brain and especially left insular glucose metabolism (see Figure 3). The opposite was true for patients who responded to the

Figure 3. Baseline Cerebral Metabolism Correlates Directly With Carbamazepine Response and Inversely With Nimodipine Response[a]



[a]Adapted with permission from Ketter et al.[48] White regions indicate significant correlations between baseline (pretreatment) cerebral glucose metabolism and response to medications. Left, Carbamazepine response correlates directly with baseline cerebral metabolism (higher baseline metabolism associated with better carbamazepine response) in 26 patients. Right, Nimodipine response correlates inversely with baseline cerebral metabolism (lower baseline metabolism associated with better nimodipine response) in 20 patients. White arrows in top left figure indicate left insular region, which had both positive correlations with carbamazepine response and negative correlations with nimodipine response. These findings were evident for both absolute (top row) and globally normalized (bottom row) metabolism.

calcium channel blocker nimodipine. Divalproex responders may have lower baseline rostral anterior cingulate and medial frontal gyrus cerebral glucose metabolism,[49] while in contrast, unipolar depressed patients who respond to fluoxetine may have higher baseline cerebral glucose metabolism in the rostral anterior cingulate.[50] Thus, complementary baseline differences were observed in the bipolar depression patients who responded to divalproex and the unipolar depression patients who responded to fluoxetine.

However, baseline cerebral glucose metabolism is not a clinical test for medication responsivity, due to limited sensitivity and specificity: for example, occasionally patients with high metabolic rates respond poorly to carbamazepine. However, it may be possible to enhance the predictive value of brain-imaging data by using biochemically specific measures relevant to the illness and to putative mechanisms of action of the medications. For example, plasma γ-aminobutyric acid (GABA) appears to be decreased in bipolar disorders; higher (nearer to normal) levels may predict antimanic[51] and possibly even antidepressant[52] responses to divalproex, a GABAergic agent.

Cerebral GABA appears to be decreased in unipolar[53] but not bipolar[54] depression, and when successfully treated with selective serotonin reuptake inhibitors (SSRIs), unipolar patients achieve cerebral GABA levels similar to those of healthy control subjects. In contrast, euthymic bipolar patients taking GABAergic agents (divalproex ± gabapentin) have occipital GABA/creatinine levels 60% higher than those of healthy control subjects.[55] Thus, unipolar depressed patients may have low baseline cerebral GABA that is normalized with effective SSRI treatment, while depressed bipolar disorder patients may have near-normal cerebral GABA that needs to rise to supranormal levels to yield euthymic mood. One hypothesis that may account for divalproex response is that patients who respond are those who have higher (closer to normal) baseline cerebral levels of the inhibitory neurotransmitter GABA (and thus lower baseline glucose metabolism), in particular, in the rostral cingulate gyrus. These could be the patients who are more likely to achieve the necessary supranormal GABA levels when they are treated with agents that can increase brain GABA.

Preliminary data of this type provide ample illustration of the potential utility and explanatory power of brain-imaging data in our attempts to understand the fundamental neurobiology of mood disorders and, thus, to more effectively target therapeutics.

Drug names: carbamazepine (Tegretol and others), divalproex (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin), nimodipine (Nimotop).

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