

Bipolar Network News

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Updates from the Annual Society of Biological Psychiatry Meeting

The following articles are based on abstracts from the Society of Biological Psychiatry meeting: 64th Annual Convention, May 14-16, 2009, Vancouver, B.C., Canada. The abstracts were published in the journal *Biological Psychiatry*, vol. 65, #8S, April 15, 2009 supplement.

Treatment Updates

Rapid antidepressant effects possible with the cholinergic antagonist scopolamine

Rapid onset of antidepressant effects was achieved with three intravenous infusions (4 µg/kg) of the acetylcholine receptor blocker scopolamine (also used to treat sea sickness), reported Furey & Drevets.

This study used a double-blind cross-over design, in which unipolar depressed patients were initially divided into two groups – one received scopolamine while the other received placebo. Then the groups switched and began using the other drug. The rapid onset effects of the three scopolamine infusions persisted into the follow-up period, while those who received placebo first improved when switched to the active infusions.

EDITOR'S NOTE: Since scopolamine is an antagonist of cholinergic muscarinic receptors, these observations are consistent with data indicating that patients with mood disorders have an increased number of these receptors or a hypersensitivity to acetylcholine. The rapid onset of antidepressant effects with intravenous scopolamine is one of several new experimental approaches that all suggest antidepressant responses can be achieved much faster than the two weeks or more it takes conventional antidepressants to have an effect.

Scopolamine joins a group of rapid-acting interventions that includes intravenous ketamine, the hypothalamic peptide thyrotropin-releasing hormone (TRH), and even one night of sleep deprivation, which all produce antidepressant effects very quickly. These procedures provoke a critical clinical treatment question: what manipulations best sustain these antidepressant effects for the longer term?

Repeated infusions of ketamine can extend its acute-onset antidepressant effects

When the acute-onset antidepressant response of a single infusion of ketamine could not be maintained with the anti-glutamatergic drug riluzol, as had been hoped, investigators from Mt. Sinai in New York began exploring the utility of repeated ketamine infusions. They were able to extend the acute onset of antidepressant effects of ketamine with three successive intravenous infusions. The infusions were well-tolerated,

and there was no increase in dissociative or psychotic symptoms.

Nancy Diazgarnados, working with Carlos Zarate at the NIMH, reported that a single i.v. (0.5 mg/kg) infusion of ketamine in patients with treatment-resistant depression led to rapid onset of improvement in suicidal ideation, in addition to the previously reported improvement in depression and anxiety.

Disappointing results in study of levetiracetam for bipolar depression

Aybala Saricicek and other researchers at Yale did a double-blind, randomized controlled clinical trial of the anticonvulsant levetiracetam (Keppra) in the management of bipolar depression. The researchers found no differences in Hamilton Depression Rating Scale scores or any other outcome measure with levetiracetam (average dose 1,132 ± 425 mg/day) compared with placebo.

Editor's Note: These data are consistent with the disappointing results with levetiracetam reported by Post et al. in 2006 when it was used as an open adjunct to other ineffective drugs in mania and depression.

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Calcium Channel Blockers As Adjuncts to Lithium

Nimodipine

Manna reported in 1991 that a year of open treatment with either lithium or the L-type calcium channel blocker nimodipine was not as effective as a year of treatment with the combination of both drugs.

Subsequently, a research group at NIMH found that nimodipine was effective in some lithium-nonresponsive patients, particularly those with extremely rapid or ultradian cycling (Pazzaglia et al. 1999, Post & Leverich 2008). Partial responses to nimodipine were then further augmented with the mood-stabilizing anticonvulsant carbamazepine.

Together with the recent data on verapamil, these studies suggest that an L-type calcium channel blocker in concert with lithium or another mood stabilizer may help manage some patients with otherwise lithium-refractory bipolar illness.

Verapamil

In a study of this calcium channel blocker as an adjunct to lithium, Zarate and Mallinger at NIMH openly treated 45 patients with lithium. In phase II Patients who didn't respond were randomly assigned to double-blind treatment with either the calcium channel blocker verapamil (N=10) or continued lithium (N=8). Patients who still didn't respond (N=10) were assigned to combined verapamil and lithium in phase III. The combination in phase III was superior to either drug alone in phase II.

Editor's note: These data further support a series of about 10 small, mostly positive double-blind, placebo-controlled trials of the calcium channel blocker verapamil in acute mania.

Editor's Note: Nimodipine may work better than verapamil

While both nimodipine and verapamil block calcium influx in a long-lasting fashion (L-type), nimodipine has a dihydropyridine structure, which acts on the inside of the calcium channel, compared with verapamil, which is a phenylalkylamine and works toward the outside surface of the calcium channel. Accordingly, the two drugs have different biological properties. For example, nimodipine is positive in animal models of depression, and in blocking cocaine-induced hyperactivity and the excess dopamine overflow caused by cocaine use, while verapamil does not share any of these properties. In parallel with these preclinical differences, verapamil does not appear to have positive clinical antidepressant effects, while nimodipine appears to improve both depression and mania. These data suggest the potential better utility of nimodipine and other dihydropyridines compared with verapamil in approaches to bipolar disorder. Further indirect support for this hypothesis that L-type calcium channels are involved in bipolar illness is presented in our section on calcium channel blockers on page 4.

Two Anti-Glutamatergic Drugs Show Positive Effects In Psychosis

Lamotrigine as adjunct to atypicals in schizophrenia

Salimi reported that the addition of lamotrigine (400 mg) to atypical antipsychotics in schizophrenic illness of less than five years' duration resulted in significant improvement in positive psychotic symptoms, such as hallucinations and delusions, over that of placebo.

Lamotrigine is an anticonvulsant that is FDA-approved for the prevention of episodes of bipolar illness, especially depression. Lamotrigine inhibits glutamine release by blocking sodium channels.

Editor's note: Salimi's data support several other studies that suggest lamotrigine augmentation has positive effects on the acute psychotic symptoms of schizophrenia (hallucinations, delusions, and disorganized or bizarre behavior), but has little effect on the chronic negative symptoms, such as thought disorder and social withdrawal. It is not clear whether lamotrigine's ability to decrease glutamate release is important to its effects in schizophrenia.

Memantine adds to clozapine's antipsychotic effectiveness more than placebo

DeLucena et al. reported that the anti-Alzheimer's drug memantine (Namenda), which has anti-glutamatergic properties (in contrast to other drugs for Alzheimers that increase acetylcholine) was effective in augmenting antipsychotic responses to the atypical antipsychotic clozapine (Clozaril) compared with placebo.

Editor's Note: Since memantine did not show this augmentation effect in another study using other atypical antipsychotics, the finding could be specific to clozapine potentiation by memantine, and replication is needed.

Bipolar Network News

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The BNN is published four times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

Although the editors of the BNN have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The BNN can thus assume no liability for errors of fact, omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the BNN.

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Minocycline's Apparent Effectiveness In Early Phase Schizophrenia Suggests the Need for Treatment Studies in Bipolar Disorder

Since increases in inflammatory cytokines, microglial activation, and cell atrophy or loss are reported both in patients with schizophrenia and in patients with bipolar disorder, a recent symposium on the potential clinical effects of minocycline in schizophrenia may be relevant to some aspects of the treatment of bipolar disorder as well.

Minocycline is a **tetracyclic antibiotic** that may have neuroprotective effects in the two disorders. It is traditionally used for its **anti-inflammatory properties in the treatment of acne and arthritis**. Minocycline is structurally similar to doxycycline and other tetracyclic antibiotics, but has improved tissue absorption into the cerebrospinal fluid (CSF) and into the central nervous system (CNS), with a longer half-life compared with first-generation tetracyclines.

Minocycline blocks microglial activation, thus reducing neural inflammation in the instance of brain trauma. In addition to minocycline's anti-inflammatory effects, it also **inhibits cell death in a number of models of neurologic disease, including Huntington's chorea, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and stroke**. Hashimoto et al., *Biological Psychiatry*, 2007, 61:577-581, reported that minocycline also significantly reduced the decline in dopamine transporters in the striatum of monkeys treated with methamphetamine. These investigators reported that minocycline blocks nitric oxide synthetase, which has also been implicated in the pathophysiology of bipolar illness.

Minocycline improves negative symptoms

Levkovitz & Mendlovich reported that **minocycline 200 mg/day for six months improved both negative symptoms** of schizophrenia such as social withdrawal and **some elements of working memory** involving cognitive shifting. Minocycline was given to 54 patients in a double-blind, randomized fashion, with a ratio of two patients receiving minocycline to every one patient receiving placebo.

Chaudhry et al. reported that following one year of treatment with **minocycline in first-episode schizophrenia**, there was significant **improvement in cognitive deficits** and a trend for improvement in negative symptoms of schizophrenia.

Minocycline may be neuroprotective

Stirling et al. reviewed minocycline as a neuroprotective agent in *The Neuroscientist* in 2005. The researchers noted that in a mouse model of ALS, minocycline also promoted survival

Minocycline, an antibiotic with anti-inflammatory and multiple anti-cell-death effects, improves negative symptoms and cognitive deficits in schizophrenia and could be effective in bipolar disorder. Treatment studies are needed.

and myelination of transplanted oligodendroglial progenitors, a type of glial cell that makes the myelin insulation that wraps around neurons and is necessary for good nerve conduction. White matter deficits and reductions in oligodendrocytes have been reported in patients with bipolar disorder.

The authors also reviewed data that minocycline inhibits phospholipase A2 and prostaglandin levels, indicating that it inhibits lipid-mediated inflammatory signaling as well. This is of considerable interest because, as reported in the previous BNN,

Rapoport and colleagues found evidence for increased arachadonic acid signaling and its downstream inflammatory consequences in the brains of autopsy specimens of those with bipolar illness compared with controls.

Minocycline inhibits pre-programmed cell death, i.e. apoptosis

Interestingly, like lithium, minocycline increases Bcl-2, an anti-apoptotic protein. Bcl-2 is deficient in bipolar patients with the genetic risk variant A/A, associated with increases in intracellular calcium. Sterling et al. (2005) suggest that minocycline may have a direct effect in upregulating anti-apoptotic proteins such as Bcl-2, or it may target mitochondria directly and prevent liberation of cytochrome C, which is the first step in the mitochondrial cell death pathway. The authors also report that minocycline appears to act by inhibiting p38 MAPK kinase, which regulates the responses of white cells during infections and inflammatory reactions.

Minocycline blocks two types of cell death

There are two main pathways to apoptotic cell death in the central nervous system. One is a "death receptor" pathway in which the binding of molecules to Fas/CD95 or tumor necrosis factor (TNF-alpha) receptors activates a sequence of steps in which enzymes called caspases start to destroy the cell. First an *initiator* caspase 8 activates an *effector* caspase 3, and this subsequently results in breakdown of critical intracellular proteins and, ultimately, death of the cell.

Continued on Page 4

Minocycline *Continued from Page 3*

The second cell death mechanism involves the mitochondrial release of cytochrome C, which then activates another *initiator* of cell death (caspase 9). This, in turn, activates the *effector* of cell death (caspase 3), which is critical to the process of cell disintegration. Minocycline prevents this type of apoptosis in oligodendrocytes (the glia cells that make myelin).

People with bipolar disorder exhibit increases in TNF-alpha in the blood and brain and show deficits in oligodendrocyte and myelin, which are factors in the first type of cell-death pathway. There is mounting evidence of mitochondrial dysfunction in bipolar illness, and minocycline could inhibit the second type of cell death that begins with mitochondrial release of cytochrome C. Thus, through its effects on TNF-alpha and mitochondria, minocycline theoretically could inhibit both types of cell death pathways.

Minocycline seems to simultaneously suppress both apoptosis and CNS inflammation. In light of minocycline's multiple targets of action that have been implicated in the pathophysiology of bipolar illness, and the promising clinical data in schizophrenia noted here, it would be especially valuable to carry out systematic treatment studies of minocycline in patients with bipolar disorder.

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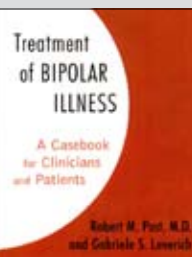
ROBERT POST, MD AND

GABRIELE S. LEVERICH, LCSW, BCD

BNN editors have written a book to provide physicians, patients and family members with the latest information about the illness and its treatments.

In a review in the *Journal of Psychiatric Practice*, Mark Frye of the Mayo Clinic gave the book 5 stars and wrote:

"This textbook by Post and Leverich is the most up-to-date, comprehensive visual teaching guide on the phenomenology, longitudinal course, and treatment of bipolar disorder currently available."



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Consistent Increases in Intracellular Calcium Seen in Bipolar Illness

The L-type calcium channel may confer genetic vulnerability to bipolar illness

Vulnerability to bipolar disorder seems to stem from the combined presence of multiple genes, but until now few studies have found reliable and replicable evidence for what those genes are. Pamela Sklar and colleagues recently carried out a large, collaborative, genome-wide association analysis, a study that links genes to the occurrence/lack of an illness. This study yielded further support for a previously reported vulnerability gene – the alpha-1C subunit of the L-type calcium channel (CNA1C). Because the study included more than 4,000 cases and 6,000 controls, the finding has a very high statistical significance. There was also another strong association between the presence of bipolar disorder and a gene

that affects sodium channels, Ankyrin-G (ANK3). The authors concluded that pathologies in calcium and sodium ion channels may be involved in bipolar disorder. (abstr. #318,pg. 95S)

Editor's note: These data converge with many studies that show there are consistent increases in intracellular calcium in blood elements (white cells and platelets) of patients with bipolar affective disorders compared with controls. This is one of the most consistent and well-replicated findings in biological psychiatry, and again suggests that alterations in calcium influx may be important in bipolar illness. These findings could also be consistent with the data noted on page 2 that blockers of calcium influx through L-type calcium channels can have therapeutic effects in bipolar patients.

The role of mitochondrial dysfunction in the calcium signaling abnormalities of bipolar disorder

Researchers led by Tadafumi Kato worked with mice genetically engineered to accumulate mitochondrial DNA polymorphisms and mutations in the brain, which shed light on the role of mitochondrial dysfunction in the calcium signaling abnormalities of bipolar disorder. Mitochondria are a cell's energy storehouse. The research group found that the transgenic mice exhibited bipolar disorder-like behaviors, which improved when they were treated with lithium.

Mitochondria from the transgenic mice showed decreased uptake of calcium, a possible

reason for the consistently-observed increased concentrations of calcium inside cells of those with bipolar illness as noted above.

The researchers also reported that BDNF-induced neurite extension was impaired in another type of animal when a gene was removed. Kato concluded that mitochondria and the endoplasmic reticulum, which also regulates intracellular calcium, could be involved in the pathophysiology of bipolar disorder.

Studies On Childhood Onset Bipolar Disorder

Decreased facial emotion recognition

Liebenluft and colleagues found that both children with bipolar disorder and those not ill but at high risk (because of a history of bipolar disorder in first-degree relatives) showed decreased recognition of facial emotions. This is a well-replicated finding in both childhood-onset bipolar illness and in adults with the illness, and now shows some promise as a marker indicating high risk in those who have not yet developed the illness.

Editor's Note: In addition, since poor recognition of facial emotion may contribute to altered emotional reactivity in children and adults, these findings support the potential utility of exploring rehabilitative therapies to enhance facial emotion recognition.

Strides have been made in this direction for children with autism, and many of the same types of training devices might be readily adaptable to children with bipolar illness and those at high risk.

Assessing risk with fMRI: Children at high risk for BP show decreased prefrontal cortical activity

Philips reported that children at high risk for bipolar disorder had decreased dorsolateral prefrontal cortical activity on functional magnetic resonance imaging (fMRI).

This finding raises the possibility that the eventual assessment of

children at high risk could involve an index combining genetic and clinical data, neuropsychological evaluation, findings on the fMRI, and results from blood tests such as markers of inflammation, as noted below.

Higher levels of inflammatory cytokines found in children with bipolar disorder

Pandey et al. reported an increased ratio of inflammatory to anti-inflammatory cytokines in children with bipolar disorder. The cytokines included interleukin-1 beta, TNF alpha, and C-reactive protein (CRP). The increases in TNF alpha were normalized with treatment.

These data are consistent with those of Quinones et al. reporting increases in the inflammatory marker CXCL5

in adults with bipolar disorder, and with previous work by that group that showed other inflammatory markers increased in children with bipolar illness. CXCL5 is of particular interest since its levels in blood, cerebrospinal fluid, and brain are correlated, suggesting that measurement in the blood may reflect what is going on in the central nervous system.

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Updates on Neurobiology

Upregulation of Type 1 immune responses in bipolar disorder

M.P. Quinones reported that there were increases in type 1 immune responses in the brains of individuals with bipolar disorder. *Type 1* responses are driven by the cytokines interleukin-12, interleukin-2, and interferon gamma. They *promote the clearance of intracellular infections*. In contrast, *type 2* responses are driven by interleukin-4 and interleukin-5, which *promote production of antibodies*.

Type 1 cytokines, interferon-gamma, and interleukin-12/24 were found to be significantly higher in the prefrontal cortex of patients with bipolar disorder compared with controls. However, these brain abnormalities were not paralleled by similar results in blood, as was found for CXCL5 on page 5.

Cytokines related to pathophysiology of major depression

Andrew Miller suggested how immune cytokines could contribute to the pathophysiology of major depression. Patients who are treated with the cytokine interferon alpha (for hepatitis C) have a high incidence of depression. Miller found that interferon alpha activates an indole 2,3 dioxygenase (IDO) pathway, leading to significant increases in kynurinic acid and quinolinic acid in the cerebrospinal fluid. Kynurinic acid and quinolinic acid levels were significantly correlated with severity of depression, as rated by MADRAS scores. Increases in kynurinic and quinolinic acid can have toxic effects on neurons and glia.

More abnormalities in frontal cortex and amygdala in bipolar disorder

Pandey also reported that in the prefrontal cortex and the amygdala of brains of patients who committed suicide, there were decreases in glucocorticoid receptors, increases in corticotrophin releasing hormone, and increases in interleukin-1B and TNF alpha (the latter two of which are inflammatory cytokines). Since decreased glucocorticoid receptors are associated with increases in cortisol (which can endanger neurons) and there is further evidence for inflammation, these findings suggest multiple pathways to cell toxicity in bipolar disorder.

Progressive deficits in BP patients with a common genetic variation in BDNF

A single nucleotide polymorphism (SNP) is a common genetic variation in the general population (as opposed to mutations, which are extremely rare events). The neuroprotective factor BDNF is a protein, made up of a long string of amino acids. At the 66th position in this string, most people have two amino acids called valines, called val-66-val, but in 20% of the population, a methionine (met) is substituted for one valine (val) and this variation or SNP is called val-66-met BDNF.

McIntosh et al. reported that bipolar patients with the val-66-met allelic variation in the proBDNF gene (which does not function as well as the val-66-val allele of proBDNF), showed progressive deficits in the volume of temporal lobe and cerebellar grey matter over a 4-year period. Thus, some progressive brain changes in bipolar illness may depend on the type of common genetic variants the patient inherits.

Low BDNF during manic and depressive episodes

Oliveira et al. from a research group in Brazil led by Flavio Kapczinski reported that there is decreased brain-derived neurotrophic factor (BDNF) in the blood in both unmedicated and medicated bipolar patients during manic and depressive episodes, but not during euthymia. These data add to a very substantial literature indicating **the degree of decrease in BDNF is correlated with the severity of a manic or depressive episode.**

Since affective episodes are also associated with abnormal increases in inflammatory cytokines and in oxidative stress (which produces free radicals and other central nervous system toxins), there is a dual set of mechanisms that endanger neurons and glia during the experience of repeated affective episodes: decreases in protective factors such as BDNF and increases in toxic factors. **These findings reinforce the importance of long-term prevention of affective episodes to avoid both their negative psychological consequences and adverse effects on the brain and cognition.**

Low folate in patients with bipolar disorder

Tunca et al. reported that folate measured in the blood was significantly lower in patients with bipolar disorder and schizophrenia than those with depressive or anxiety disorders. Folate helps lower homocysteine, a major cardiovascular risk factor. Higher levels of homocysteine correlate with greater cognitive deficits in patients with bipolar disorder. Increased levels of homocysteine were particularly evident in males with bipolar disorder. **These data add further support to the routine use of folate to treat bipolar patients who are having a difficult time with depression, usually at doses of 2 mg/day for males and 1 mg/day for females, in order to help treat the depression and lower homocysteine levels.**

Methylation of BDNF in bipolar patients

John Strauss from Toronto, Canada, reported that bipolar patients had increased promoter methylation of the BDNF gene measured in their white cells (lymphocytes), which produce antibodies for the body's immune system. Such methylation is usually associated with suppression of gene transcription, and since the methylation is mediated by environmental events such as repeated stress, the process is known as an epigenetic mechanism.

In contrast to an inherited genetic mechanism involving differences in DNA sequences, epigenetic mechanisms involve extra methyl groups added to the DNA or acetylation or methylation of histones around which DNA is wrapped. If DNA is wound tightly around histones, fewer genes in that area of the DNA get transcribed. Such DNA methylation induced by environmental events and stressors could account for the low levels of BDNF in both blood and the hippocampus that have been reported in patients with bipolar disorder.

Brain abnormalities in patients who died by suicide

Dwivedi et al. reported that the receptor for BDNF, called TrkB, and an activated or phosphorylated form of the TrkB receptor were decreased in the brains of patients who died by suicide. At the same time, expression of what's known as a low affinity p75 neurotrophic receptor (thought to be involved in cell death) was increased in both the prefrontal cortex and hippocampus. TrkB receptors are important for maintaining the neurotrophic and neuroprotective effects of BDNF, while activators of the p75 receptor can result in increases in cell death pathways. Together, these data could account for some of the cellular deficits in neurons and glia identified in specific brain areas in those with unipolar or bipolar affective disorder who have died by suicide, compared to non-psychiatrically ill controls who died by other causes. Brains of patients who died with bipolar illness show low BDNF and increases in cell death factors. (See on left.)

Evidence of increased apoptosis (cell death) in BP

Rao, working with Stanley Rapoport at the National Institute on Aging at the National Institutes of Health, reported that in the brains of patients with bipolar illness who died, there were significant decreases in protein and mRNA levels of the neuroprotective factors BDNF and Bcl-2, as well as synaptophysin and drebrin. At the same time, the researchers found increases in activators of cell death caspase 3 and 9, as well as levels of apoptotic cell-death factors BAD and BAX.

Neuroprotective effects of the mood stabilizers lithium and valproate

DeMaw Chuang of the NIMH, Abstr. 593, reported on glia (brain cells that, unlike neurons, do not conduct electrical activity) as a target of mood stabilizers.

In a rat model of cerebral ischemia (lack of oxygen due to loss of blood-flow), both lithium and valproate had robust neuroprotective effects. Lithium stimulated proliferation of astrocytes, glial cells that pull glutamate out of a synapse, and induced a neuroprotective factor called vascular endothelial growth factor (VEGF) in brain astrocytes.

Valproate treatments suppressed three processes that contribute to brain injury: ischemia-induced microglia activation, nitric oxide synthetase induction, and over-expression of the gene Cox2. In rat midbrain neuronal-glia co-cultures, valproate prevented microglial activation and protected dopamine neurons from multiple inflammatory insults. Valproate also acted directly on astrocytes to induce the neuroprotective factors glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) through the hyperacetylation of their DNA promoter sequences.

These changes could be intrinsic to bipolar disorder and related to excitotoxic and inflammatory markers associated with cognitive decline and brain atrophy. The changes may also be related to comorbid conditions such as obesity and diabetes that commonly occur with the illness.

Editor's Note: The investigators also thought that drug side effects were a possible cause of these changes, but this is unlikely since lithium, valproate, carbamazepine, some atypicals, and all antidepressants have been shown to increase BDNF.

Apoptosis-related gene irregularities in bipolar disorder

Catalina Lopez deLara reported that in the select group of bipolar patients who responded well to long-term lithium treatment, there was higher than expected presence of an apoptosis-related gene (Bcl-2L2) on chromosome 14q. These data are intriguing in relationship to other evidence that neuroprotective factors such as BDNF and Bcl-2, an antiapoptotic factor, are low in a subgroup of bipolar patients. This study now suggests that there is also upregulation of a cell death gene in lithium-responsive patients.

This adds one more factor to the multiple alterations that result in a lower ratio of neuroprotective to apoptotic factors in bipolar disorder. Since lithium increases levels of protective factors BDNF and Bcl-2 and decreases levels of cell death factors BAX and p53, it is possible that lithium is particularly effective in the subgroup of patients that have an upregulation of the cell death factor Bcl-2 L2, because lithium helps counter this abnormality.