

# Bipolar Network News

Published since 1995

The latest news on bipolar disorder research from around the world

<http://bipolarnews.org>

## News from the 4th Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March, 2010

Vol. 14, Issue 4, 2010

### More Early Onsets and Difficult Courses of Bipolar Illness Occur in the US than in the Netherlands And Germany

This editor was invited to give a plenary presentation at the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March. The talk, titled "A greater incidence of early onset bipolar illness and poor prognosis factors in patients in the US compared with those in The Netherlands and Germany," was based on studies in our Bipolar Collaborative Network.

We found that patients who were studied and treated at the four sites in the US (Los Angeles, Dallas, Cincinnati, and Bethesda) had more poor-prognosis factors and indices of difficult courses of bipolar illness compared with patients studied in the same fashion at the three sites in Utrecht, Netherlands and Freiberg and Munich, Germany. We presented some of these data in a preliminary report in the *British Journal of Psychiatry* in 2008 and further analyzed these data for an article just published in the *Journal of Clinical Psychiatry*.

Compared with the patients in Europe, patients from the US sites had a significantly increased incidence of early onset bipolar disorder, positive family history of unipolar or bipolar affective illness in first-degree relatives, psychosocial adversity, anxiety and substance abuse comorbidities, more than 20 prior episodes, and rapid cycling (four or more episodes) in the year prior to Network entry. Most of these factors are associated with a more difficult course of illness. In addition to these self-reported assessments of the

prior course of illness, we also found that fewer patients from the US entered the Network in a well state (and maintained that well state for six months), and more patients from the US who entered the Network ill were nonresponders to naturalistic treatment.

The geographical differences in outcomes appeared despite use of approximately equal numbers of medications, although there were some qualitative differences in medication use noted on the two continents. Patients in Europe were administered more lithium and typical antipsychotics as well as benzodiazepines, while those in the US were treated more often with valproate, atypical antipsychotics, and unimodal antidepressants. Aside from differences in prescribing practices, patients treated in Europe with lithium or the atypical antipsychotics had significantly more positive long-term outcomes than those treated with these same drugs in the US, and there were nonsignificant trends in the same direction for many other drugs.

#### Assortative mating

When we examined the incidence of a positive family history of affective illness in the parents of the patients in the Network, among US patients there was a greater incidence not only of one parent having bipolar disorder, but also of both parents having an affective disorder. This latter effect is referred to as assortative mating, because it suggests that patients with unipolar and bipolar illness select partners

#### Also in this issue:

More Treatment Studies Needed for Children	p. 2-3
Treatment Options for Children and Teens	p. 4-5
Inflammation and Oxidative Stress in Bipolar Disorders	p. 6-8
Long-term Prevention of Mood Disorders	p. 9
Smoking Risky for Patients with Bipolar Disorder	p. 10
Thyroid Treatment	p. 11

who also have mood disorders or are vulnerable to developing them.

It is not clear why there is an increased positive parental history of disorder in the US compared with Europe and an increased incidence of assortative mating, but these genetic and familial risk factors could be associated not only with the earlier onset of illness in the US, but also with the more pernicious course of bipolar illness in the US. Ascertaining the mechanisms that lead to the more adverse illness course and outcome in the US might shed light on clinical and public health measures that could make the illness more benign. While it appears difficult to do much about the earlier age of onset of illness in the US at present, the delay to first treatment appears to be a risk factor that could be reduced with greater attention to the public health consequences.

*Continued on Page 5*

## Kids Fail to Receive Necessary Treatment, More Treatment Studies Needed

The abstract of an article by Geller et al. we reprinted on page 3 illustrates the crisis in the treatment of childhood-onset bipolar illness in the US. It is unfortunate when children fail to receive appropriate treatment because of ambiguity about a diagnosis, but it is even more frustrating when one of the world's experts makes a diagnosis, and a child still fails to receive treatment based on consensus guidelines.

The article indicates that **almost 40% of the children with a credible diagnosis of bipolar disorder in this study never received anything near the appropriate treatment for their illness.** Over 8 years of follow-up treatment in their communities, these very ill children not only did not receive helpful drugs such as atypical antipsychotics or mood stabilizers, but they often received treatments that can be counterproductive, such as

antidepressants or psychomotor stimulants. Those children who did receive appropriate treatment with lithium fared better and recovered significantly earlier than the others.

A variety of factors complicate early identification of bipolar illness and adequate treatment intervention. The diagnosis continues to be controversial, and the press often suggests that physicians and pharmaceutical companies conspire to inflate diagnoses for monetary gain. Treating children with bipolar disorder is difficult, often requiring long periods of time and several medications used in combination to achieve even short-term remissions, and relapses are common. At the same time, many physicians are leery of treating young children with major psychotropic agents, some of which have substantial side effects. Most importantly, there are not enough treatment-related studies to guide clinical decision-making.

There are some consensus treatment guidelines written for children of ten years of age or older with Bipolar I illness, including positive placebo-controlled data on all of the newer atypical antipsychotics. This class of drugs in addition to mood stabilizers are recommended first treatments. However, subsequent treatment options and those for different subtypes and comorbidities of bipolar disorder in children remain virtually unstudied. In addition, there are still no FDA-approved treatments for children with bipolar illness under age ten, despite the growing recognition that the illness appears in substantial numbers of children before puberty and in the earliest years of life.

These deficits in diagnoses and clinical treatment are an urgent public health problem, particularly in the U.S. where there has been a recent marked increase in the diagnosis in children. While some have argued that the illness is over-diagnosed in

the U.S., even children who may not ultimately meet formal diagnostic criteria for bipolar illness are nonetheless adversely impacted by their "bipolar-like" illness, so these variants deserve systematic study and assessment of adequate treatment approaches as well.

The figures are actually even worse than the abstract suggests. The treatment deficiencies noted by Geller et al. were found among patients who were carefully evaluated and diagnosed in a research setting and then treated in the community. The majority of children with bipolar illness lack access to this kind of careful evaluation. In the research network in which I participated for many years, **22% of US adults had childhood onsets of their illness (prior to age 13), and these individuals were not treated with any medications for their depressions or manias for an average of more than 15 years.** The length of the delay to first treatment in childhood and adolescence was directly correlated with prospective clinician-rated measures of a poor outcome in adulthood. The longer the treatment delay, the greater the severity and duration of depression in adulthood, the fewer the days of euthymia, and the greater the number of mood episodes and days of ultradian cycling (switching within a 24 hour period).

These long delays to first treatment are ruining the lives of children, adolescents, and adults, and devastating families. Investigators in the field have called for further research in scores of articles over the past decade, but unfortunately, this has not been enough to bring attention to this issue and cause a shift in funding priorities for research. Therefore, we must publicize this issue in every conceivable realm, by calling attention to it in the media, by writing campaigns to senators and congresspeople, and by searching for private funding.

This treatment research gap could readily be fixed. It is not necessary for

### Bipolar Network News

**Editor-in-Chief:** Robert M. Post, MD  
**Managing Editor:** Moira McCauley

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.

As per recent journal disclosure requirements, Dr. Post has consulted to or spoken for Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

The opinions expressed in the BNN are solely those of the editors, and do not represent the views of any scientific entity or foundation.

Send any comments or suggestions to:

**BNN**  
5415 W. Cedar Lane  
Suite 201B  
Bethesda, MD 20814

To subscribe:  
Please email us at

**info@bipolarnews.org.**

Note that we do not accept requests to subscribe friends or family members. Please have them contact us directly.

**Website:** <http://bipolarnews.org>

**Emails about content :** [mccauleybcn@gmail.com](mailto:mccauleybcn@gmail.com)

novel treatments to be invented. The many treatments that we already know are effective in adults with bipolar disorder should be studied more systematically for their effectiveness and tolerability in children across the spectrum of bipolar disorders ranging from Bipolar I, II, and NOS to potentially nonbipolar illnesses such as severe mood dysregulation (SMD).

During the 35 years I worked for the National Institute of Mental Health (NIMH) and my tenure as chief of the Biological Psychiatry Branch, any editorial piece like this one had to include the statement that “the views expressed here do not necessarily reflect those of the NIMH.” Because I retired from the NIMH 4 years ago after publishing close to 900 scientific manuscripts, I am no longer required to add this disclaimer. However, the views expressed here about the disastrous underfunding of research in bipolar illness, which are shared by many of my colleagues (who are not as free to comment as I am because they depend on the NIMH for funding support), do not seem to be those of the NIMH—but they should be.

The NIMH is by far the largest funding agency for research in psychiatric illness. Grants are highly competitive, and because bipolar disorder in children and adults is such a complicated illness, the needed treatment-related studies almost never get a high enough priority score to be funded. Without money set aside for treatment studies in bipolar disorder specifically, the neglect of this illness will continue indefinitely. (For example, a search of articles dating from 1980 to the present at PubMed.gov found eight times more articles on schizophrenia than on bipolar disorder, even though more than three times more people have bipolar disorder than schizophrenia).

**Hundreds of thousands of children in the US will continue to get suboptimal care until new treatment-related studies are funded to better guide the**

### **Pharmacological and non-drug treatment of child bipolar I disorder during prospective eight-year follow-up.**

Geller B, Tillman R, Bolhofner K, Zimmerman B. *Bipolar Disorders*, 2010 Mar; 12(2): 164-71.

Department of Psychiatry, Washington University in St. Louis, St. Louis, MO 63110-1093, USA. gellerb@wustl.edu

#### **ABSTRACT**

**OBJECTIVES:** The Phenomenology and Course of Pediatric Bipolar Disorders study, a National Institute of Mental Health-funded study of child bipolar I disorder (BP-I) begun in 1995, is a prospective follow-up study that included collecting pharmacological and non-drug treatment data.

**METHODS:** There were 115 first-episode subjects who fit full DSM-IV criteria for BP-I, mixed or manic phase, with severity scores in the clinically impaired range, ascertained by consecutive new case ascertainment. Subjects were assessed with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASHU-KSADS), given separately to parents about their children and to children about themselves. All treatment was provided by the subjects' own community practitioners, exactly as if they had not been in the research study. Thus, families were only seen for research assessments, and research staff were not at all involved in their treatment. Data

on type, dose, and duration of pharmacological and non-drug treatment were collected. During follow-up, 93.9% (n = 108) were assessed at each of the nine assessment times.

**RESULTS:** During the eight years, only 62.6% received any antimanic medication (antipsychotic, anticonvulsant, lithium) at any time. Percents who received non-antimanic medication included 77.4% medication for attention-deficit hyperactivity disorder and 64.3% antidepressants. A total of 67.8% of subjects were taking two or more concurrent medication classes. Subjects ascertained from psychiatric versus pediatric sites received antimanics significantly more frequently (p = 0.006). Earlier recovery during eight-year follow-up was predicted by greater percent of weeks on lithium (p = 0.017).

**CONCLUSIONS:** Given these findings, and the poor prognosis from prospective follow-up of this sample reported elsewhere, **there is a need for further research that informs the development of effective treatment strategies.**

**clinical therapeutics of childhood onset bipolar disorder.** There is one thing upon which everyone knowledgeable about the illness agrees; the children who have various bipolar disorders are very ill, and their parents are desperate for information about the best treatment approaches. Is it not about time we did something about this?

For more information about the harm caused by the lack of treatment studies in childhood onset bipolar disorder, see “The healthcare crisis

of childhood-onset bipolar illness: some recommendations for its amelioration” by Post and Kowatch in the *Journal of Clinical Psychiatry*, Volume 67, Issue 1 from 2006, and “The perfect storm of childhood onset bipolar illness” by Post in *Psychiatric Annals*, Volume 39, Issue 10 in 2009.

**Have you visited the BNN online?  
<http://bipolarnews.org>**

# Treatment Guidelines for Two Hypothetical Cases in Children

On page 2, we report that there are no FDA-approved treatments for children under age 10 with bipolar disorder. For an article in *Psychiatric Annals*, this editor and Janet Wozniak asked experts how they would sequence treatment of a hypothetical case of a 6-year-old with extreme mood instability consistent with a diagnosis of BP -NOS (see Table I). We also asked how the experts would treat a different case

of a 9-year-old with a full-blown psychotic BP-I mania (see Table II).

The results are presented and discussed in detail in the article by Post and Wozniak in *Psychiatric Annals*, 2009; 39 (10): 879-886, and are presented here to reinforce several points. The recommendations for children under 10 and for BP NOS are highly similar to those in published consensus guidelines by Kowatch et al. for

old BP I children. Treatments in face of non-response to option A or others are sequenced differently by different experts, but almost always involve an atypical antipsychotic (AA) or a mood stabilizer (MS) such as lithium, valproate, carbamazepine/oxcarbazepine, or rarely, lamotrigine. Revisions of atypical antipsychotics and mood stabilizers and use of combinations are the common next strategies.

## 6-year-old with BP NOS

TABLE 1.

**Drug Treatments Endorsed for Case 1 (presumptive BP-NOS) with Sequential Options (B to D) in the Face of Inadequate Response**

Respondent #	Option A	Option B	Option C	Option D
1	Aripiprazole	Risperidone	Quetiapine	Lamotrigine (augment) or risperidone (augment)
2	Aripiprazole	Ziprasidone	Valproate (augment)	Quetiapine alone
3	Divalproex	Lithium	Aripiprazole	Risperidone
4	Lithium	Aripiprazole (augment)	Risperidone	Quetiapine
5	Methylphenidate	Quetiapine (augment or switch)	Aripiprazole	Lithium
6	Quetiapine	Aripiprazole or lithium (augment)	Lithium	Risperidone
7	Quetiapine	Aripiprazole	Lithium (augment)	Valproate (augment)
8	Risperidone	Lithium (augment)	Oxcarbazepine	Aripiprazole
9	Risperidone	Augment methylphenidate after stable	Olanzapine	Olanzapine + atomoxetine

## 9-year-old with BP I

TABLE 2.

**Drug Sequences Endorsed for Case 2 (Presumptive BP-I mania)**

Respondent #	Option A	Option B	Option C	Option D
1	Aripiprazole	Lithium	Valproate	Risperidone
2	Aripiprazole	Quetiapine	Risperidone or lamotrigine	Quetiapine (augment) or lamotrigine (augment)
3	Aripiprazole	Ziprasidone	Valproate (augment)	Quetiapine alone
4	Lithium	Aripiprazole (augment)	Risperidone	Quetiapine
4	Quetiapine	Aripiprazole or lithium or lamotrigine (augment)	Risperidone	Valproate
5	Quetiapine or aripiprazole	Atypical + lithium	Atypical or valproate (augment)	Carbamazepine
6	Quetiapine	Lithium	Aripiprazole	Risperidone
7	Risperidone	Lithium (augment)	Oxcarbamazepine	Aripiprazole
8	Valproate	Seroquel + lamotrigine	Risperidone	Olanzapine + valproate

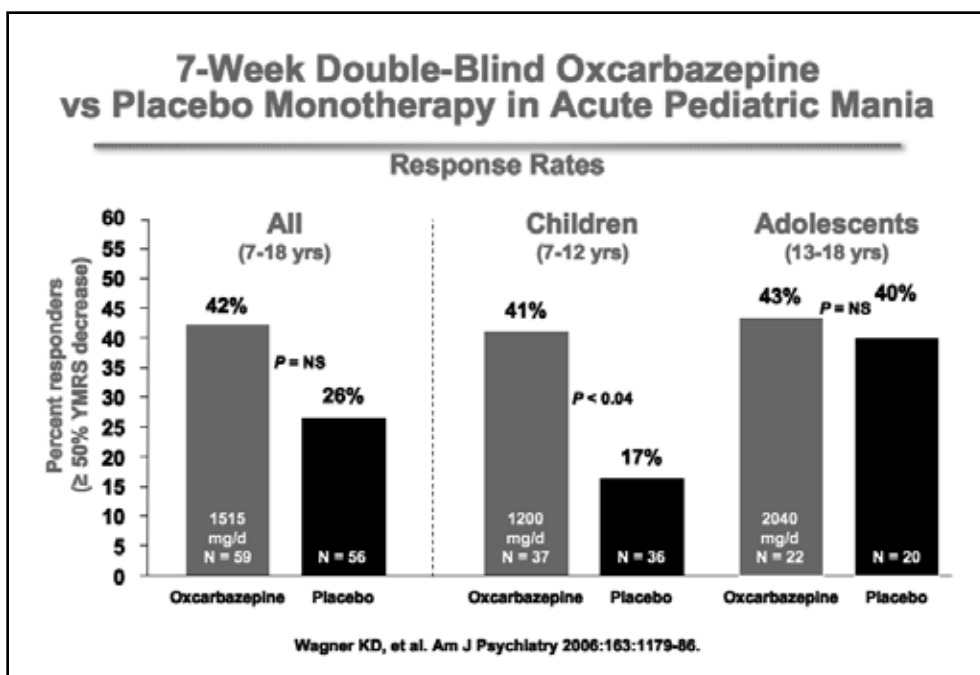
## Oxcarbazepine May Be Helpful In Pediatric Mania

Oxcarbazepine (OXC; Trileptal) is a close structural relative of carbamazepine (CBZ; Tegretol; Equetro), but unlike CBZ, OXC is not an enzyme inducer, nor does it have CBZ's risks of rare agranulocytosis or aplastic anemia.

Wagner et al.'s report on OXC in the *American Journal of Psychiatry* in 2006 is typically cited as evidence the drug is ineffective for pediatric mania. But observe the figure below. While this was true of OXC's efficacy in adolescents (due

to a large placebo response—see right column), **OXC worked well in children ages 7-12**. These younger children often have more chronic presentations and BP-NOS. This may explain the low placebo response rate in the younger children.

Oxcarbazepine is considered helpful by many clinicians (See Post and Wozniak's survey of expert treatment approaches to childhood illness, published in *Psychiatric Annals* in 2009) and should not be dismissed altogether.



## Faster, Better Response to Risperidone than Valproate in Adolescents with Bipolar Disorder

An article by Pavuluri et al. published in *Bipolar Disorders* last month reported that both divalproex sodium (valproate, or Depakote) and risperidone (Risperdol) were effective in youth with bipolar disorder, but improvements appeared more quickly with risperidone. Risperidone also produced higher response rates, higher remission rates, and fewer dropouts from side effects.

A presentation by the research group at an earlier conference suggested that it was particularly among those with comorbid disruptive behavioral disorders (DBD), which include attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD),

and conduct disorder (CD), that risperidone worked faster and produced greater early results than divalproex.

In the study, 66 children with type I bipolar disorder and a mean age of 11 years were assessed. Treatment with risperidone was initiated at 0.5 mg/day and titrated to 2 mg, while divalproex was initiated at 60 µg/mL and titrated up to 120 µg.

*Editor's Note: The possibility that children with different comorbid disorders respond differently to different antimanic agents suggests more studies are needed to determine which subgroups of patients are most responsive to typical treatments.*

## More Early Onsets and Difficult Courses of Bipolar Illness Occur in the US than in the Netherlands And Germany

*Continued from Page 1*

### Early onset bipolar illness and treatment delay are risk factors for a poor outcome in adulthood

In 2008 we published research that there was a greater incidence of early onset illness (prior to age 13) in the US (22% of people with bipolar illness) than in Europe (2%), and that delays to first treatment for the illness were highly inversely correlated with earlier age of onset.

More recent data showing that early onset bipolar illness and treatment delay are risk factors for a poor outcome in adulthood raise the possibility that earlier intervention in the illness in the US could lead to a less severe course of illness and a better long-term outcome.

The duration of the treatment delay from illness onset to first treatment for mania or depression was an independent correlate of poor outcome upon followup among adults in the Network (average age 42).

Those with the longest delays to first treatment experienced greater amounts and severity of depression, more episodes, and less time euthymic compared with patients with shorter treatment delays.

These data published this year in the *Journal of Clinical Psychiatry* now parallel a robust literature that the duration of the untreated interval (DUI) is a poor prognosis factor for schizophrenia as well.

# Inflammation and Oxidative Stress in Bipolar Disorders

A number of studies presented at the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders conference in Sao Paulo, Brazil in March reported new data relevant to inflammation and oxidative stress. **Both inflammation and oxidative stress increase risk of cardiovascular disorders, and patients with inadequately treated mood disorders lose 10 or more years of life expectancy from cardiovascular disorders compared to the general population.** Inflammation and oxidative stress may also contribute to the symptoms, evolution, and progression of the mood disorders themselves. It is possible that these two processes could become new targets for therapeutic intervention in addition to more traditional psychopharmacological drugs that primarily target the neurotransmitters dopamine, norepinephrine, serotonin, and the neurotrophic factor BDNF.

## Increases in inflammatory cytokines in the affective disorders

Various researchers have recently reported finding increases in inflammatory markers among patients with mood disorders.

Izabela Barbosa and colleagues reported increases in the cytokine CCL24 in patients with mania, as well as increases in plasma levels of soluble TNF-alpha receptors in bipolar patients, particularly TNF-R2. These elevated levels of Type 1 and Type 2 TNF-alpha receptors were correlated with duration of bipolar disorder, making these data consistent with other studies in which increases in oxidative stress and inflammatory cytokines occur as a function of either number of episodes or duration of illness.

Researcher Breno Diniz also found that TNF-R2 increases in unipolar depression and in late-life depression. In late-life depression there were also decreases in BDNF and

increases in levels of the cytokine IL-1B, another sign of inflammation.

Mauricio Kunz and colleagues reported that patients with bipolar disorder exhibited increases in cytokines TNF-alpha, IL-6, and IL-10. IL-10 is an anti-inflammatory cytokine and its increase may be compensatory. Most interestingly, increases in IL-6 (an inflammatory cytokine) were proportional to the number of days depressed subsequently observed in one-year follow up, suggesting that some inflammatory markers may have prognostic significance.

From a therapeutic perspective, the findings suggest that clinical intervention directed at reducing inflammatory cytokine production and inhibiting its effects may be useful. There are not many data about this strategy in mood disorders, but there are data from other illnesses suggesting that this approach could work. Patients with rheumatoid arthritis (who have a high incidence of depression), when treated with genetically engineered inhibitors of TNF-alpha receptor activity, not only show improvement in their rheumatoid arthritis, but also in accompanied symptoms of depression.

Other anti-inflammatory approaches are possible. The anti-inflammatory/antibiotic minocycline has been used in the treatment of schizophrenia with some positive effects, not only on symptomatology, but cognitive function as well. Since minocycline has multiple positive ways of acting on systems that are abnormal in patients with bipolar disorder, it deserves to be more systematically studied in bipolar illness the way it is beginning to be studied in schizophrenia.

Among the many different mechanisms of action of minocycline that counter abnormalities found in bipolar illness are that it: decreases inflammatory cytokines; decreases cell suicide (apoptosis); inhibits high levels of PKC and GSK-3 alpha; and decreases nitric

oxide synthetase, a substance that increases the levels of free radicals which damage neurons and glia. Surprisingly, minocycline has therapeutic effects on each one of these target areas as measured in a variety of *in vivo* animal systems and *in vitro* as well.

## Oxidative stress increases in bipolar disorder

When energy is created within cells, toxic by-products can accumulate and potentially damage cells. This process is known as oxidative stress, and the toxins created include peroxides, nitrates, and free radicals.

Keila Ceresér and colleagues reported increases in serum levels of thiobarbituric acid reactive substances (TBARS) in patients with bipolar disorder. TBARS are indicators of damage to cells' lipid membranes, and carbonyl is a measure of protein oxidative damage. These findings were replicated by Brisa Fernandes and colleagues, who found increases in TBARS during mania.

*Editor's note: These data on peripheral markers of oxidative stress and of inflammatory cytokines support the idea that cellular toxicity occurs in the affective disorders, a theory that has been described by Flavio Kapczinski. Patients with mood disorders face a double liability for cellular toxicity, experiencing increases in inflammation and oxidative stress at the same time as deficits in neuroprotective factors such as BDNF (brain derived neurotrophic factor) that occur with each episode of depression and mania in proportion to their severity. Thus, the increases in toxic factors that would be dangerous on their own may damage cells more because substances that protect neurons and glia are produced in smaller amounts during each affective episode.*

*The cell damage that results from these two processes occurring together could explain why cognitive dysfunction*

*Continued on Page 7*

# Inflammation and Oxidative Stress in Bipolar Disorders

*Continued from Page 6*

increases as a function of the number of affective episodes experienced.

## Brain-derived Neurotrophic Factor

There were several findings about BDNF at the Conference of the International Society of Bipolar Disorders. BDNF is a substance that is necessary for long-term learning and memory, neural and glial cell health and survival, and for neurogenesis (the production of new neurons for the hippocampus that occurs throughout life).

Brisa Fernandes et al. reported that in a study of bipolar patients, BDNF decreased as a function of duration of illness, suggesting that with long-term illness and many recurrences, BDNF may eventually fail to normalize between episodes.

Marcia Kauer-Sant'Anna et al. reported that BDNF measured in blood decreases with aging, and does so more profoundly in women than in men.

Ronald Duman and colleagues reported that another neurotrophic factor, vascular endothelial growth factor (VEGF), like BDNF, decreases with episodes of affective illness and may be another important loss of neuroprotection that occurs in the mood disorders.

Antidepressants increase the low levels of BDNF and VEGF found in depressed patients.

Fernandes and colleagues reported that in contrast to the low levels of BDNF and VEGF found during depression, another neurotrophin, NT3, increases in both mania and depression. In animal models of stress, while BDNF decreases in the hippocampus, NT3 increases in the brainstem areas where norepinephrine cell bodies are located (the locus coeruleus), and may be a mechanism for increasing long-lasting anxiety responses to places and cues that signal danger. Whether the NT3 increases represent a compensatory

alteration in response to the decreases in BDNF and VEGF that occur with affective episodes, or whether the increases in NT3 are a part of the pathophysiology of the illness conveying mechanisms for increased anxiety, remains for further investigation.

*Editor's Note: As discussed in previous BNNs, this general pattern of episode-related increases in toxic factors (inflammation, cytokines, oxidative stress, and free-radicals) and decreases in neuroprotective factors (BDNF and VEGF) yields a plausible set of rationales for the increase in neural, glial, and somatic cell endangerment that occurs as a function of number of affective episodes.*

*These concepts could explain why so many neuropathological findings vary as a function of number of prior episodes and, in particular, why several measures of cognition in bipolar disorder, especially in frontal lobe-based executive functioning and long-term verbal learning and memory, are inversely correlated with number of prior episodes or duration of illness.*

Data from Lars Vedel Kessing and collaborators illustrate the importance of long-term prophylaxis and episode prevention with medications and psychotherapy. While analyzing

information from the huge number of patients in the Danish Case Registry, their research group found that a history of two prior unipolar or bipolar depressions was not associated with an increased risk of dementia in old age. However, a total of four depressions doubled the risk of a diagnosis of dementia in old age, and every depression thereafter further increased that risk.

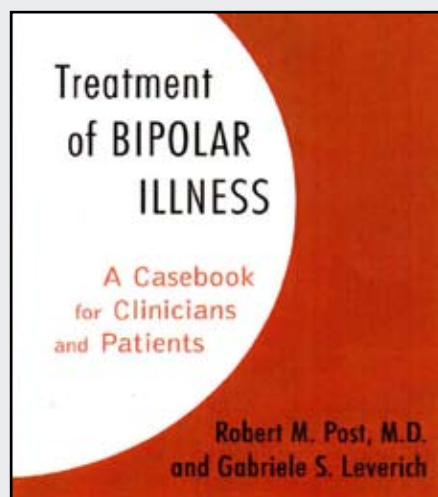
This editor has recently reviewed the substantial evidence that many types of neurobiological dysfunction correlate with either duration of illness or number of previous episodes experienced. The results are reported in *Neurotoxicity* in 2010 and involve alterations in multiple areas of brain biochemistry, structure and function. While it cannot be definitively established that the number of episodes or duration of illness are causal in producing these defects (because it is possible that some of these defects may, themselves, be productive of greater severity of illness), nonetheless, it is clinically important to assume the relationship is causal so that it helps encourage the

*Continued on Page 8*

Advertisement

From W.W. Norton & Company:

**TREATMENT OF BIPOLAR ILLNESS: A CASEBOOK FOR CLINICIANS AND PATIENTS**  
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."*

**Hardcover: \$65.00 \$52.00**  
Available now on [Amazon.com](http://Amazon.com)  
Or email [mcerminaro@wwnorton.com](mailto:mcerminaro@wwnorton.com)

# Inflammation and Oxidative Stress in Bipolar Disorders

*Continued from Page 7*

most careful and judicious prevention of recurrent episodes possible.

This approach makes clinical sense because episode prevention in and of itself is of great benefit to patients, and any other potential benefit such as preventing disease progression and the worsening of neurobiological abnormalities would then only be a further bonus. However, with the considerable evidence that each episode is, in fact, associated with oxidative stress, increases in free radicals and toxic cytokines, as well as decrements in neuroprotective factors such as BDNF, scrupulous prevention of episodes appears to take on even greater importance beyond preventing considerable morbidity and disability associated with recurrence of a manic or depressive episode.

**Preventing episodes of unipolar and bipolar affective episode could also change the long-term course of illness (i.e. preventing episode sensitization and kindling-like increases in vulnerability to recurrence), as well as preserving more optimal brain function.**

## Lithium has neuroprotective effects

*There is a hopeful side to this story. Many treatments are neuroprotective and lower the risk of such adverse long-term outcomes. In particular, in the recurrent unipolar disorders, Yvette Sheline et al. reported that compared with patients treated with antidepressants less of the time, patients who were treated with antidepressants for more of the time did not experience hippocampal atrophy with aging. Similarly, lithium has been shown to increase hippocampal volume.*

Preliminary findings from Kessing show that patients who have been on more chronic lithium and have renewed their lithium prescriptions at least once have a lower incidence of dementia in late life compared with patients who have not been exposed to regular

lithium treatment. The bottom line from these and other studies is that not only can effective long-term prophylaxis prevent episodes of illness, but may also protect the brain and cognition.

Three studies have reported that bipolar patients treated with lithium have increases in grey matter volume in areas of the brain in which they were originally deficient and, interestingly, normal volunteers included in some of these studies did not show significant increases. Thus, it appears that lithium selectively acts on

---

***Four lifetime mood episodes double the risk of late life dementia. Preventing episodes may thus protect both mood and mind.***

**PREVENT EPISODES,  
PROTECT THE BRAIN!**

---

areas of brain that may be deficient in patients with bipolar disorder.

Now, in addition, new data from Brenda MacQueen of the University of Calgary shows that short-term treatment with lithium significantly increases hippocampal volume in patients with bipolar disorder. These investigators also had preliminary evidence that this was associated with improvement in recollective memory function as well.

Lithium also increases levels of a marker of neuronal integrity, n-acetyl aspartate (NAA), which can be measured directly in the brains of patients using magnetic resonance spectroscopy (MRS).

These new data on increases in hippocampal volume with lithium add to the growing rationale that lithium may have neurotrophic and neuroprotective effects in both animals and in humans. In particular, lithium not only increases neurotrophic factors such as BDNF and cell survival factors such as Bcl-2, but it inhibits factors that induce

cell death, including BAX and P53. It also has a variety of other actions in cells that have appeared to increase cellular viability and function. Thus, the data that lithium actually increases hippocampal volume in patients with bipolar disorder provides further rationale for extended use of this compound in patients with the disorder.

This is particularly important for patients in the U.S., where new prescriptions for valproate have actually exceeded those of lithium. In a recent study in Europe, there were indications that both lithium and the lithium/valproate combination led to much better long-term outcomes than treatment with valproate alone (see BNN Issue 3 from 2009). In addition, studies of lithium have produced the best data for an anti-suicide effect in patients with bipolar disorder. This finding is crucial because some 25-50% of patients with the disorder make a serious suicide attempt during their course of illness, and some 10-15% of patients with this illness die via suicide.

The data about neuroprotective effects of lithium and other medications is important information for patients to be aware of while making choices about maintaining long-term treatment. Discontinuing effective treatment places the patient at high risk for relapse, and can potentially lead to further types of brain dysfunction. Patients get good information about the nature of the side-effects profiles of the various treatments most widely used for bipolar illness, but often fail to get the message that some of the treatments may also have direct neurochemical benefits and may help protect the brain. In addition to lithium, drugs used in the treatment of bipolar illness that also increase BDNF include valproate (Depakote), carbamazepine (Tegretol/Equetro), lamotrigine (Lamictal), the atypical antipsychotic quetiapine (Seroquel), and omega-3 fatty acids.



## Psychotherapy & Psychoeducational Approaches, Long-Term Psychopharmacology, and Combination Therapy All Play a Role in Preventing Recurrent Mood Episodes

### Psychotherapeutic and Psychoeducational Approaches Are Critical

A number of studies presented at the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March indicated that cognitive-behavioral therapy (CBT) and individual and group psychoeducational approaches enhance both short- and long-term outcomes for patients with bipolar illness. These studies add to an already substantial literature that shows that **focused psychotherapies (such as cognitive/behavioral, interpersonal, and social rhythms therapies) and psychoeducation are superior to treatment as usual.**

These therapies can provide a variety of approaches to stress management and reduction, and can enhance family and interpersonal communication. Another way these focused psychotherapeutic approaches help patients is by demonstrating the benefits of effective long-term preventive treatment and encouraging its consistent use.

Without consistent prophylactic treatment, patients are at high risk for recurrences and their multiple psychosocial and neurobiological consequences. Greater number of prior episodes is associated with an increased risk of psychosocial dysfunction, treatment resistance, cognitive dysfunction, medical comorbidities, and even dementia in old age.

### The role of preventive psychopharmacology

Long-term preventive psychopharmacology typically involves the mood stabilizers (lithium, valproate, carbamazepine, and lamotrigine) or an atypical antipsychotic. For example, the atypical antipsychotic quetiapine

(Seroquel) is FDA-approved as an adjunct to lithium or valproate for preventing both manic and depressive episodes, which it does with a high degree of clinical and statistical significance. Moreover, there are new data that monotherapy with quetiapine also has the ability to reduce both manic and depressive episodes. Thus, quetiapine has a broad spectrum of

---

*Family  
psychoeducation and  
other psychotherapeutic  
strategies are a  
necessary part of  
treatment of childhood  
bipolar disorder.*

---

efficacy; it not only treats acute episodes of mania and bipolar depression, but also prevents recurrences of both types of episodes. Virtually all of the other atypicals also have shown acute and long-term adjunctive efficacy compared with mood stabilizers used alone.

Quetiapine has also just been FDA-approved for adjunctive use in unipolar depression when patients do not achieve an adequate response on traditional unimodal antidepressants such as serotonin-selective reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), or dopamine-active agents such as bupropion. The only other atypical antipsychotic that is FDA-approved for adjunctive use in unipolar depression is aripiprazole (Abilify).

### Complex combination therapy typically needed for long-term remission

Treatment with only one of the effective agents noted above is often insufficient to bring bipolar patients to a complete remission and to maintain it once it is achieved. Combination therapy and at times complex combination therapies are increasingly being used to maintain a long-term remission. Some authorities in the field such as Paul Grof in Canada and Muller Oerlinghausen in Germany continue to emphasize the use of monotherapy, particularly lithium monotherapy, in the treatment of bipolar patients. However, in the US, multiple investigators and academic institutions have found that monotherapy with lithium or other agents is rarely sufficient to achieve the desired goals, and combinations of mood stabilizers and/or atypical antipsychotics are often needed to achieve adequate treatment outcomes.

In the Bipolar Collaborative Network, we found that **an average of three medications and 1.5 years of treatment revisions were required in order to achieve excellent mood stabilization for at least six months** in outpatients who entered the Network in an ill state. While lithium and valproate were the agents most often associated with these successful long-term treatment regimens, other mood stabilizers, atypical antipsychotics, adjunctive antidepressants, and thyroid augmentation were often used as well. The need for complicated treatment regimens is further driven by the high degrees of Axis I comorbidities that very often accompany bipolar disorder, such as anxiety disorders and alcohol or substance abuse. (See Table on page 10).

# Smoking Adds to Risks for Patients with Bipolar Disorder

Seetal Dodd and colleagues reported at the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March that smoking was associated with a less successful outcome in the naturalistic treatment of bipolar patients. Smoking was also found to be a risk factor for new onset of depression, as reported in a recent article in the *New England Journal of Medicine*.

In addition to these direct effects on mental health, smoking is also a major additional risk factor for cardiovascular disease when combined with the presence of any three of the five primary risk factors that constitute the metabolic syndrome. These five factors are increased waist circumference, high blood pressure, increased cholesterol, increased triglycerides, and insulin

resistance or elevated fasting blood glucose. Cardiovascular disease co-occurs with bipolar disorder at a high rate and is one of the major causes of decreased life expectancy in those with inadequately treated illness.

Because smoking is a powerful risk factor for comorbid illnesses such as heart attack and stroke and is itself associated with a poor clinical outcome in the treatment of bipolar disorder, **every effort should be made to help patients with smoking cessation.**

## Pharmacological treatment for assisting smoking cessation

In addition to nicotine chewing gum, patches and related products, bupropion, a drug with one of the best antidepressant profiles in bipolar patients because it does not seem to

induce switches into mania, may also be helpful in smoking cessation.

A new option may also be emerging. Mark Frye and colleagues at the Mayo Clinic have been studying varenicline, a drug that stimulates a nicotine receptor subunit in the brain. The initial open study of this drug in patients with bipolar disorder found that it was generally well tolerated and effective. However, another study indicated varenicline may cause the new onset of aggressive thoughts. See Varenicline article on page 11.

*Editors note: In light of the substantial incidence of smoking in patients with bipolar disorder and smoking's deleterious effects on medical and psychiatric outcome, further study of optimal approaches to smoking cessation in those with bipolar disorder is indicated.*

## Adjuncts of Potential Utility in the Treatment of Common Comorbidities of Bipolar Disorder

(Note: All are Off-Label for Bipolar Disorder Patients)

	TOP	ZON	Bupropion	NAC	Modafinil
Weight Gain	+++	+++	+		0
Bulimia	+++	+++			
Alcohol	+++	+++		(+++)	0
Cigarettes	+		+++		
Cocaine	+++		±	+++	+++
PTSD	++				
Depressed Mood	+		+++	+++	+++
Manic Mood	-		--	+	d.n.w.

TOP = Topiramate (Topamax); ZON = Zonisamide (Zonegran); Bupropion (Wellbutrin); NAC = N-Acetyl cysteine; Modafinil (Provigil)

+++ = Placebo controlled data in the primary disorder or condition;  
 ++ = substantial evidence;  
 + = some evidence; ± = ambiguous data; 0 = no evidence;  
 - = negative study; -- = may worsen; d.n.w. = did not worsen

## Low-Dose Thyroid (T<sub>3</sub>) Augmentation Can Help Depression; High Dose T<sub>4</sub> Effective for Women with Treatment-Resistant BP Illness

Low dose thyroid replacement treatment with T<sub>3</sub> (Cytomel) (25-37.5 µg) is typically recommended for acute antidepressant augmentation in unipolar and bipolar depression. This is a benign approach with few side effects and works even in those with normal thyroid function at baseline.

There is also a modicum of data supporting use of relatively high (supraphysiological) doses of T<sub>4</sub> (Synthroid) late in the treatment of

highly treatment-resistant patients with unipolar and bipolar disorder. These supra-physiological doses of T<sub>4</sub> typically ranged from 300-500 µg/day, producing a free thyroxine index of 150% of normal. This is usually moderately well tolerated, although minor degrees of sweating, tachycardia (fast heartbeat), and other signs of hyperthyroidism can accompany this regimen. If this approach is employed, it is particularly

important to increase the dose of T<sub>4</sub> (Synthroid) very slowly because of its relatively long half-life—about 12 days. (That is, if a patient takes a high dose of T<sub>4</sub> and then stops their medication completely, 12 days later blood levels will only have decreased to half of what they originally were.)

At the 4<sup>th</sup> Biennial Conference of the International Society for Bipolar Disorders in Sao Paulo, Brazil in March, Mike Bauer presented new data from a randomized placebo-controlled study of supraphysiologic T<sub>4</sub> compared with placebo in bipolar patients. In this study, he increased the dose by 100 µg/week toward a target dose of 300 µg/day. There was no overall statistical significance of this high dose thyroid regimen compared with placebo in the group as a whole, but the results were highly statistically significant in women treated with this strategy. Earlier studies of low dose T<sub>3</sub> augmentation also suggested that women were more responsive to thyroid augmentation strategies than men.

Thus, in the face of inadequate treatment responses to complex combination strategies, it appears that, for the first time, there are double-blind, placebo-controlled data supporting the use of supraphysiological doses of thyroid in women whereas, heretofore, the only evidence of efficacy of this approach existed in small case series studied across institutions in the U.S. and Europe.

### Thoughts and Acts of Aggression/Violence Toward Others Reported in Association with Varenicline

Moore TJ, Glenmullen J, Furberg CD. *Annals of Pharmacotherapy*. 2010 Sep; 44(9): 1389-94.

Institute for Safe Medication Practices, Horsham, PA.

#### ABSTRACT

**BACKGROUND:** Thoughts and acts of aggression/violence toward others have been reported in postmarketing surveillance of varenicline, an aid to smoking cessation.

**OBJECTIVE:** To identify the common characteristics of these thoughts and acts of aggression/violence toward others and assess the likely relationship to varenicline treatment.

**METHODS:** We obtained 78 adverse event reports from the Food and Drug Administration MedWatch database containing medical terms describing possible acts or thoughts of aggression/violence; 4 additional cases were reported in clinical trials, and 3 others came from the published literature. We used psychiatric diagnostic criteria and an adverse event causality assessment tool to identify 26 case reports for study.

**RESULTS:** The selected cases described 10 events with assault, 9 cases of homicidal ideation, and 7 cases of other thoughts or acts of aggression/

violence. The most frequent common characteristics were (1) inexplicable and unprovoked event, (2) the victim was anyone nearby, (3) no indication of a prior history of similar behavior in the patient, and (4) early onset of psychiatric adverse effects, often before stopping smoking. Where dechallenge/rechallenge information was available, psychiatric adverse effects resolved in 13/14 (93%) cases after discontinuation.

**CONCLUSIONS:** The clear temporal relationship, lack of prior history of this behavior, and unusual nature of these events strengthens the accumulating scientific evidence that varenicline is associated with thoughts and acts of aggression/violence. **We recommend that physicians and pharmacists ensure that all patients are informed of possible psychiatric symptoms of varenicline, including violent and aggressive thoughts.** All patients should be advised to contact a health-care provider immediately if these symptoms occur and varenicline should be discontinued without delay.

**Help us stay green!**

**Switch from the print BNN to our email version here:**

**<http://bipolarnews.org>**

---

BNN  
PO Box 18  
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED