

# Bipolar Network News

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## News from the 65th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry in May 2010

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### Ketamine Effective in ECT-Resistant Depression

In an abstract presented at the Society of Biological Psychiatry meeting in May, Lobna Ibrahim and Carlos Zarate of the National Institute of Mental Health reported that intravenous infusions of ketamine were **effective in a majority of patients with highly treatment-resistant depression**, i.e. even those who had been unresponsive to a course of electroconvulsive therapy.

*Editor's note:* Few treatments have been explored for this subgroup of highly treatment-resistant patients, although some have been referred for experimental protocols with intracranial deep brain stimulation (DBS) and others have been successfully treated by Mark George and colleagues at the Medical University of South Carolina with very high intensity rTMS over the left prefrontal cortex (at 130% of motor threshold, 10 Hz stimulation). Further study is needed to determine what follow-up procedures can be used to sustain an acute response to ketamine, rTMS, or ECT for the long term.

*Prudic, Sackeim and colleagues have reported that 40% of patients with a good response to three times a week ECT relapsed within a month of completing that course of treatment. This loss of effect occurred even when ECT was continued more intermittently, suggesting that other therapeutic options need to be developed for this rapidly relapsing subgroup.*

*Most of the data suggest that if patients fail to respond to a drug treatment regimen prior to ECT and then respond to ECT, a different or an increased intensity of the earlier drug regimen is required in order to sustain their response. Nonresponse to a drug treatment regimen prior to ECT predicts nonresponse to the same regimen following ECT. Since there are now numerous drugs for the primary and auxiliary treatment of depression, research should focus on determining optimal treatment algorithms for patients, both those who are responsive to ECT and those who are not.*

*Having a potential treatment such as intravenous ketamine that is rapidly effective*

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*for ECT nonresponders is a good start. However, at the present time it is not clear how the acute onset antidepressant effects of intravenous ketamine may be sustained for the long term. Since intravenous ketamine also exerts positive effects on acute suicidal ideation, it is likely that IV ketamine will develop into an emergency room procedure for patients in suicidal crisis.*

### MAO-I Moclobemide May Help with Depression and Post-Partum Blues

Monoamine oxidase inhibitors (MAO-Is) are a type of antidepressant that is often effective for people with anxious depression or comorbid panic attacks, especially when other antidepressants don't work. This may be because MAO-Is work on all three neurotransmitter systems implicated in depression: dopamine, norepinephrine, and serotonin.

In a recent study presented at the 65th Annual Scientific Convention of the Society of Biological Psychiatry, Julia Sacher et al. found that six weeks of therapeutic doses of the MAO-I

**moclobemide (at doses of 300 mg twice a day) significantly decreased monoamine oxidase A**, as measured by PET scans in brain regions implicated in mood disorders. In a comparison of moclobemide, placebo, and the herbal preparation St. John's Wort, only moclobemide had a significant effect.

There are various types of MAO-Is, and their different effects are currently being investigated. Moclobemide is an MAO-I that is selective for monoamine oxidase A, and it is currently only available in Canada. Two nonselective MAO-Is, tranylcypromine (Parnate)

and phenelzine (Nardil), are available in the US. A selective monoamine oxidase type B (MAO-B) inhibitor, selegiline, is FDA-approved for the treatment of depression as a patch. St. John's Wort is thought to inhibit monoamine oxidase type A in addition to its other potential antidepressant mechanisms.

*Editor's Note:* MAO-Is prevent monoamine oxidase from metabolizing norepinephrine, as it normally would, and the large amounts of norepinephrine that remain when one is

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## Valnoctamide Effective in Mania, Maybe Without Valproate's Side Effects

Valproate (Depakote), also known as divalproex sodium and valproic acid (VPA), is highly effective in the treatment of mania, seizures, and migraine. However, its use in pregnant mothers can cause birth defects and developmental delay. A closely related compound, valnoctamide, may not pose the same dangers, but its efficacy in mania has only recently been investigated.

Yuly Bersudsky et al. reported at the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders conference in Sao Paulo, Brazil in March that **valnoctamide was more effective than placebo as an add-on to risperidone for the treatment of mania.**

Since there is now evidence that valnoctamide does work in mania, it is plausible that some of the shared characteristics of valproate and valnoctamide, such as increasing brain GABA and blocking

sodium channels, are responsible for both drugs' antimanic effects.

VPA is thought to cause birth defects through its epigenetic effects. The emerging field of epigenetics has shown that environmental factors can influence the structure of DNA or tightness of its packaging, and these alterations may even be passed on to the next generation.

VPA has epigenetic effects because in addition to being an anticonvulsant, it is also a potent histone deacetylase inhibitor (HDAC-I). HDAC-Is make DNA easier to transcribe by keeping acetyl from detaching from histones.

Valnoctamide, on the other hand, is an anticonvulsant that does not get converted to VPA, and is not an HDAC-I. Valnoctamide's efficacy in mania suggests that VPA's epigenetic effects (as an HDAC-I) do not account for its anticonvulsant or antimanic efficacy. Moreover, valnoctamide

does not appear to be as teratogenic (causing birth defects) in animals as is VPA, and may ultimately be shown to be safer in pregnancy than VPA.

*Editor's Note: VPA is associated with increased risks of spina bifida and other major birth defects as well as major decreases in a child's IQ (9 points on average). Neurologists suggest that all women of childbearing age and potential who are treated with VPA should take folic acid, B6, and B12 regularly in case they have an unplanned pregnancy. It is hoped that these vitamins might help prevent birth defects, but this has not been proven.*

*In any event, women of child-bearing age who are taking VPA should use reliable birth control regimens to avoid becoming pregnant. This is especially the case as mania can be associated with poor judgment and sexual indiscretions, making unplanned pregnancies more common.*

### 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.

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## MAO-Is Help Depression and Post-Partum Blues

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*treated with an MAO-I can lead to high blood pressure and severe headaches.*

*The selective monoamine oxidase inhibitors moclobemide and selegiline have fewer cardiovascular side effects than the nonselective MAO-Is tranylcypromine and phenelzine. With the nonselective MAO-Is, it is important to avoid foods that have high levels of tyramine, such as aged cheeses, because tyramine can release norepinephrine.*

*The MAO-I tranylcypromine has often shown excellent antidepressant effects in bipolar depression, but moclobemide and the selegiline patch have not been widely studied in bipolar depression.*

### Brain MAO-A Linked to Post-Partum Depression

*The Sacher et al. study that moclobemide inhibits MAO-A in human brain takes on added importance when combined with another study by the same research group published in the Archives of General Psychiatry this year, which*

*found that women with post-partum blues have more monoamine oxidase type A in their brains 4 to 6 days following delivery than nonpregnant women do. Because post-partum blues are a risk factor for developing full-blown post-partum depression, these findings raise the possibility that treatment with monoamine oxidase inhibitors may be able to reduce the incidence of post-partum depression.*

*During the post-partum period, monoamine oxidase type A increases as a result of the drop in circulating estrogens that occurs at this time; estrogens normally suppress MAO-A. This increase in MAO-A leads to the more rapid metabolism of many neurotransmitter monoamines, reducing their levels in blood and brain, thus potentially propelling a subsequent depression. Given the findings of Sacher et al., that clinical treatment with usual doses of the selective monoamine oxidase A inhibitor moclobemide clearly inhibits human MAO-A in brain, drugs such as moclobemide and the selegiline patch deserve further investigation for potential treatment and/or prevention of post-partum depression.*

## N-acetylcysteine Affects Electrical Activity in Brain

At the 65th Annual Scientific Convention of the Society of Biological Psychiatry, researcher Christian Carmeli reported that N-acetylcysteine (NAC, 2 gm/day for six months) increased electroencephalogram (EEG) synchrony over the frontal cortical and left temporal regions in patients with schizophrenia. The EEG measures the frequency and amplitude of electrical activity on both sides of the brain.

*Editor's note: These data provide a neurophysiological mechanism that could explain the positive effects of NAC previously observed by researcher Mike Berk and associates in both schizophrenia and bipolar disorders and published in Biological Psychiatry in 2008. NAC is both a glutathione precursor providing antioxidant effects and a modulator of hyper-responsive glutamate reactivity in the n. accumbens or ventral striatum, the reward area of the brain. In placebo-controlled studies NAC appears effective in treating cocaine, heroin, and gambling addiction, as well as trichotillomania (compulsive hair-pulling). These effects are thought to be related to NAC's dampening of glutamate responses in the n. accumbens, which, along with the dorsal striatum, appears to mediate habit memory.*

*The EEG findings are also of interest in relationship to data presented at the conference by Jeremy W. Gawryluk that bipolar patients have decreased glutathione in their prefrontal cortex. This included both total levels and those of reduced and oxidized levels of glutathione. NAC, which is converted into glutathione, could help ameliorate these deficiencies. Whether the positive effects of NAC in bipolar disorder and schizophrenia are related to its antioxidant properties or to its dampening of cued glutamate hypersecretion in the n. accumbens remains to be further studied and clarified.*

## The Role of Calcium in Genetic Vulnerability, Pathophysiology, and Treatment Of BP Illness

One of the most consistent findings in biological psychiatry is that **levels of intracellular calcium in blood elements (platelets and white cells) are higher than normal in patients with mood disorders, particularly bipolar disorder.** These data are now supported by genome-wide association studies that have identified a relationship between alterations in a calcium channel and vulnerability to bipolar illness. The specific alteration is in the alpha-1C subunit of the L-type calcium channels, otherwise referred to as CACNA1C. These findings were initially reported by one group funded by the Wellcome Trust, a charitable organization that funds health research, in a series of studies that included thousands of patients and controls. Investigator Pamela Sklar later replicated these findings in another large independent sample.

At the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry, investigator Tyson Tragon reported that there were higher levels of CACNA1C in the cingulate cortex in autopsy specimens of those with bipolar illness than in controls. In a study of mice, some of which had the gene for the glutamate receptor subunit GLuR6 knocked out (i.e. production of the gene was artificially limited), the researchers found that the L-type dihydropyridine calcium channel blocker nimodipine decreased hyperactivity, amphetamine supersensitivity, risk-taking behavior, and aggression in those with the gene removed. The dihydropyridine-type drugs like nimodipine also decreased stress-related immobilization in the wild type (the animal with normal genes) but not the knockout animals (the ones lacking GLuR6). These data suggest that alterations in a subunit of the dihydropyridine-

responsive L-type calcium channel are a risk factor for bipolar illness, a brain abnormality in those who have the illness, and relevant to behavioral/pharmacological models.

**Several research groups have noted that treatment with the L-type calcium channel blocker nimodipine (Nimotop) can sometimes have positive effects in mania and depression in those poorly responsive to lithium carbonate.** This has been documented by Pazzaglia and Post in double blind off-on-off-on clinical trials (i.e. during off trials patients received placebo and during on trials patients received nimodipine, but the raters were unaware which pill the patient had received). In several instances, a positive response continued when the patient was switched from nimodipine to another dihydropyridine, isradipine (DynaCirc), but not when patients were switched to a different L-type calcium channel blocker, the phenylalkylamine verapamil (sold under the names Calan, Covera, Isoptin, and Verelan), which acts at a slightly different site on the channel.

*Editors Note: These data are reviewed in detail in the 2008 book by myself (Post) and Leverich, Treatment of Bipolar Disorder: A Casebook for Clinicians and Patients, published by WWNorton. Taken together, the findings make it likely that the calcium channel plays a role in the pathophysiology and treatment of bipolar disorder. Those with the CACNA1C gene are at risk for the development of bipolar disorder, patients with the illness have high levels of intracellular calcium in their blood elements and high levels of CACNA1C in the brain (through which too much calcium presumptively flows into cells), and a drug which blocks this type of*

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calcium influx, nimodipine, is an effective treatment for some patients with the illness.

## **Combination of Nimodipine and Lithium Is Superior to Lithium Alone and to Nimodipine Plus Valproate or Carbamazepine**

In line with these findings is a new study by Haroon R. Chaudhry et al. on nimodipine in bipolar disorder. This research group randomized a large group of bipolar subjects to: lithium alone, N= 49; lithium plus nimodipine, N= 55; valproate plus nimodipine, N=54; and carbamazepine plus nimodipine, N=52. They found evidence of a good response to all of these treatment options, but the combination of lithium and nimodipine was superior to the other treatments at the  $p < 0.05$  level, with a 73% response rate to this combination compared with 61% to nimodipine with valproate, 54% to nimodipine with carbamazepine, and 59% to lithium alone.

*Editor's note: These data are clinically important for several reasons. Combination treatment with lithium plus nimodipine has again been shown to be superior to lithium monotherapy, as was originally reported by Manna in a non-randomized study published in 1991. Manna found that **one year on the combination was superior to both one year of lithium alone and one year of nimodipine alone.** While combinations have generally been shown to be superior to monotherapy in a number of studies (as summarized in the last BNN), controlled studies to determine which combinations are preferable to others had not previously been carried out.*

*Pazzaglia and myself (Post) had reported that the combination of nimodipine plus carbamazepine was beneficial to a number of patients with treatment-refractory bipolar illness, and had postulated that the blockade of calcium influx through the L-type calcium channel may have been strengthened by carbamazepine's effects on calcium influx, including slowing calcium entry through the*

*glutamate NMDA receptor. While lithium and valproate also share this ability to slow calcium influx through the NMDA receptor, lithium has many other effects on intracellular calcium and other systems. What makes the combination of nimodipine and lithium superior to nimodipine in combination with either carbamazepine or valproate in Chaudhry's study is not yet clear.*

Nimodipine is a dihydropyridine L-type channel blocker and has an excellent side-effects profile that makes it better tolerated than lithium. For example, lithium can be associated with increases in tremor, gastrointestinal distress, weight gain, thyroid suppression, diabetes insipidus, and impairment in glomerular filtration (renal function, as indicated by slow increases

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***Nimodipine does not cause many of the side effects that typically occur on lithium.***

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in creatinine in a small subgroup of patients on very long-term lithium treatment). Nimodipine does not cause any of these side effects, and thus is a potentially useful adjunct to lithium, particularly for those who are unable to tolerate lithium doses that are sufficient to achieve a complete remission.

*Nimodipine is FDA-approved only for the treatment of subarachnoid hemorrhage and is inordinately expensive compared with the other dihydropyridines, which are used for the treatment of high blood pressure. Thus, one treatment suggestion is to optimize treatment with nimodipine, then see if the same response can be achieved with other agents of the dihydropyridine class, such as isradipine (DynaCirc) or amlodipine (Norvasc). Both nimodipine and isradipine have short half-lives and require dosing three times daily as opposed to amlodipine, which can be administered once a day. In the double-blind studies mentioned above, we saw*

*responsiveness to nimodipine cross to isradipine in some patients, while such cross-responsivity to amlodipine has not yet been demonstrated in systematic crossover trials in individual patients.*

## **The evolving ANK-3 gene story**

Another gene, ANK3, has also been found to be a vulnerability factor to bipolar illness in two large gene-wide association studies. Melanie P. Leussis reported at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry that in an animal model, when ANK3 was knocked-in partially (i.e. the gene production was increased artificially by molecular genetic techniques), the animal engaged in bipolar-like behaviors that could be partially reversed with lithium treatment. Together, the data with CACNA1C and ANK3 thus begin to suggest that some findings from the genome-wide association studies may be further supported by direct studies in patients with bipolar disorder and by animal models.

In the case of the CACNA1C gene, the convergent evidence that nimodipine treatment, which blocks the increase in calcium influx through the dihydropyridine-type calcium channel CACNA1C, is an effective treatment strengthens the evidence that the calcium channel plays a role in the etiology and treatment of bipolar disorder. The fact that CACNA1C is increased in the brains of patients in bipolar disorder compared to other patient groups and controls provides further direct evidence for a link between the calcium channel and bipolar illness.

However, it is now thought that multiple genes, each of small effect, contribute to the vulnerability to bipolar disorder, and it remains to be seen how powerful a relationship may exist between the CACNA1C gene and bipolar disorder, and whether those with the gene would be more specifically responsive to treatments such as nimodipine which act directly at this site.

## Lamotrigine for BP II depression: Not FDA-Approved, but Likely Effective

At the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March, Jae Seung Chang of South Korea reported that in a year-long naturalistic, open label study of long-term adjunctive lamotrigine therapy in 109 patients with bipolar II depression, **depression severity decreased when lamotrigine was added to patients' regular treatment with mood stabilizers.**

Interestingly, in addition to the data on lamotrigine, these investigators also found that having had a higher number of prior episodes was associated with a decreased response to lithium, a finding that has often been reported in the literature. Another finding was that a history that included a serious

suicide attempt was associated with a decreased lamotrigine response.

*Editor's Note: The data on lamotrigine recall related findings by Mark Frye and Gabriela Obrocea in a study (in which this editor also participated) at the National Institute of Mental Health. In a six-week double-blind triple-crossover study between lamotrigine, gabapentin, and placebo, lamotrigine was more effective than gabapentin or placebo in reducing depression, as measured by Clinical Global Impression (CGI) scale scores. In that study, a greater number of prior episodes was associated with decreased clinical responsiveness to lamotrigine.*

*Lamotrigine is only FDA-approved in bipolar I disorder for the prevention of depressed, manic and mixed episodes,*

*and while it has some efficacy in preventing mania and mixed states, it is not effective in the acute treatment of mania.*

*Given this efficacy profile, lamotrigine (while not FDA approved for BP II disorder) appears to be a useful treatment option for BP II illness, where depressions are the central problem and hypomanias are typically of lesser concern.*

*Lamotrigine's side effects are typically well tolerated. While the incidence of a severe rash in about 1 of 5,000 patients is a concern, very slow dose titration can prevent the emergence of this serious side effect, and lamotrigine does not cause weight gain, sexual dysfunction, or much sedation. This last is important since hypersomnia is a common presentation of BP II depression.*

## Nimodipine in the Treatment of Bipolar Disorder

H.R. Chaudhry, R.M. Khan, A. Shabbir, & K.A. Mufti

*Biological Psychiatry* 67 (9S), 2010, p. 232S, Abstract #806

Patients with Bipolar Disorder Randomly Assigned for 6 months to:

	I Lithium Alone (N=49)	II Nimodipine + Lithium (N=55)	III Nimodipine + Valproate (N=54)	IV Nimodipine + Carbamazepine (N=52)
<b>RESPONSE</b>				
Good	59%	<b>73%*</b>	61%	54%
Partial	31%	22%	28%	15%
Poor	11%	5%	11%	31%

\*Group II differed significantly from the other three groups ( $p < .05$ )

Nimodipine in Combination with Lithium is Most Effective in the Treatment of Bipolar Disorder

# Insights Into the Clinical and Neurobiological Risk Factors in Schizophrenia Versus Bipolar Disorders

Robin Murray gave a plenary presentation at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry this year, indicating that the genetic risk for schizophrenia and other major mental disorders may be overestimated. He indicated that even in identical twins there are considerable differences in incidence of major psychiatric illnesses, and sharing an environment could further inflate the appearance of genetic risk.

Evidence of some genetic vulnerability factors has been replicated, such as neuregulin, disbindin, DISC-1, zinc finger transcription factors, and neurexin. However, these genes appear to contribute only about 1% of the vulnerability to schizophrenia or bipolar illness. Copy number variations (CNVs, extra or missing copies of a gene, which may alter its activity) and gene micro deletions (in which small bits of DNA are missing) have been found in about 5% of patients with schizophrenia, in some patients with autism and mental handicaps, but not in those with bipolar illness.

Murray emphasized the importance of psychosocial and neuromotor markers of neural development in determining risk of subsequent major psychiatric illness, rather than the relatively weak genetic effects. He cited the work of MacCabe (2009), who collected information from 907,000 individuals in Sweden. Their scholastic achievement at age 15–16 was rated, and hospitalizations for psychosis were recorded from age 17–31. Of the 315,000 followed in the long term, 493 developed schizophrenia and 208 developed bipolar disorder.

Predictors of cognitive and motor development in these two major psychiatric illnesses appeared to differ. In those who went on to develop schizophrenia, there was a slower rate of motor development, receptive

language, and overall IQ in adolescence, while in those who went on to develop bipolar disorder, there was a faster rate of motor development, more language facility, and higher IQ in adolescence.

The IQ risk was notable. People who fell within the two standard deviations below the mean had almost 4-fold higher rates of schizophrenia, while those who scored higher than two standard deviations above the mean were at decreased risk. In contrast, those with IQs two standard deviations

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*Those who went on to develop schizophrenia had a slower rate of motor and language development and lower IQ in adolescence, while those who went on to develop bipolar disorder had a faster rate of motor development, more language facility, and higher IQ in adolescence.*

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above the mean were at 3-fold increased risk for bipolar disorder, with a smaller subgroup showing mildly increased risk with lower IQs as well.

These data are partially consistent with observations of increased obstetrical complications in schizophrenia, including neonatal insults to the brain (during delivery) resulting in brain damage, small growth, and a 7-fold increased incidence of neonatal hypoxia (low blood oxygen concentration). In contrast there is generally little evidence for an

increase in obstetrical complications in bipolar illness. Instead, being highly creative and an exceptional, enthusiastic student appears associated with a slightly increased risk for bipolar illness. Other risk factors for schizophrenia included: living in a bigger city, experiencing childhood abuse and neglect, social isolation, adverse life events (of the intrusive variety, such as being in a car accident, and not of the loss variety, such as losing a job or significant other, which are more associated with bipolar illness).

*Editor's Note: We have postulated that the increased intelligence and creativity seen in those with bipolar disorder (or at risk for it) could be related to the findings that a common variant in the gene for brain-derived neurotrophic factor (BDNF) that functions more efficiently (val 66 val proBDNF) is a risk factor for bipolar disorder. The poorer functioning allele (val 66 met proBDNF) is a risk factor for mild cognitive dysfunction in both patients with bipolar disorder and schizophrenia, as well as in normal volunteer controls.*

Murray formulated the hypothesis that environmental events could alter the dopamine system, which has been closely linked to psychosis and its treatment with dopamine antagonists (antipsychotics). He cited data indicating that dopamine synthesis, as measured by PET scan, was increased in those with prodromal psychosis. Since dopamine is associated with reward learning and the salience of ideas and objects, he reasoned that increases in dopamine could account for delusions, because the increases in dopamine might involve assigning salience to unimportant stimuli.

Murray noted that pre-term hypoxia leads to a 50% increase in the size of the ventricles and a decrease in

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## Schizophrenia and Bipolar Disorder

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hippocampal volume, and other investigators have shown that ventral/hippocampal lesions lead to sensitization of the dopamine systems. Tony Grace has postulated that decreased hippocampal excitatory output reverses the break on dopamine release in the n. accumbens, and increases dopamine and cell firing in the midbrain ventral tegmental dopamine neurons that synapse in the n. accumbens.

Such a model may also have relevance for the pathophysiology of bipolar disorder. Those experiencing a first psychotic episode have higher than normal levels of cortisol in their blood, and increased cortisol is associated with decreased hippocampal volume.

*Editor's note: These findings may intersect with data that show that BDNF appears decreased in the hippocampus of patients with depression, rodents subjected to defeat stress, and cocaine-sensitized animals. Increases in BDNF have been noted in the n. accumbens of depressed patients who died via suicide compared with controls (Krishnan et al. 2008). Moreover, increases in BDNF in the n. accumbens are also seen in animals experiencing defeat stress-induced depressive-like behaviors, and in cocaine sensitization paradigms.*

*Thus, deficient hippocampal function as marked by decreased volume in those with schizophrenia, or decreased hippocampal BDNF in those with mood disorders, could be associated with disinhibition of firing of dopamine neurons in the ventral/tegmental area and increased release of dopamine in that area of the brain along with increases in BDNF as well. This BDNF formulation is also consistent with the environmental vulnerabilities Murray describes acting to alter dopamine functioning in the psychoses. Environmental stressors and exposure to abused substances could cause hippocampal volumetric and functional deficits in concert with n. accumbens hyperactivity.*

## Early Life Stressors Linked to Persistent Inflammation and Endocrine Abnormalities

Epigenetics is a relatively new area of study that examines changes in DNA regulation and structure that can come about as a result of environmental events, as opposed to the genetic inheritance (DNA sequence) people receive through their parents' genes. Epigenetic effects occur when an environmental stressor or chemical causes methyl or acetyl groups to attach to DNA or to histones (around which DNA are wound). These epigenetic changes determine how difficult it is to turn on genes coded in the DNA (see *BNN Vol. 14, Issue 2* from 2010 for more information about the way the environment produces these epigenetic effects).

Several studies presented at the 65th Annual Scientific Convention of the Society of Biological Psychiatry earlier this year suggested a link between environmental stress and both inflammation and abnormalities in DNA.

Researcher Alicia K. Smith of Emory University reported that in a population of African American patients, **a history of total life stressors was associated with increases in inflammatory cytokines interleukin 2, interleukin 6, and TNF-alpha.** In addition, there was evidence of increased DNA methylation in almost a fifth of 27,578 specific binding sites in the participants with more stress.

**A history of trauma in patients experiencing a first episode of psychosis was associated with significant increases in the inflammatory markers c-reactive protein (CRP), interleukin 6, and TNF-alpha,** reported Valeria Mondelli of King's College London.

**A history of childhood maltreatment was associated with evidence of inflammation in adults with major depressive disorder,** according to a study presented by Sara Zeugmann of the University of Medicine in Berlin. Neglect was associated with increases in the proteins fibrinogen and resistin,

sexual abuse with increases in the protein adiponectin, and physical abuse with increases in TNF-alpha.

**A history of childhood physical abuse was associated with decreases in cortisol response to stress in adulthood** among healthy women, reported Linda L. Carpenter of Brown University.

A history of neglect was associated with lower levels of CSF  $\beta$ -endorphin and met-enkephalin in a study presented by Barbara Stanley of Columbia University. These lower levels were also found among study participants who engaged in repetitive self-injury in adulthood.

Victoria Arango of Columbia University reported that in the brains of suicide victims who had undergone childhood adversity compared with those without such a history, there was evidence of decreased cell replication in the dentate gyrus, a part of the brain that plays a critical role in learning and memory.

*Editor's note: These data from studies of people converge with data from animal studies that show that early life adversity is associated with reductions in BDNF and neurogenesis and increases in markers of inflammation. Taken together, these abstracts form an increasingly strong story indicating that a history of early life adversity can have long-lasting neurobiological consequences including inflammation and changes in brain chemistry that can affect the health and behavior of animals and humans throughout their lifetime.*

*This evidence may shed light on an earlier research question. The data of Banks et al. (published in the Journal of the American Medical Association in 2006) indicated that white males aged 55 to 65 in the British Isles were healthier than their well-matched counterparts in the US. The greater abnormalities in those from the US included a variety of measures, such as*

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## New Developments in Repeated Transcranial Magnetic Stimulation (rTMS)

At the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry, several findings related to repeated transcranial magnetic stimulation (rTMS) were reported.

E. Baron Short reported that two weeks of 10 Hz rTMS at 120% of motor threshold (MT) was highly effective in the treatment of fibromyalgia. Pain ratings decreased 45% by day six and 80% by day 10 in this randomized sham-controlled double-blind study.

Also at the convention, Motoaki Nakamura reported that either **1 Hz or 20 Hz rTMS at 90-100% of motor threshold over left prefrontal cortex in depressed patients increased gray matter** in left dorsolateral prefrontal cortex and left hippocampus in association with almost 50% reductions in Hamilton depression rating scale scores and associated increases in performance on the Wisconsin card sort test.

*Editor's note: These data are of particular interest in light of increasing evidence for prefrontal and hippocampal neurochemical and volumetric deficits*

*in major depression and other evidence that rTMS may be capable of increasing neurotrophic and neuroprotective factors. This is the first clinical evidence suggesting that rTMS may have direct effects on brain volume as well. These data would converge with other data indicating that long-term antidepressant therapy can prevent hippocampal atrophy and short-term lithium can increase gray matter and hippocampal volume.*

*The first large multi-center study of rTMS, which was sponsored by industry, gained FDA approval for the apparatus. As reported in previous BNNs, Mark George and collaborators conducted a second large multi-center study sponsored by the National Institute of Mental Health (NIMH), which indicated that rTMS can produce significantly greater rates of remission than those achieved by sham rTMS, as reported in the Archives of General Psychiatry this year. Hopefully, these new efficacy data by George and colleagues will increase the ease of receiving insurance reimbursement for the expensive procedures of a full course of rTMS*

*for the treatment of an acute depression that has been unresponsive to at least one prior clinical trial of an antidepressant.*

*The data of Nakamura et al. noted above are also of interest in relationship to data from a study in which this editor participated (Speer et al., 2010), which indicated that both 1 Hz and 20 Hz stimulation were more effective than sham rTMS in improving the condition of patients with highly treatment-refractory depression. Moreover, in that study, we observed that 1 Hz rTMS at 110% of a patient's motor threshold decreased brain activity as measured with cerebral blood flow on PET scan, while 20 Hz markedly increased brain activity in a widespread fashion that remained for at least 48 hours following the last of 15 rTMS sessions spread over a period of three weeks. The Nakamura data indicating that both 1 and 20 Hz increase indices of gray matter in left dorsolateral and left hippocampus suggests that this neurotrophic effect may, in fact, occur at both high and low frequency rTMS, even though they produce opposite effects on brain activity.*

## RTMS for Adolescent Depression

In an abstract presented at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry, Christopher Wall reported that treatment with rTMS (10 Hz at 120% of motor threshold) was successful in the treatment of adolescent depression.

These data from an open (as opposed to blind) study deserve further and more systematic investigation. Alternatives to antidepressant drug treatment are desirable for adolescents with depression since increases in suicidal ideation are a potential side effect during the first two months after initiation of pharmacological antidepressant treatment in teens.

(Suicidal ideation and actions among adolescents decrease with longer-term antidepressant treatment, especially when it is used in conjunction with cognitive/behavioral psychotherapy.) Children and adolescents treated with antidepressants may also be at higher risk for switching into mania than adults treated with antidepressants.

*Editor's Note: The rTMS parameters used in this study are the same as those used successfully in adults with depression in the two large positive multi-center sham-controlled studies (one by industry and one by the National Institute of Mental Health) mentioned in the article above.*

## Early Life Stressors Linked to Endocrine Abnormalities and Inflammation

*Continued from Page 7*

*increases in blood pressure, hemoglobin A1C (a marker of diabetes and insulin resistance), cholesterol, and triglycerides. Banks and collaborators did not know the reasons for such findings, but they suggested the possibility of greater exposure to stressful life experiences in the US compared with the British Isles. The new data about the link between early life stressors and later inflammatory processes makes such an explanation at least plausible.*

*These data also indicate that individuals who never receive a formal diagnosis of post-traumatic stress disorder (PTSD) can still have long-lasting neurobiological consequences from adverse environmental experiences they have experienced.*

## Brain Volume Reduced As Early As First Episode Of Mania

Researchers Manpreet K. Singh and Kiki D. Chang et al. from Stanford reported at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry that adolescents experiencing a first episode of mania show reduced volume in the subgenual anterior cingulate cortex (Brodmann area 25). Previous studies have indicated that teens and adults with bipolar disorder exhibit decreased volume in prefrontal gray matter.

*Editor's note: The new data suggest that some deficits in volume may occur very early in the course of bipolar illness, and thus indirectly support the potential use of treatments that can increase gray matter volume, such as lithium and potentially rTMS.*

Lithium has repeatedly shown consistent positive effects on brain measurements in humans. Lithium and the other mood stabilizers carbamazepine, valproate, and lamotrigine, in addition to the atypical quetiapine, all increase BDNF (brain-derived neurotrophic factor), which may be responsible for preventing gray matter loss. Lithium also increases: neurogenesis; N-acetylaspartate (NAA), a measure of neuronal integrity; grey matter volume in several cortical areas in patients with bipolar disorder (but not controls); and hippocampal volume; and lithium decreases cell death factors BAX and p53.

## Increased Uric Acid In Mania and Increased Risk of Gout in Bipolar Patients

At the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry this year, Giacomo Salvatore reported that significantly higher levels of uric acid are found in patients with mania compared with normal controls.

*Editor's note: This study was particularly interesting because there was a highly significant difference between patients and controls, with very few values overlapping. The data suggest the possibility that uric acid may be a useful biological marker for mania, and is one that should be studied in childhood-onset bipolar illness to determine whether uric acid is a marker for mania in children as well.*

*Allopurinol, a widely used treatment for gout that reduces levels of uric acid in the blood, is an effective antimanic agent (based on data from two placebo-controlled studies, one by Machado-Vieira et al. and one by Akhondzadeh et al.). The new data on uric acid raise the possibility that high levels of uric acid may be a specific predictor of responsiveness to Allopurinol, although this hypothesis has not yet been explored.*

*In an article by Chung et al. just published in Psychiatry Research, it was reported that in a very large epidemiological study in Taiwan, patients with bipolar disorder have increased risk of gout.*

## Oxytocin, the Social Affiliation Drug, Has Interesting Effects in Autism and Now Schizophrenia

In 2007, investigator E. Hollander from Mt. Sinai published data indicating that intranasal oxytocin was associated with increases in target behaviors in patients with autism.

Now a study by David Feifel of the University of California, San Diego presented at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry showed that patients with schizophrenia showed improvement in symptomatology and increases in the recognition of positive facial affect after oxytocin was added to their antipsychotics regimen. Morris Goldman of Northwestern University reported that patients with schizophrenia, who often make mistakes assessing fear on facial emotion recognition tests, described fewer faces as fearful after receiving intranasal oxytocin.

*Editors note: These new findings are built on the pioneering preclinical work of Tom Insel. He found marked differences in oxytocin and its receptors in the brains of mountain voles (who are largely asocial) compared to prairie voles (who are highly social and form lifelong bonds with their mates). Although these oxytocin findings have not yet produced a treatment for any psychiatric syndrome, they illustrate the potential of general scientific findings to inform new approaches to human illnesses.*

## Children with ADHD and Oppositional Symptoms Respond to Guanfacine

Researcher Daniel Connor reported at the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry that children aged 6-12 with oppositional symptomatology and attention-deficit/hyperactivity disorder (ADHD) improved on guanfacine XR. Doses ranged from

1 to 4 mg/day, with a mean dose of 2.9 mg/day. There was a substantial decrease in oppositionality (a finding with a moderate effect size of 0.59) and a marked decrease in ADHD symptomatology (a finding with a large effect size of 0.92). Side effects included drowsiness (in 51% of

subjects), headache (22%), sedation (13%), abdominal pain (12%) and fatigue (11%). Guanfacine is not a psychomotor stimulant, like most of the treatments for ADHD are, but an agonist (activator) of norenergic  $\alpha_2$  receptors in the brain.

## Deep Brain Stimulation Parameters Investigated

In the 1990s, the pioneering studies of Helen Mayberg and colleagues showed that stimulation of an area in the ventral part of the prefrontal cortex called the subgenual anterior cingulate gyrus (or Brodmann area 25, the part of the brain under the anterior corpus callosum) is associated with improvement in depression that resisted almost all other treatments. At the 65<sup>th</sup> Annual Scientific Convention of the Society of Biological Psychiatry this year, a number of research groups reported following up on Mayberg's studies. The latest positive data on stimulation of Brodmann area 25 for treatment-resistant depression mirror new findings from other research groups who have stimulated the dopaminergic reward area of brain called the nucleus accumbens or ventral striatum with successful results.

In one of the first systematic studies intended to identify the best frequency and pulse width duration parameters for this type of intracranial stimulation in patients with treatment-resistant depression, researcher Swati Chavda of the University of Calgary reported that patients with depression improved when they were stimulated at 130 Hz (cycles/sec.) with a pulse width of 90 micro-seconds. In this double-blind study, depression neither improved nor worsened under other conditions, such as when the stimulation was turned off, when a low frequency (20 Hz) was used, or when much higher frequencies (185 Hz) with a pulse width of 420 micro-seconds were used.

*Editor's note: These data indicate that the positive effects of deep brain stimulation on clinical depression may depend on the frequencies used, with more intermediate stimulation parameters better than very high or very low ones. More clinical exploration is required in order to define optimal stimulation parameters for different brain regions. For the moment, this type of deep brain stimulation remains highly experimental, but is being pursued by a number of investigative groups in the US and Europe.*

## Anti-Alzheimers's Drug Memantine (Namenda) May Augment the Antidepressant Effects of Lamotrigine

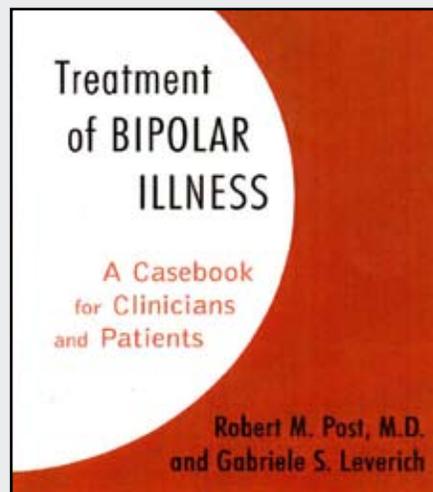
At the 65th Annual Scientific Convention of the Society of Biological Psychiatry in May, Amit Anand reported that the anti-Alzheimer's drug memantine (20 mg/day) was superior to placebo in augmenting the acute antidepressant effects of lamotrigine. These data are of particular interest since one of the assumed mechanisms of action of lamotrigine is to decrease the release of glutamate.

Memantine is a drug approved for the treatment of Alzheimer's disease and is a partial antagonist (blocker) of glutamate NMDA receptors. This suggests that the dual actions of inhibiting glutamate's release pre-synaptically (with lamotrigine) and blocking glutamate receptor activity post-synaptically (with memantine) combine to produce a better effect than that of lamotrigine alone.

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# Track Your Moods with Life Charting

If you have unipolar depression or bipolar disorder and are having trouble stabilizing your mood, we recommend nightly charting of mood, medications and side effects on the easy-to-use Monthly Mood Chart Personal Calendar (pictured below) or the National Institute of Mental Health Life Chart (NIMH-LCM), both of which are found on our website.

Visit us at <http://bipolarnews.org> and click on the Life Charts tab to download the personal calendar, which includes space for rating mood, functioning, hours of sleep, life events, side effects, and other symptoms such as anxiety. Then bring the chart to each visit with your physician to help in the assessment of treatments. Life charting can help determine which medications

are working partially and need to be augmented further, and which need to be eliminated because of side effects. Since there are now many potential treatments for depression and bipolar disorder (some FDA-approved and some not), a careful assessment of how well each new treatment works for a particular patient is essential to finding the optimal treatment regimen.

			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31				
<b>MEDICATION NAME</b>			<b>TOTAL NUMBER OF TABLETS TAKEN PER DAY</b>																																		
LITHIUM	300	mg	3	3	3	3	3	3	3	3	2	2	3	3	2	2	3	3	3	4	4	3	3	3	2	3	3	3	3	3	3	3	3	3	3		
DEPAKOTE	500	mg																																			
NORTRIPTYLINE	25	mg	3	3	3	3	3	4	4	4	4	4	4	4	4	4	3	0	0	0	0	0	0	0	0	0	0	0	2	2	3	3	3	3			
SYNTHROID	0.1	mg	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1			
LORAZEPAM	0.5	mg																																			
			<b>↑ SAMPLE PAGES ↓</b>																																		
<b>RECORD HOURS OF NIGHTTIME SLEEP</b>			7	7	7	6	6	7	8	10	9	6	7	7	6	5	4	4	2	1	0	0	1	2	3	6	7	7	7	8	8	6	6				
<b>M A N I A</b>	<b>DYSPHORIC MANIA</b> (✓)IF YES																																				
	<b>SEVERE</b> Essentially incapacitated or HOSPITALIZED																																				
	<b>HIGH MODERATE</b> GREAT difficulty with goal-oriented activity																																				
	<b>LOW MODERATE</b> SOME difficulty with goal-oriented activity																																				
	<b>MILD</b> More energized & productive with little or no functional impairment																																				
<b>D E P R E S S I O N</b>	<b>STABLE</b>																																				
	<b>MILD</b> Little or no functional impairment																																				
	<b>LOW MODERATE</b> Functioning with SOME effort																																				
	<b>HIGH MODERATE</b> Functioning with GREAT effort																																				
	<b>SEVERE</b> Essentially incapacitated or HOSPITALIZED																																				
<b>MOOD (0-100)</b> 0=Most depressed ever, 100=Most manic (activated) ever			49	50	50	40	40	38	36	34	30	30	30	45	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50		
<b>NUMBER OF MOOD SWITCHES / DAY</b>																																					
<b>MENSTRUAL PERIOD</b> (✓)IF YES																																					

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