

# Bipolar Network News

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## Preventative Treatment Should Begin After First Manic Episode

Evidence from multiple studies has indicated the importance of beginning preventative treatment, particularly with lithium, early in the course of bipolar disorder. A 2016 comprehensive literature review by researcher Katie Joyce and colleagues in the *International Journal of Bipolar Disorders* concluded that **psychoeducation and medication are more effective in bipolar disorder when applied in earlier stages of the illness rather than later stages.**

Several studies suggest that treatment for bipolar disorder should be started specifically after the first manic episode.

A 2014 study by researcher Lars Kessing and colleagues in the *British Journal of Psychiatry* examined 4,700 patients treated with lithium in Denmark. Kessing and colleagues found that those who started treatment after one manic

episode were less likely to find lithium ineffective than those who started later.

Another study by researcher Michael Berk and colleagues presented at the International Society for Bipolar Disorders found that after a first manic episode, a year of treatment with lithium was much more effective on all measures of outcome, including mania and depression ratings, brain imaging, and neuropsychological functioning, than a year when patients were randomized to quetiapine (Seroquel).

Researcher Lakshmi Yatham and colleagues presented research at the International Society for Bipolar Disorders showing that patients recovered from the neuropsychological deficits associated with a first episode of mania if they were well treated and had no further episodes,

while those who had new episodes did not return to their baseline capabilities. This suggests that early treatment that prevents future episodes helps maintain a healthy brain.

Kessing and colleagues previously reported in the *British Journal of Psychiatry* in 2013 that patients randomized to two years of treatment in an outpatient clinic specializing in mood disorders following a first hospitalization for mania had 40% fewer recurrences of bipolar episodes over the next six years than those who received treatment as usual. These data indicate that early treatment, which may include psychotherapy, medications, mood charting (i.e. keeping a daily record of symptoms) and illness education, can improve the long-term course of illness. Lithium is often a key component of such treatment.

*Editor's Note: This type of intensive, ongoing treatment is not the norm after a first manic hospitalization in the United States, but it should be. Given the new data on the impact of starting lithium after a first episode of mania, and lithium's superiority over quetiapine in the year following a first episode, lithium treatment should be standard following a diagnosis of bipolar disorder.*

*In the past, sometimes doctors have recommended waiting until a patient has had multiple episodes of mania before beginning preventative treatment with lithium. This now appears to be a mistake.*

*Lithium protects against depressive as well as manic recurrences, and there is also evidence that it increases hippocampal and*

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### Thank you!

Dear readers and supporters,

Thank you so much for your generation contributions to our first-ever fundraiser! You contributed close to \$15,000 to help support the BNN. That's enough to print and mail several issues!

Sincerely,  
Editor-in-Chief Robert M. Post  
and  
Managing Editor  
Moira McCauley

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## How Stress Triggers Inflammation and Depression

Depression and bipolar disorder are associated with increases in markers of inflammation that can be found in the brain and blood. It is increasingly clear that **the mechanisms that cause depression are not just in the brain, but actually throughout the body.** These include two signaling systems that begin in the bone marrow and the spleen.

When a small mouse is repeatedly defeated by a larger animal, they show depression-like symptoms known as defeat stress. Animal studies have shown that stress and danger signals are perceived and relayed to the

amygdala and the hypothalamus. The sympathetic nervous system releases the neurotransmitter norepinephrine into bone marrow, where stem cells are turned into activated monocytes (a type of white blood cells) that are then released into the blood. The monocytes travel to the brain, leading to the activation of more inflammatory cells.

Blocking part of this process can prevent the depression-like behaviors from occurring. If the bone marrow monocytes are blocked from entering the brain, inflammation and defeat stress behaviors like social avoidance do not occur. However, if there is a second bout of defeat stress, primed monocytes that have been stored in the spleen are released and travel to the brain, producing further increases in inflammatory cells and even more defeat stress behaviors.

If these monocytes from the spleen are blocked, the inflammation and the reaction to the new stressor do not occur.

Stress also activates lymphocytes (another type of white blood cells) to secrete the inflammatory cells Il-6. If this Il-6 secretion is inhibited, defeat stress behaviors can be prevented.

Defeat stress also leads to the release of the neurotransmitter glutamate. Some of this cascade begins in the brain, which evaluates stressors and releases IL-1 beta, another type of inflammatory cell. It slows down the production of glutamate, while IL-6 can endanger neurons and is associated with anhedonia—loss of interest in pleasurable activities. This cascade also leads to the production of another type of inflammatory cell, TNF-alpha, which has adverse effects on biochemistry, brain, and behavior.

This understanding of the role of the brain and body provides new targets for drug development. If inflammatory processes are blocked, defeat stress behaviors do not occur. Researcher Michael D. Weber and colleagues described this process in detail in the journal *Neuropsychopharmacology Reviews* in 2017.

Together these observations suggest that inflammatory processes in the body are crucial to the development of some stress- and inflammation-related depressive behaviors.

### Bipolar Network News

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**Managing Editor:** Moira McCauley

The *BNN* is published 4–6 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 or 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*.

Dr. Post has consulted on behalf of drug companies including Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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

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## Anti-Inflammatory Treatments Improve Depression

Inflammation can interfere with the balance of neurotransmitters in the brain, making antidepressants less effective. Anti-inflammatory treatments (such as those used to treat rheumatoid arthritis) may help. In a 2016 meta-analysis published in the journal *Molecular Psychiatry*, researchers led by Nils Kappelmann analyzed the results of 20 clinical trials of chronic inflammatory conditions where depressive symptoms were also recorded. In a subset of seven clinical trials that compared anti-inflammatory treatment to placebo, they found that anti-inflammatory treatment improved depressive symptoms significantly compared to placebo.

**The anti-inflammatory drugs studied most often targeted the inflammatory marker tumor necrosis factor (TNF) alpha using an antibody. Some of the anti-inflammatory drugs that improved depressive symptoms were adalimumab, etanercept, infliximab, and tocilizumab.**

The researchers also found that those participants with the most inflammation when they began treatment saw the largest improvement in their depression after taking anti-inflammatory treatments.

Kappelmann and colleagues suggest that inflammation may cause depression, and that anti-inflammatory drugs may be useful in the treatment of depression in people with high inflammation.

## Inflammatory Marker CRP Higher in Bipolar Disorder, Particularly Mania

Inflammation has been linked to mood disorders. A 2016 meta-analysis in the journal *Lancet Psychiatry* described the role of inflammatory marker C-reactive protein (CRP) in bipolar episodes. Researchers led by Brisa S. Fernandes identified 27 studies that measured CRP levels in a total of 2,161 patients with bipolar disorder and 81,932 healthy participants. The researchers determined that compared to healthy controls, people with bipolar disorder have higher levels of CRP. **CRP levels were moderately elevated between episodes and during depression, and substantially elevated during episodes of mania.**

*Editor's Note: This meta-analysis shows that CRP is linked to bipolar disorder, and the inflammatory burden is highest during mania. It remains to be seen*

*whether anti-inflammatory treatments work best in patients with high CRP levels compared to normal CRP levels.*

*CRP is also a risk factor for cardiovascular disease, and lithium and other treatments for bipolar disorder probably lower CRP levels.*

*The same group of researchers previously showed that statins, drugs typically used to lower cholesterol, could help alleviate depression. Since statins have anti-inflammatory effects, they can probably reduce depression risk in addition to lowering cardiovascular risk, as initial studies suggest.*

*Other drugs with anti-inflammatory effects that may improve depression include the anti-arthritis drug celecoxib (see article below) and the antibiotic minocycline. The amino acid N-acetylcysteine and omega-3 fatty acids also have anti-inflammatory effects and have been found to improve depression in some studies.*

## Arthritis Drug Celecoxib May Improve Bipolar Depression When Paired with Escitalopram

A new study suggests that for people with bipolar depression, the anti-inflammatory drug celecoxib (Celebrex), typically used to treat arthritis, can boost the effectiveness of the antidepressant escitalopram (Lexapro).

In the 8-week study by researcher Angelos Halaris and colleagues, adults with bipolar depression were randomly assigned to one of two groups. The first group received the selective-serotonin reuptake inhibitor (SSRI) antidepressant escitalopram plus celecoxib to target inflammation. The second group received just the antidepressant escitalopram and a placebo.

**By the end of the study, 78% of the group taking the anti-arthritis drug had seen major improvement in their depression, with 63% reporting that it had lifted completely.** Meanwhile in the placebo group,

only 45% reported major improvement, and 10% reported remission.

The group that received celecoxib with their escitalopram also began seeing improvement within one week of beginning treatment, instead of after four to six weeks, which is typical of antidepressant treatment.

Researchers think depression creates an immune response leading to chronic inflammation, which can upset the balance of neurotransmitters in the brain and make antidepressants less effective. Halaris suggests that reducing this inflammation with a drug like celecoxib can make antidepressants more effective.

The research was presented at the Fifth International Congress on Psychiatry and the Neurosciences and has not yet been published.

## Measuring Inflammation in Neuropsychiatric Disorders May Shed Light on Treatment

Meta-analyses have found links between elevated levels of inflammatory markers and many neuropsychiatric disorders, including depression, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD) and traumatic brain injury. Multiple studies also show that **those with elevated inflammatory markers such as interleukin-1, interleukin-6, tumor necrosis factor (TNF) alpha, and c-reactive protein (CRP) also respond less well to typical treatments than those with normal levels of these markers in the blood.**

These links suggest that it could be useful to measure levels of these inflammatory markers in the blood of people who are responding poorly to medications. If one or more of these markers are elevated, it might be a sign that treatment with an anti-inflammatory agent could be helpful. Preliminary studies have shown that some neuropsychiatric disorders may improve after treatment with anti-inflammatory drugs such as aspirin, celecoxib (Celebrex), and the antibiotic minocycline, among others.

## Prevention (cont.)

*Continued from Page 1*

*cortical volume, helping prevent cognitive deterioration in those with mild cognitive impairment. Lithium is also the most effective mood stabilizer for preventing suicide, and it increases the length of telomeres (caps on the end of DNA strands), thus preventing a wide range of medical and psychiatric illnesses. Lithium may need to be combined with other drugs to achieve a complete remission, but using it after a first mania is a good place to start.*



## Mysteries Remain in the Relationship Between Inflammation and Depression

At the 2017 meeting of the American College of Psychiatrists, researchers Charles L. Raison and Vladimir Maletic gave a plenary lecture on the role of inflammation in depression. Meta-analyses have confirmed that inflammatory markers including Il-1, Il-6, TNF alpha, and CRP are elevated in about 1/3 of depressed patients. However, Raison and Maletic made the point that anti-inflammatory medications are not for everyone. While patients with elevated levels of CRP at baseline responded to an anti-TNF alpha antibody, patients with low CRP values at baseline actually got worse.

Raison and Maletic cited three studies that have also linked CRP to differential response to traditional antidepressants. In unipolar depression, those with low CRP respond well to selective serotonin reuptake inhibitor (SSRI) antidepressants, while those with elevated blood levels of CRP seem to respond better to a dopamine-active antidepressant such as bupropion or a noradrenergic-active antidepressant such as nortriptyline or the serotonin norepinephrine reuptake inhibitor (SNRI) antidepressant duloxetine. Patients with high inflammation at baseline also seem to respond better to intravenous ketamine and oral doses of omega-3 fatty acids.

Studies of animals have suggested that inflammation throughout the body is implicated in depression. **Studies in which rodents are repeatedly defeated by larger animals show that these animals have increased inflammation from lymphocytes (a type of white blood cells) in the blood, and monocytes (another type of white blood cells) from the bone marrow and spleen.** This

inflammation can induce depression-like behaviors in the rodents, which is prevented if the inflammatory mechanisms are blocked. These data suggest that depression is not just in the brain—inflammation from all over the body plays an important role.

Psychosocial stressors can also increase inflammation. Inflammation in response to a stressor is more dramatic in patients with a history of adversity in childhood.

One key issue that needs clarification is the sequence in which inflammatory changes occur. Patients who undergo

Depression is not just in the brain — inflammation from all over the body plays a role in it.

an immune challenge with the inflammatory cytokine interferon-alpha (used to treat hepatitis C) experience depression, and there is a large acute increase in inflammatory markers (such as p38 and MAP kinase) in proportion to the severity of the depression. However, weeks later the elevated markers are no longer evident.

Paradoxically, some immune challenges may even have therapeutic effects in depression. For example, an infusion of lipopolysaccharides (molecules that make up the outer membrane of certain bacteria) actually improves depression. Whole body hyperthermia is another inflammation-causing treatment in which the body's temperature is increased from 98.7 degrees Fahrenheit to well over 100 degrees using hot water blankets or large incubator-like chambers. This produces increases in inflammatory marker IL-6. Surprisingly, this therapy sometimes used for cancer produces antidepressant effects the following day, which correlate with the degree of increased inflammation.

## Astrocytes Can Turn Toxic

Astrocytes usually play a helpful role in the brain. **These glial cells facilitate neural connections and prune unnecessary ones.** However, new research details how infection or trauma can render astrocytes toxic, leading to brain disorders. In a 2017 article in the journal *Nature*, researcher Shane A. Liddelow and colleagues describe how resting astrocytes can become harmful reactive astrocytes.

The researchers determined that reactive astrocytes are found in brain tissues following brain injuries, or in neurological disorders including Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS), and multiple sclerosis. Liddelow and colleagues also determined that microglia play a role in transforming resting astrocytes into a subtype of harmful reactive astrocytes, dubbed A1 astrocytes, and that the latter secrete a neuron-killing toxin.

A1 astrocytes lose their ability to promote neuronal survival and to create new synapses. The researchers showed that blocking the formation of A1 astrocytes prevented certain neuron deaths, and they hope this finding will lead to new treatments for brain injuries and neurological disorders.

*Editor's Note: It is possible that A1 astrocytes are also induced in patients with bipolar disorder, post-traumatic stress disorder (PTSD), and schizophrenia, as well as head traumas and neurological disorders.*

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## Supplement Acetyl-L-Carnitine May Treat Stress and Depression

N-acetylcysteine (NAC), an antioxidant sold in health food stores, has several beneficial effects on brain and behavior. It improves depression and can reduce cravings for cocaine, alcohol, marijuana, and nicotine, and can also help control habit-driven behaviors such as gambling, compulsive hair-pulling, and symptoms of obsessive-compulsive disorder (OCD).

New research, particularly by researcher Nascia and colleagues in 2014 and 2016, has identified a related compound, acetyl-L-carnitine (ALC), as an anti-stressor and antidepressant in animals, and researchers have begun to explore its use in people. ALC has been found to improve mitochondrial function and improve

recovery from peripheral nerve damage. ALC also inhibits the release of glutamate, which can prevent depressive behaviors following stress.

A 2004 study by P. Ruggenenti and colleagues in the journal *Hypertension* found that in people, **1 gm of ALC taken twice daily safely improved arterial hypertension, insulin resistance, impaired glucose tolerance, and low levels of adiponectin in the blood (a risk factor for diabetes) in subjects at increased cardiovascular risk.**

In a 2014 article in the *Journal of Psychiatric Research*, researcher S.M. Wang and colleagues reviewed evidence that ALC improves mild depression. Two randomized clinical trials indicated that ALC was more

effective than placebo for mild depression. Two other randomized clinical trials showed that ALC was as effective as the antidepressants fluoxetine and amisulpride for mild depression. The supplement was as tolerable as placebo and better tolerated than fluoxetine and amisulpride. Wang and colleagues suggested that more clinical trials are needed to confirm that ALC is effective in depression.

*Editor's Note: If further clinical trials confirm the antidepressant effects of ALC, it could represent a new way to treat chronic stress and depression and regulate insulin. Together these effects could reduce the cardiovascular risks that accompany depression.*

## Inflammation Predicts Poor Response to Fluoxetine in Kids

Inflammation upsets the balance of neurotransmitters in the brain and can make antidepressants less effective. In new research by Maya Amitai and colleagues, children and adolescents were less likely to respond to the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine if they had high levels of inflammation measured in the blood.

Amitai's study included 41 patients between the ages of 9 and 18. They met criteria for a diagnosis of either major depression or an anxiety disorder. The participants were treated with the SSRI fluoxetine for eight weeks. **Those with high levels of the inflammatory markers tumor necrosis factor (TNF) alpha, interleukin-6, and interleukin 1 beta were less likely to respond to the antidepressant treatment.** The research was published in the *Journal of Child and Adolescent Psychopharmacology* in 2016.

*Editor's Note: These findings parallel those from studies of adults, suggesting that inflammation can predict poor response to antidepressants in all age groups.*

## Immune Response to Repeated Stress Alters Behavior in Mice

In research presented at the 2016 meeting of the Society of Biological Psychiatry, Jonathan P. Godbout described how an immune reaction to repeated stressors may lead to anxious behaviors in mice.

Mice were repeatedly defeated by a larger animal, a form of stress that produces a depression-like state. This provoked an immune response in the mice—the release of a type of white blood cells called monocytes from the bone marrow into the circulatory system. These inflammatory monocytes then traveled to the brain and spleen, attracted by signaling proteins called chemokines. The monocytes in turn produced inflammatory marker interleukin-1beta.

The defeat stress also provoked a reaction in the central nervous system, where microglia were activated.

These changes produced inflammation and anxiety-like behaviors in the mice. **Blocking the microglial activation, monocyte recruitment to the brain, or interleukin-1beta signaling each reversed the anxiety-like behaviors.**

Another researcher, Scott Russo, has shown that leukocytes, another type of white blood cells, secrete inflammatory interleukin-6 following defeat stress, and blocking this secretion prevents defeat stress-related behaviors.

Learn about the Child Network study: See page 11

## Combo of Memantine and Sertraline Effective for Unipolar Depression

A 2016 study in the *Journal of Clinical Pharmacy and Therapeutics* finds that the combination of memantine (Namenda), a drug used to treat Alzheimer's disease, and the antidepressant sertraline (Zoloft) improved unipolar depression more than sertraline plus placebo.

The study by Meysam Amidfar and colleagues included 66 patients with moderate to severe unipolar depression. They were divided into two groups — one received sertraline plus

memantine for six weeks, while the other received sertraline and a placebo.

**The memantine group showed significantly greater improvement at 2 weeks, 4 weeks, and 6 weeks, and significantly greater response at 4 and 6 weeks.** There were also more early improvers in the memantine group, and more rapid response to treatment. Both groups improved significantly over the six weeks of treatment.

Larger studies are needed to learn more about the safety and efficacy of memantine combined with sertraline for the treatment of unipolar depression, but this initial study is promising. In 2012, researcher Amit Anand and colleagues reported that in bipolar depression, memantine potentiates the effects of lamotrigine. Memantine also helped rapid cyclers when added to ongoing treatment in an open study of the drug treatment by Athanasios Koukopoulos and colleagues in 2012.

## Only Fluoxetine is More Effective Than Placebo for Children and Adolescents with Depression

In a meta-analysis published in 2016, researchers Andrea Cipriani, Xinyu Zhou, and colleagues reported that many antidepressants are not effective in children and adolescents. Fluoxetine alone was more effective than placebo. Other antidepressants also caused high study drop-out rates compared to placebo.

In an article published in the journal *The Lancet*, Cipriani, Zhou, and colleagues analyzed 34 randomized, controlled clinical trials of antidepressants in children and adolescents. These trials included a total of 5,260 participants and 14 different antidepressants.

The researchers determined that much of the evidence was of a low quality. **Only fluoxetine was statistically significantly more effective than placebo. Fluoxetine was also more tolerable to patients than duloxetine or imipramine.** Patients who received imipramine, venlafaxine, or duloxetine were more likely to drop out of studies due to adverse events compared to patients who received placebo.

The authors suggest that prescribing antidepressants to children or adolescents may not necessarily be beneficial, and that fluoxetine is probably the best option to consider.

*Editor's Note: It may be best to use caution when prescribing antidepressants to children or adolescents. First, these data that suggest that many antidepressants are ineffective in young people. In addition, depression in children and adolescents may be a sign of bipolar disorder, and antidepressant use may cause activation or switching into mania in vulnerable patients.*

*While there is a warning about using antidepressants in young people because of the risk of increased suicidal ideation, the actual suicide rate in young populations decreases when these patients take antidepressants and cognitive behavioral therapy. Psychotherapy should be a high priority. Other safe adjunctive approaches might include omega-3 fatty acids, N-acetylcysteine, vitamin D3, and folic acid. Evidence for the efficacy of rTMS in young people is also positive and growing.*

## Lithium May Work by Restoring Dendritic Spines

New research on mice clarifies lithium's effects on neurons and suggests how it can lead to improved symptoms. Dendrites are the long projections on neurons that seem to reach out to form synapses with other neurons. The surface of these dendrites is covered in mushroom-shaped spines that help create these synaptic connections. A 2016 article by research Ben Cheyette and colleagues in the journal *Molecular Psychiatry* reports that in mice with a genetic mutation common to people with autism, schizophrenia, and bipolar disorder, lithium restored healthy numbers of the mushroom-shaped spines. **The lithium treatment also reversed symptoms such as lack of interest in social interactions, lack of motivation, and anxiety in the mice.**

Cheyette and colleagues first identified a genetic mutation that affects signaling in what is known as the brain's Wnt pathway. The mutation, while rare, is 80% more common in people with bipolar disorder, autism, and schizophrenia than in people without these disorders.

When the mice were given a similar mutation, they exhibited symptoms such as anxiety, decreased sociability, and lack of motivation. They also had reduced numbers of dendritic spines and impaired Wnt signaling.

Lithium can improve Wnt signaling by blocking an enzyme called GSK-3 beta that impairs the signaling.

Treating the mice with lithium restored their dendritic spines and improved their behavior.

Wnt signaling and dendritic spines may offer the key to lithium's success in treating a variety of psychiatric disorders in people.



## Lithium May Reduce Cancer Risk

New research suggests that cumulative exposure to lithium may correlate with reduced cancer risk in patients with bipolar disorder. A 2016 article by Yi-Hsin Yang and colleagues in the *British Journal of Psychiatry* reports findings from a Taiwanese population database study of 4,729 adult patients with bipolar disorder, 115 of whom were diagnosed with cancer. **Those who had been prescribed lithium (with or without anticonvulsants) had lower rates of cancer (1.96%) than those who received only anticonvulsants (2.65%).**

Incidence of cancer was higher among the patients with bipolar disorder than the general population in the study. Other studies have indicated that cancer risk is higher among people with bipolar disorder than those without.

Those people who took a recommended maintenance lithium dose for 215 days or longer had a 44.8% lower risk of cancer than those who took only anticonvulsants.

## Mood Stabilizers with Atypical Antipsychotics Reduce Relapses Compared to Mood Stabilizers Alone or with Typical Antipsychotics

An Israeli study reports that treatment with mood stabilizers and atypical antipsychotics reduces bipolar relapses compared to treatment with mood stabilizers alone or mood stabilizers combined with typical antipsychotics. The study, by Eldar Hochman and colleagues in the journal *Bipolar Disorders*, compared one-year hospitalization rates after patients with bipolar disorder were discharged from the hospital following a manic episode. All of the 201 discharged patients were prescribed a mood stabilizer (lithium or valproate), and some were also prescribed an antipsychotic, either atypical or typical.

**Those participants who received the combination of a mood stabilizer and an atypical antipsychotic had re-hospitalization rates of 6.3% compared to 24.3% of those who received mood stabilizers alone and 20.6% of those who received mood stabilizers with a typical antipsychotic.**

While the study did not determine which treatment is best for ongoing maintenance treatment of bipolar disorder, it does suggest that the combination of mood stabilizers and atypical antipsychotics can reduce hospitalizations during the one-year period following a manic episode.

## Therapy Reduces Relapses, Promotes Medication Adherence

A 2017 meta-analysis published in the *British Journal of Psychiatry* indicates that psychosocial interventions were linked to reduced relapse rates, better adherence to medication, and other benefits in people with bipolar disorder. The meta-analysis by researcher Mary Lou Chatterton and colleagues evaluated data from 41 studies with a total of 3,119 participants. The studies examined psychosocial interventions such as cognitive-behavioral therapy, psychoeducation, and family-focused therapy compared to treatment as usual.

Chatterton and colleagues found that **interventions that targeted family members who act as caregivers reduced manic and depressive relapse rates. Combined psychoeducation and cognitive-behavioral therapy was more successful than any other intervention, and had a large effect in reducing symptoms of mania.** This combination also improved general functioning. Psychoeducation alone and in combination with cognitive behavioral therapy reduced medication non-adherence. Unfortunately, no intervention reduced depressive symptoms.

## Specific Regions of Hippocampus Linked to Bipolar Disorder

It has been clear for some time that the volume of the hippocampus, a brain region implicated in mood and memory processing, plays a role in bipolar disorder. A 2017 article by researcher Bo Cao and colleagues in the journal *Molecular Psychiatry* links loss of volume in specific sub-regions of the hippocampus with bipolar disorder.

The study by Cao and colleagues used magnetic resonance imaging (MRI) and a special segmentation technique to compare the volume of certain hippocampal sub-regions across people with bipolar disorder, people with major depression, and healthy control participants.

**Participants with bipolar disorder had lower volumes in subfield 4 of the cornu ammonis, two cellular layers (the granule cell layer and the molecular layer), and the tail part of the seahorse-shaped hippocampus compared to the other subjects. Participants with bipolar I disorder had particularly severe volume loss in these areas.**

Cao and colleagues also found that volume loss progressed along with the illness. The volumes of the right cornu ammonis, the molecular layer, and the subiculum decreased further in patients who had bipolar disorder for longer. As manic episodes increased, the volume of both sides of the cornu ammonis and the hippocampal tail decreased.

## Recent Birth Cohorts May Have More Depression and Bipolar Disorder

In medicine, the 'cohort effect' describes the idea that more recent birth cohorts have an increased incidence and younger age of onset of their illness. A 2016 article by this editor (Robert M. Post) and colleagues in the *Journal of Clinical Psychiatry* presented evidence that younger patients with bipolar disorder have an earlier age of onset of bipolar disorder and more relatives with mood disorders than older patients with bipolar disorder.

The research was carried out by the Bipolar Collaborative Network in four US cities (Dallas, Cincinnati, Los Angeles, and Bethesda) and three northern European ones (Utrecht, Freiburg, and Munich). On both continents, **patients born more recently had an earlier age of onset of their bipolar disorder. Younger patients also had parents and grandparents with a greater incidence of depression, bipolar**

**disorder, and alcohol and substance abuse compared to older patients.**

*Editor's Note: Other researchers have found evidence of a cohort effect for unipolar depression, substance abuse, and attention-deficit hyperactivity disorder (ADHD). The data indicate that childhood onset of psychiatric illnesses may be becoming more common. Research aimed at earlier detection and treatment is needed to reverse these trends.*

## Adherence to Antidepressants Associated with Lower Mortality

A large study from Israel suggests that **over a 4-year period, people who regularly took their prescribed antidepressants were less likely to die of any cause during that period.**

The study, published in the *Journal of Clinical Psychiatry* in 2016, used data from an Israeli health provider that covers 53% of the nation's population. It included 251,745 patients aged 40 and up who filled a prescription for an antidepressant at least once between 2008 and 2011.

Researchers led by Amir Krivoy looked at how much of the time people actually filled their prescriptions. Patients who filled their prescriptions more of the time were less likely to die during the study period than those who did not fill their prescriptions regularly.

*Editor's Note: This study by Krivoy and colleagues provides more evidence of the benefit of long-term antidepressants. People who have had two or three episodes of unipolar depression should consider long-term prevention with antidepressants over the course of their lifetime, in the way that people take blood pressure medications long-term to prevent heart attacks. In addition to lowering mortality, antidepressants also reduce the rate of relapse by 75% compared to placebo. More time on antidepressants also preserves hippocampal volume with aging.*

## Parents' History of Mood and Anxiety Disorders Increases Risk of These Disorders in Offspring

A 2016 article by researcher Petra J. Havinga and colleagues in the *Journal of Clinical Psychiatry* suggests that offspring of a parent with a mood or anxiety disorder are at higher risk for these disorders than offspring from non-ill parents. Havinga and colleagues studied 523 offspring of parents with one of these disorders. **Among these offspring, 38.0% had had a mood or anxiety disorder by age 20, and 64.7% had had such a disorder by age 35. (Rates of these disorders in the general population are closer to 10%.)**

The risk of offspring developing one of these disorders was even higher when both parents had a history of a mood or anxiety disorder, when a parent had an early onset of one of these illnesses, and when the offspring was female. The good news is that balanced family functioning had a protective effect, reducing the likelihood that the offspring would develop a mood or anxiety disorder.

Researcher David Axelson reported in a 2015 study published in the *American Journal of Psychiatry* that approximately 74% of the offspring of a parent with bipolar disorder went on to have a major psychiatric diagnosis over 6.7 years of followup. Similarly, researcher Myrna Weissman and colleagues reported in 2006 that the same high incidence of psychiatric diagnoses was true of the offspring of a parent with unipolar depression over 20 years of followup.

*Editor's Note: It is important to be vigilant for mood or behavioral disorders that may emerge in the offspring of a parent with a mood or anxiety disorder. Children at high risk should maintain a healthy diet and good sleep hygiene, exercise regularly, and perhaps try practicing mindfulness and meditation, as recommended by researcher Jim Hudziak. Family-focused therapy (developed by researcher David Miklowitz) can help when early symptoms appear in the offspring of a parent with bipolar disorder.*

Another option is joining our Child Network, a secure online program that allows parents to track their children's symptoms of anxiety, depression, attention-deficit hyperactivity disorder (ADHD), oppositional behavior, and mania. This may facilitate earlier recognition and treatment of dysfunctional symptoms, which can be treated with psychotherapy and medication.



## More News About Genetic Risk for Bipolar Disorder

In a 2017 article in the *Journal of Clinical Psychiatry*, researcher Paul E. Croarkin and colleagues describe findings from their study of genetic risk factors for early-onset bipolar disorder. **The researchers focused on single nucleotide polymorphisms (SNPs), which are variations in a single base pair of a DNA sequence.** SNPs are normal variations or copying errors that occur when DNA is replicated. Croarkin and colleagues tracked 8 SNPs that had been linked to bipolar disorder in previous studies. They examined 69 patients from a study of early-onset mania, 732 adult patients with bipolar disorder (including 192 with early-onset illness), and 776 healthy controls. The researchers compared patients with early-onset illness to controls, and also looked for connections between specific SNPs and early-onset illness.

The SNPs analyzed in the study map to three genes that have repeatedly been associated with the risk for bipolar disorder in other studies. These include CACNA1C (one of several genes that create calcium channels), ANK3, and ODZ4. **Croarkin and colleagues determined that the presence of these SNPs, particularly the ones that involved**

**the CACNA1C gene, were associated with early-onset bipolar disorder.**

*Editor's Note: These findings may lead to better treatment for early-onset bipolar disorder. The CACNA1C calcium influx gene that has repeatedly been connected to bipolar illness can be blocked by the calcium channel blocker nimodipine. Nimodipine has lithium-like effects in mania and depression in adults. One case report by Pablo A. Davanzo in the Journal of Child and Adolescent Psychopharmacology described success using nimodipine and the thyroid medication levothyroxine to treat a 13-year-old boy with very rapid cycling bipolar disorder that had previously failed to respond to multiple medications.*

*Nimodipine deserves further study in children showing symptoms of bipolar disorder. The company Genomind provides testing for the CACNA1C gene. We hope it will soon be determined whether the presence of this SNP predicts a good response to nimodipine.*

*Being able to predict who will get bipolar disorder is a long way off. However, there are some clear risk factors. Young people from families that have had several genera-*

*tions of bipolar disorder or related disorders are at increased risk for bipolar disorder. This risk increases for children who experience adversity in childhood, such as abuse or neglect. The presence of early mild symptoms of mania, depression, or disruptive behavior further increase this risk.*

*For doctors, a patient's clinical history of these three types of risk factors can help identify whether they are at increased risk of developing bipolar disorder. Patients with several risk factors should be observed closely and treated with psychotherapy or medication as needed.*

*Parents of children between the ages of 2 and 12 who have shown some signs of mood or behavioral symptoms are encouraged to join our Child Network. We provide a secure online platform where parents record their children's symptoms of anxiety, depression, attention-deficit hyperactivity disorder (ADHD), oppositional behavior, and mania on a weekly basis. Symptoms are charted over time in a graphical depiction that can be shared with the child's doctor. For more information, see page 11 of this issue. To join, visit our website bipolarnews.org and click on the tab for the Child Network.*

### It's now faster and easier to join the Child Network!

The consent form for the Child Network has been simplified. If you previously tried to sign up and gave up in frustration, **please try again.** The new consent form is much easier to complete.

The Child Network is a study designed to evaluate how children with mood disorders are being treated for their illness. Parents who enroll in the study complete an online checklist of their child's symptoms once a week using a secure web-based system. Parents of children aged 2–12 who have mood or behavioral problems should consider joining. See page 11 for more information.

As a benefit, parents can print out a chart of their child's symptoms and responses to treatment to show the children's physician. This should facilitate early recognition and treatment of a range of common psychiatric disorders that begin in childhood.

## Immune Therapy with IVIG May Help Children with PANDAS

**A small number of children exposed to streptococcal bacteria have an autoimmune response that manifests in sudden, severe obsessive-compulsive behaviors and tics. This disorder is known as PANDAS:** pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, and it resembles the broader disorder PANS, which can occur after other types of bacterial or viral infections.

Research on treatments for PANDAS and PANS is scant, but therapies that target the immune system seem to have more success than typical psychiatric treatments. In a 2015 article in the *Journal of Child and Adolescent Psychiatry*, researcher Miro Kovacevic

and colleagues described a case series of 12 youths with PANDAS who were treated with intravenous immunoglobulin (IVIG), a treatment designed to regulate the immune system. (The participants also met diagnostic criteria for PANS.)

The authors suggest that **PANDAS symptoms result from a misdirected immune response that attacks the patient's brain instead of or in addition to attacking the initial infection.** IVIG treatment uses a mixture of antibodies from about 1,000 people. When this mixture is infused into the patient's blood, the antibodies help deflect the autoimmune attack on the patient's body. All of the 12 patients had a good

long-term response to IVIG. Some did well after just one infusion, while two needed a second infusion because they did not respond to the first, and five had recurring symptoms that required a second infusion. All of the patients had previously received two other types of treatment: a 5-day course of steroids and antibiotics, neither of which produced immediate improvements.

The authors concluded that effective long-term treatment of PANS or PANDAS should combine immune therapy, prevention of future infections with antibiotics, and treatment that targets their psychiatric symptoms, such as anti-obsessional medication or cognitive-behavioral therapy.

## Melatonin May Improve Headaches

A 2016 article in the *Journal of Head and Face Pain* reviewed randomized placebo-controlled trials of melatonin for the treatment of headaches. Author Amy A. Gelfand and colleagues reported that **10 mg of melatonin was superior to placebo in the treatment of cluster headaches. For treatment of migraines, 3 mg of immediate-release melatonin improved headaches compared to placebo**, while 2 mg of sustained-release melatonin was insufficient.

The authors also found non-placebo controlled data suggesting that melatonin may be helpful for other types of headaches. More research is needed to clarify melatonin's effects in different headache disorders.

## In Population Near Uranium Plant, Headaches Predicted a Thyroid Problem

People with headache disorders may be at greater risk of developing hypothyroidism, a condition in which the thyroid does not produce enough thyroid hormone and various body processes start to slow down. A study by researcher Andrew Martin and colleagues in the *Journal of Head and Face Pain* is the largest to examine the likelihood that headache sufferers may be at risk for hypothyroidism.

About 2% of Americans develop hypothyroidism. The study by Martin and colleagues used data from a 20-year medical monitoring program for people who lived near a uranium processing plant in Ohio. The authors reported that **people with pre-existing headache disorders had a 21% increased risk of new onset hypothyroidism during that period, while people who reported that they had migraines or regularly used headache medication had a 41% increased risk of hypothyroidism.** People with migraines were most likely to develop hypothyroidism in the study. Female sex and age are additional risk factors for hypothyroidism. About 12% of the US population experiences migraines.

Have you visited us online?

**bipolarnews.org**

## Is Your Child at Risk for a Mood Disorder? Join the Child Network

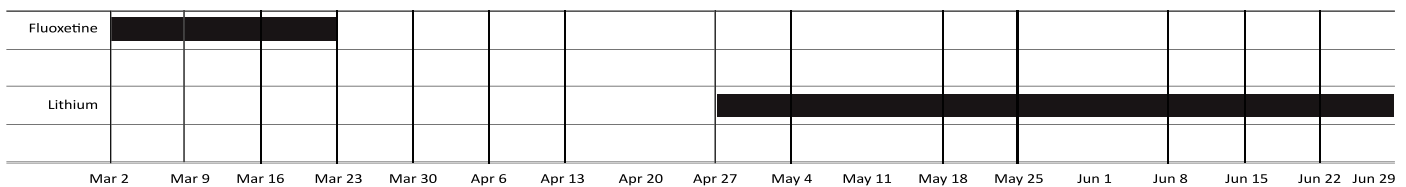
74% of children who have a parent with bipolar disorder (Axelson et al. 2015) and 80% of those who have a parent with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness upon long-term follow up. These illnesses, including depression, anxiety, oppositional behavior, substance abuse, often go unrecognized for long periods of time.

**Joining the Child Network could help families and doctors identify these illnesses earlier.**

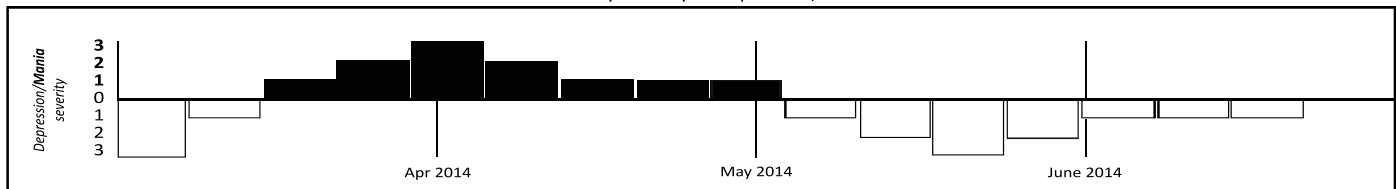
**The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website.** There is also a short demographic questionnaire and a more detailed symptom checklist to be filled out once a year. The network will collect information about which treatments children are already taking, how effective they are, and for which children.

We believe that this network will be helpful to its participants. Parents will be able to print out the ongoing weekly ratings in a graphic form so that the child’s symptoms and responses to any treatments they receive over time can easily be visualized (as illustrated below).

**Weekly Mood and Medication Chart**



**Weekly Severity of Depression/Mania**



- 0 - Severity None: None
- 1 - Severity Mild/Infrequent: Minimal impact on usual roles
- 2 - Moderate Symptoms/Often: Definitely some dysfunction in usual roles
- 3 - Severe Symptoms/Much of the Time: Major dysfunctions in usual roles

We hope that this brief description of the Child Network study helps to orient you to its purpose. Please urge parents to use this new tool. Visit **bipolarnews.org** and click on the tab for the Child Network or go directly to [http://bipolarnews.org/?page\\_id=2630](http://bipolarnews.org/?page_id=2630) to learn more about the Child Network and to access the informed consent documents.

Thank you for your time and interest in the Child Network.

Robert M. Post, MD and Michael Rowe, PhD  
 Bipolar Collaborative Network, and  
 Robert L. Findling, MD, MBA, Principal Investigator  
 This research study is IRB approved by the Johns Hopkins University School of Medicine  
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