

Bipolar Network News

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The latest news on bipolar disorder research from around the world

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Updates from the 2015 Meeting of the American Academy of Child and Adolescent Psychiatry

Vol. 20, Issue 2, 2016

Music, Mindfulness and Exercise Improve Brain Functioning

Psychiatrists should take the lead in endorsing general wellness and encouraging healthy behaviors, says researcher James Hudziak. He suggests that opportunities to practice music, mindfulness, and exercise should be made available to all school children to increase brain health, and that more intensive efforts are necessary for children in families that are at risk for mood and behavioral difficulties or in children who show some dysfunction in these areas. Hudziak has implemented a statewide program in Vermont that encourages families to engage in these healthy practices.

Hudziak and colleagues analyzed brain scans of 232 children ages 6 to 18, looking for relationships between cortical thickness and musical training. They found that **practicing an instrument such as the piano or violin increased working memory, gray matter volume in the brain, and the ability to screen out irrelevant noise. Practicing mindfulness increased white matter volume and reduced anxiety and depression. Exercise also increased brain volume and neuropsychological abilities.**

Now Hudziak urges parents to advocate for the teaching of music, mindfulness, and exercise in schools as a way of improving general health, especially since music and gym are often the first programs to be cut when schools face budget shortages. Hudziak suggests that opportunities for athletics should be provided to all children, independent of their skill level, rather than only for the best athletes who "make the team." Intramural teams

should be open to all children, including those with less ability or minimal athletic skills. Exercise, teamwork, and friendships benefit all children.

For more information about the programs Hudziak implemented in Vermont, use the internet to search for the Vermont Family Based Approach, see his book *Developmental Psychopathology and Wellness: Genetic and Environmental Influences*, or call the University of Vermont Medical Center at (802)847-0000 or (800)358-1144.

Another tool that may be useful to parents of children aged 2 to 12 who are at risk for mood disorders is our Child Network, a secure online portal where parents can complete quick weekly ratings of their child's mood and behavior, which is then graphed over time and can be used to show the child's doctors how his or her symptoms are fluctuating and how well any treatment is working. See ad below for instructions on joining the study.

A STUDY ASSESSING YOUR CHILD'S MOOD AND BEHAVIOR

Parents, if your child (aged 2 – 12) has mood or behavioral difficulties, we would like to enlist your participation in a study called the Child Network. Parents who enroll in the study will complete an online rating checklist of your child's symptoms once a week by a secure web-based system.

In addition, adults who have been diagnosed with depression or bipolar disorder and are the biological parent of a child (ages 2-12) who is currently healthy and has no troublesome mood or behavioral symptoms may also be eligible to participate in this study.



If you are interested in participating in this study, go to <http://bipolarnews.org> and click on the tab for Child Network. For more information, call 301-530-8245, or email questions to childnetworkbnn@gmail.com.

Research Study
Principal Investigator: Robert L. Findling, MD, MBA
IRB Study #00026940

Family-Based Health Program Successful in Vermont

A statewide program to promote healthy behaviors within families has been successful in Vermont. The approach, described by researcher James J. Hudziak at the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, is based on three assumptions. The first is that emotional and behavioral health is the cornerstone of all health. The second is that health behaviors are formed and sustained within families. The third is that

promoting healthy behaviors, preventing illness, and intervening for better health outcomes are all important to enhancing the health of the population.

Vermont used community outreach (including town-hall public events), the media (including Twitter, blogs, radio, television, public service announcements, and a short film), and group trainings of community professionals to successfully spread health messages to families. The

program targeted pediatricians' offices, schools, community mental health centers, federally qualified health centers, and Departments of Health, Mental Health, and Child Welfare.

Hudziak has also suggested that programs of exercise, music, and mindfulness (all of which enhance brain growth and development) should be made universally available to children in school.

Bipolar Network News

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

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact 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*.

As per recent journal disclosure requirements, Dr. Post has consulted with drug companies including 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.

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Exercise Improves Cognition and Normalizes Brain Activity

Exercise isn't just good for the body – new research suggests it can improve cognition and normalize brain activity.

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Benjamin I. Goldstein reported that **20 minutes of vigorous exercise on a bike improved cognition and decreased hyperactivity in the medial prefrontal cortex in adolescents with and without bipolar disorder.**

At the same meeting, researcher Danella M. Hafeman reported that offspring of parents with bipolar disorder who exercised more had lower levels of anxiety.

A plenary address by James J. Hudziak also suggested that exercise,

practicing music, and mindfulness training all lead to improvements in brain function and should be an integral part of treatment for children at high risk for bipolar disorder and could be beneficial for all children.

Editor's Note: Recognizing and responding to mood symptoms is key to the prevention and treatment of bipolar disorder in children and adolescents at high risk for the illness. For these young people, exercise, a nutritious diet, good sleep habits, and family psychoeducation about bipolar disorder symptoms may be a good place to start. Joining our Child Network may also be helpful.

Omega-3 Fatty Acids Associated with Small Improvement in Depression in Children Aged 7–14

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Mary A. Fristad reported that omega-3 fatty acid supplements had a small beneficial effect on depression in children aged 7–14. The supplements did not noticeably improve bipolar disorder

not otherwise specified (NOS) or mania. The supplements consisted of several types of omega-3 fatty acids, including 1400mg of EPA, 200mg of DHA, and 400mg of others per day. The children were also undergoing psychotherapy during the study.

Depression and Obesity Linked in Study of Mexican Americans

A 2015 study by Rene L. Olvera and colleagues in the *Journal of Clinical Psychiatry* indicated that among 1,768 Mexican-Americans living along the border from 2004–2010, 30% were currently depressed, 14% had severe depression, and 52% were obese. Women were more likely to be depressed, and more likely to have severe depression. Other factors making depression more likely included low education, obesity, low levels of “good” cholesterol, and larger waist circumference. Low education and extreme obesity were also linked to severe depression.

In a commentary on the article in the same issue, researcher Susan L. McElroy wrote that **“the medical field needs to firmly accept that obesity is a risk factor for depression and, conversely, that depression is a risk factor of obesity.”** She suggested that people with obesity, those who carry excess weight around their middles, and those who have related metabolic symptoms such as poor cholesterol should all be evaluated for depression. Likewise, those with depression should have their weight and body measures monitored. People with both obesity and depression should be evaluated for disordered eating.

Inflammation Linked to Bipolar Illness in Young People

The Course and Outcome of Bipolar Youth study, or COBY, has been collecting information on young people with bipolar disorder and tracking their symptoms into adulthood since 2000. A 2015 study by Benjamin I. Golstein in the *Journal of Clinical Psychiatry* analyzed COBY data, identifying links between higher than average levels of inflammatory markers measured in the blood and participants’ histories of illness and familial risk factors.

High levels of the inflammatory marker hsCRP were associated with longer duration of illness, substance use disorder, and family history of suicide attempts or completed suicides. High levels of TNF-alpha were linked to suicide attempts, self-injury behaviors, and family history of substance use disorders. IL-6 was also linked to family history of substance use disorders.

There were also links between inflammatory markers and participants’ symptoms over the 6 months leading up to the blood tests. Levels of the inflammatory marker TNF-alpha were linked to the percentage of weeks patients had psychotic symptoms. Levels of IL-6 were associated with percentage of weeks with subthreshold mood symptoms and also with any suicide attempt. Levels of HsCRP were linked to maximum severity of depressive symptoms.

It is possible that targeting the elevated levels of inflammatory markers with anti-inflammatory treatments could improve patients’ response to treatments, but this topic requires further study.

Vitamin D3 Reduces Symptoms of Bipolar Spectrum Disorders

Vitamin D3 tends to be low in children and adolescents with mania, but supplements may help. In a small open study published in the *Journal of Child and Adolescent Psychopharmacology* in 2015, Elif M. Sikoglu and colleagues administered 2000 IU of vitamin D3 per day to youth aged 6–17 for eight weeks. Sixteen of the participants had bipolar spectrum disorders (including subthreshold symptoms) and were exhibiting symptoms of mania. Nineteen participants were typically developing youth.

At the beginning of the study, the youth with bipolar spectrum disorders had lower levels of the neurotransmitter GABA in the anterior cingulate cortex than did the typically developing youth. **Following the eight weeks of vitamin D3 supplementation, mania and depression symptoms both decreased in the youth with bipolar spectrum disorders, and GABA in the anterior cingulate cortex increased in these participants.**

Editor’s Note: GABA dysfunction has been implicated in the manic phase of bipolar disorder. While larger controlled studies of vitamin D supplementation are needed, given the high incidence of vitamin D deficiency in youth in the US, testing and treating these deficiencies is important, especially among kids with symptoms of bipolar illness.

L-methylfolate Improves Depression; More Effective in Overweight Patients with Inflammation

A 2012 study by George I. Papkostas and colleagues found that 15mg/day of the nutritional supplement l-methylfolate calcium (a form of the B vitamin folate that the body can more readily use) improved depression in people who had not responded adequately to treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant. In a follow-up study by Richard C. Shelton and colleagues published in the *Journal of Clinical Psychiatry* in 2015, the same researchers further analyzed these data and found that **l-methylfolate worked better in patients who were overweight (with body mass indexes (BMIs) of 30 or above) and those who had higher than average levels of inflammation** at the beginning of the study. Inflammatory markers linked to greater improvement with l-methylfolate included TNF-alpha, IL-8, high sensitivity CRP, and leptin. In overweight participants, higher than average levels of IL-6 were also linked to more improvement on l-methylfolate.

Children of Bipolar Parents in US More Ill than Those in the Netherlands

New research shows that bipolar disorder risk is higher in the US than in the Netherlands. At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researchers Manon Hillegers and Esther Mesman described a study in which they compared the offspring of mothers with bipolar disorder in the US to those in the Netherlands. The offspring ranged in age from 10–18.

In the US, the mothers had, on average, an earlier age of onset, more substance abuse comorbidity, and were more likely to have been diagnosed with bipolar II disorder. Among the US offspring, 66% had been diagnosed with a psychiatric illness compared to 44% of the Dutch offspring. **This included significantly higher rates of anxiety, ADHD, and disruptive be-**

havior disorders in the US offspring. Among the offspring who had been diagnosed with a mood disorder, 80% of those in the US had other additional psychiatric disorders, but only 34% of the Dutch did. Bipolar disorder is more rare among children under the age of 12 in the Netherlands compared to the US.

Dutch children and adolescents were typically treated with lithium and with only one drug at a time. In the US, lithium is less widely used, and simultaneous treatment with several medications (usually including atypical antipsychotics) is common.

Editor's Note: The research by Hillegers and Mesman replicates research by this editor (Robert M. Post) and colleagues that compared bipolar disorder incidence and severity in the US, Germany, and the Netherlands. Other comparisons have been

made between the US and Europe. A 2014 article by Frank Bellivier and colleagues in the World Journal of Biological Psychiatry also showed that bipolar disorder onset occurs earlier in the US than in 10 different European countries, while Bruno Etain and colleagues found that bipolar disorder onset occurs earlier in the US than in France in a 2012 article in the Journal of Clinical Psychiatry.

Together this research shows that bipolar disorder is more serious in the US than in a number of European countries. Two-thirds of US adults with bipolar disorder report that their illness began in childhood or adolescence. Most of these cases are not properly diagnosed or treated. A concerted effort must be made by the medical establishment and healthcare policymakers in the US to provide better and earlier treatment of bipolar illness.

Children at Risk for Bipolar Disorder May Have Adverse Reactions to Antidepressants

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Jeffrey R. Strawn reported that among children at high risk for bipolar disorder (because of a family history of the disorder) who are prescribed antidepressants for depression and anxiety, adverse reactions are common. **These reactions include irritability, aggression, impulsivity, and hyperactivity,** and often lead to discontinuation of the antidepressant treatment.

Younger patients at risk for bipolar disorder were more likely to have an adverse reaction to antidepressants. Risk of an adverse reaction decreased 27% with each year of age.

Offspring of Parents with Bipolar Disorder at High Risk for Psychiatric Disorders

Researcher Juan David Palacio reported at the 2015 meeting of the American Academy of Child and Adolescent Psychiatry that compared to offspring of non-ill parents, children of parents with bipolar I disorder are at high risk for psychiatric disorders, particularly bipolar spectrum disorders and substance use disorders. They were also at risk for symptoms of anxiety disorders and conduct disorder. Palacio's findings from Colombia mirror those from other studies of familial risk and suggest the importance of vigilance to detect these disorders early and provide appropriate treatment. Joining the Child Network could help. See ads on pages 1 and 8.

Topiramate Added to Quetiapine Can Reduce Marijuana Craving in Young People

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Melissa P. DelBello reported that compared to placebo, the anticonvulsant topiramate reduced marijuana craving in young people aged 12–21 who were already taking the antipsychotic quetiapine. **Functional magnetic resonance imaging (fMRI) revealed that topiramate altered the activation of brain regions common to both drug craving and mood dysregulation.** Topiramate could be a good treatment to reduce marijuana abuse. The antioxidant n-acetylcysteine (NAC) is another option.

Diagnosing PANS

Pediatric Acute-Onset Neuropsychiatric Syndrome, or PANS, describes a condition in which a child develops acute onset of psychiatric symptoms following an infection. At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Tanya K. Murphy reported on symptoms that differentiate PANS from other childhood-onset illnesses. Kids with PANS are more likely to have:

- sudden onset of symptoms
- earlier age of onset
- personality changes
- new onset of attention deficit hyperactivity disorder (ADHD) symptoms
- food refusal and weight loss
- behavioral regression
- deterioration in handwriting
- severe sleep disruption
- psychosis
- memory problems
- frequent urination
- dilated pupils
- an infection at the time of onset, particularly a group A streptococcal infection

A child with sudden onset of these symptoms following an infection may have PANS. It is important to differentiate PANS from traditional psychiatric diagnoses because treatment of PANS often consists of antibiotics, anti-inflammatory medications, and other treatments that target the immune system. See our case report about a boy with PANS in BNN Volume 19, Issue 6 from 2015.

Micronutrient Formulas Treat A Variety of Behavioral Disorders

At the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Charles Popper reviewed the literature to date about broad-spectrum micro-nutrient treatments for psychiatric disorders in young people, concluding that these formulations of vitamins and minerals can reduce symptoms of aggressive and disordered conduct, attention deficit hyperactivity disorder, mood disorders, anxiety, and stress. Four randomized controlled trials showed that micronutrient formulas reduced violence and major misconduct in children.

Popper warned that while these micronutrients can be helpful in treating children who have never been prescribed psychiatric medication, they can interact dangerously with psychiatric medications in children who do take them.

At the same meeting, researcher Bonnie Kaplan reported that six randomized controlled trials of broad-spectrum micro-nutrients and B-complex vitamins in adults with and without psychiatric disorders showed that both of the formulas reduced anxiety and stress following natural disasters (which are associated with the development of post-traumatic stress disorder (PTSD)).

Successful Double-Blind Placebo-Controlled Study of Lithium for Acute Mania in Kids 7–17

Lithium is the treatment of choice for adults with bipolar disorder, but has rarely been studied in children or adolescents. One of the first double-blind placebo-controlled trials of lithium for the treatment of mania in children and teens aged 7–17 showed that the drug produced greater improvement in mania than did placebo. Side effects included blurred vision, abdominal pain, diarrhea, nausea, vomiting, fatigue, thirst, increased thyroid-stimulating hormone, decreased appetite, dizziness, sedation, tremor, increased urination, and rash.

In the study by researcher Adelaide S. Robb and colleagues, which was presented at the 2015 meeting of the American Academy of Child and Adolescent Psychiatry, doses began at 300mg twice a day, were based on each child's weight, and were slowly increased.

At the same meeting, researcher Russell Scheffer presented data on 41 children who continued lithium treatment for 16 weeks with good results. The mean dose was 27.8 +/- 6.7 mg/kg per day.

RTMS Improves Executive Function in Kids with Schizophrenia and Autism

Researcher Stephanie Ameis reported at the 2015 meeting of the American Academy of Child and Adolescent Psychiatry that following repeated transcranial magnetic stimulation (rTMS), a treatment in which a magnetic coil placed over the scalp delivers electric pulses to the brain, children with schizophrenia and autism spectrum disorders showed improvements in executive function, including working memory. The rTMS treatment targeted the left dorsolateral prefrontal cortex.

Cool News: Raising Body Temperature Can Relieve Depression

Raising body temperature by a few degrees may produce antidepressant effects as the body's cooling mechanisms kick in. At the US Psychiatric and Mental Health Congress in 2015, researcher Charles Raison described a study comparing the effects of exposing participants to a special heating coil in a tent that retained the heat until their body temperatures increased by a few degrees to those of a sham procedure that did not raise body temperature. Those participants whose body temperature was increased had a lower body temperature the following day, and their depression improved as their bodies cooled. These improvements lasted six weeks or more.

Depressed patients tend to have elevated body temperatures. Raison suggests that raising body temperatures even more prompts the body's cooling mechanisms to compensate, bringing cooling activity to normal levels from the skin to the brain and improving depression.

**See page
right for an
opportunity
to rate
children's
mood or
behavioral
symptoms.**

Light Therapy Effectively Treats Non-Seasonal Depression

Doctors have known for some time that treatment with high-intensity light (7,000–10,000 Lux) can improve seasonal depression. In an 8-week study published in the journal *JAMA Psychiatry* in 2015, researcher Raymond Lam compared four different treatment options for non-seasonal major unipolar depression: bright light therapy for 30 minutes per day first thing in the morning, 20 mg of the antidepressant fluoxetine per day, combined bright light therapy and fluoxetine, and a placebo device paired with a placebo pill.

The combination of bright light therapy and fluoxetine produced remission in 58.6% of the participants who received it, compared to remission rates of 43.8% for bright light alone, 19.4% for fluoxetine alone, and 30% for placebo. It is notable that the effects of fluoxetine did not exceed those of placebo, but the effects of light alone did. There were few side effects in any group.

These data provide convincing evidence of the efficacy of light therapy in the treatment of non-seasonal unipolar depression. Use of light therapy for non-seasonal depression should now be more routinely considered, particularly when combined with antidepressant treatment.

Patients who had previously failed to respond to two or more antidepressants and patients with bipolar depression were excluded from the study. Bright light therapy administered in the morning can sometimes bring about mixed states in people with bipolar disorder. A 2007 case study by D. Sit and colleagues in the journal *Bipolar Disorders* found that midday light led to more improvement and less risk of mixed states than morning light among women with bipolar disorder.

Oxytocin May Reduce PTSD Symptoms

The hormone oxytocin, best known for creating feelings of love and bonding, may help treat post-traumatic stress disorder, since it also reduces anxiety. A study by Saskia B.J. Koch and colleagues that will soon be published in the journal *Neuropsychopharmacology* reports that a single intranasal administration of oxytocin (at a dose of 40 IU) reduced anxiety and nervousness more than did placebo among police officers with PTSD.

Oxytocin also improved abnormalities in connectivity of the amygdala. Male participants with PTSD showed reduced connectivity between the right centromedial amygdala and the left ventromedial prefrontal cortex compared to other male participants who had also experienced trauma but did not have PTSD. This deficit was corrected in the men with PTSD after they received a dose of oxytocin. Female participants with PTSD showed greater connectivity between the right basolateral amygdala and the bilateral dorsal anterior cingulate cortex than female participants who had experienced trauma but did not have PTSD. This was also restored to normal following a dose of oxytocin.

These findings suggest that oxytocin can not only reduce subjective feelings of anxiety in people with PTSD, but may also normalize the way fear is expressed in the amygdala.

Additional Information about the Child Network:

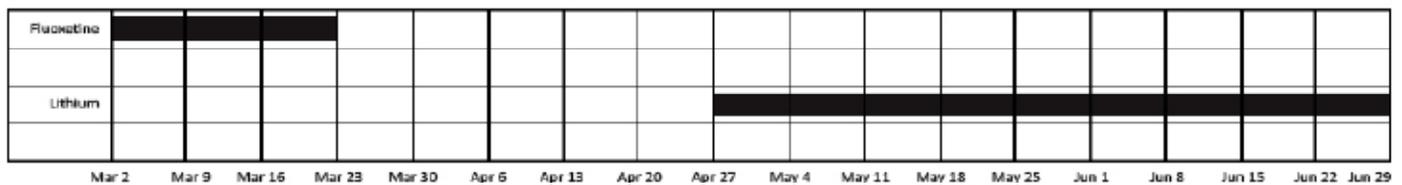
74% of children who have a parent with bipolar disorder (Axelson et al. 2015) and 80% of those who have a parent with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness upon long-term follow up. These illnesses, including depression, anxiety, oppositional behavior, substance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

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

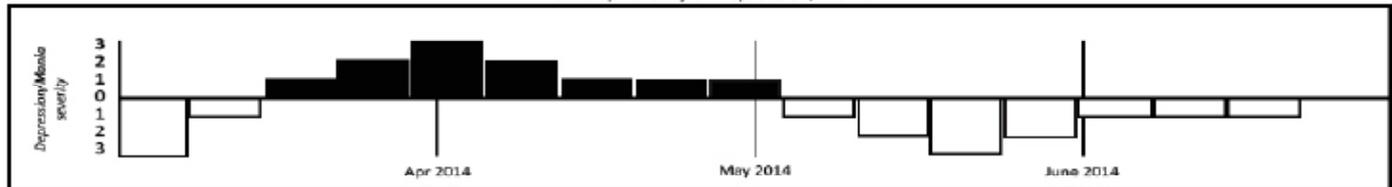
The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographics questionnaire and a more detailed symptom checklist to be filled 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 <http://bipolarnews.org> and click on the tab for the Child Network or 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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