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Bipolar Network News

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Teens with Bipolar Disorder at Increased Risk for Cardiovascular Disease

A scientific statement from the American Heart Association reported in 2015 that youth with major depressive disorder and bipolar disorder are at moderate (Tier II level) increased risk for cardiovascular disorders. The combined prevalence of these illnesses in adolescents in the US is approximately 10%.

There are many factors that contribute to this risk, including inflammation, oxidative stress (when the body falls behind neutralizing harmful substances produced during metabolism), dysfunction in the autonomic nerve system, and problems with the endothelium (the inner lining of blood vessels). Lifestyle factors including adversity in early life, sleep disturbance, sedentary lifestyle, poor nutrition, and abuse of tobacco, alcohol, or other substances.

Taking some atypical antipsychotics as treatment for bipolar disorder also contributes to the risk of cardiovascular problems by increasing weight and/or lipid levels. Among the atypicals, ziprasidone (Geodon) and lurasidone (Latuda) come with the lowest likelihood of weight gain.

The statement by Benjamin I. Goldstein and colleagues that appeared in the Heart Association-affiliated journal *Circulation* suggested that **therapeutic interventions should address some of these risk factors to help prevent cardiovascular problems and improve life expectancy for young people with depression or bipolar disorder.** These could include a good diet, regular exercise, and treatments with good long-term tolerability that are aimed at preventing episodes.

The Role of Inflammatory Markers and BDNF

Inflammation worsens the risk of cardiovascular problems, while brain-derived neurotrophic factor (BDNF), which protects neurons and plays a role in learning and memory, may improve prospects for someone with depression or bipolar disorder.

A 2017 article by Jessica K. Hatch and colleagues including Goldstein in the *Journal of Clinical Psychiatry* suggests that inflammation and BDNF are mediators of cardiovascular risk in youth with bipolar disorder. The study looked at 40 adolescents with bipolar disorder and 20 healthy controls.

Those with bipolar disorder had greater waist circumference, body mass index, and pulse pressure than the controls. The youth with bipolar disorder also had higher levels of the inflammatory cytokine Il-6. Participants who had lower BDNF had greater thickness of the carotid vessel internal lining (intima media).

Hatch and colleagues point to the importance of prevention strategies in adolescents with these indicators of increased cardiovascular risk. These data complement the American Heart Association's recognition of adolescent mood disorders as a large problem that deserves wider attention both in psychiatry and in the media.

In This Issue:

and more!

Depression Increases Heart Disease Risk to Same Extent That Obesity, High Cholesterol Do

In men, depression seems to be equal to obesity and high cholesterol in increasing heart disease risk. A German study about heart disease risk included 3,428 men between the ages of 45 and 74 who were observed over a period of 10 years.

In an article in the journal *Atherosclerosis*, lead researcher Karl-Heinz Ladwig reported that while high blood pressure and smoking are the most powerful risk factors for fatal cardiovascular disease, depression is comparable to obesity and high cholesterol levels. **Depression accounts for about 15% of cardiovascular deaths.**

Ladwig suggests that depression screening should be standard in patients with other risk factors for heart disease.

Editor's Note: Long-term preventive treatment for depression may have the added benefit of preventing heart attacks. In people with two prior depressions, most guidelines now recommend lifetime continuation of antidepressant treatment.

In Case Control Study, Two-Thirds of Patients With Severe Depression Had Underlying Metabolic Abnormalities

A recent study suggests that potentially treatable metabolic abnormalities in the central nervous system may underlie a large proportion of cases of severe, treatment-resistant depression. These abnormalities, such as folate deficiency in the cerebrospinal fluid, are not screened for regularly, as they require a spinal tap to diagnose.

Researchers led by Lisa A. Pan were inspired to assess metabolic function in people with treatment-resistant depression after a young patient with severe, persistent depression who had attempted suicide several times improved dramatically after being diagnosed with a tetrahydrobiopterin deficiency in his cerebrospinal fluid and treated for the deficiency. Tetrahydrobiopterin is critical to the production of monoamine neurotransmitters.

The researchers carried out a case-control study of 33 teen and young adult patients who had had treatment-resistant depression since childhood and 16 healthy control participants. **Twenty-one of the 33 patients with severe depression had metabolic abnormalities in their cerebrospinal fluid. Twelve had cerebral folate deficiencies (but no folate deficiency in blood tests).** Those who took folinic acid for at least six weeks (1–2 mg/kg/day) in addition to their regular medications showed sometimes dramatic improvement in their depression.

Other metabolic issues identified in the patients with severe depression included abnormal levels of acylcarnitine in five patients, low tetrahydrobiopterin intermediates in one, low guanidinoacetate in another, and unusual creatine/creatinine ratios in three patients. None of the healthy participants had any metabolic abnormality.

While the study, published in the *American Journal of Psychiatry* in 2017, was small, it suggests that the underlying causes of some severe depression cases are going undiagnosed and untreated. The authors suggest that assessment of metabolic function should be more common in cases of severe treatment-resistant depression.

Bipolar Disorder and Diabetes Linked

A systematic literature review in 2016 showed a definitive link between bipolar disorder and diabetes. **Bipolar disorder almost doubles the risk of diabetes while diabetes more than triples the risk of bipolar disorder.** The article by Ellen F. Charles and colleagues was published in the *International Journal of Bipolar Disorders*.

The review included seven large cohort studies. The studies, based on elderly populations only, examined bipolar disorder and diabetes rates. Charles and colleagues suggested that shared mechanisms could cause both illnesses. New disease models that explain the link between bipolar disorder and diabetes could lead to better treatments.

The review also reported that both bipolar disorder and diabetes were independently associated with risk of cognitive decline and dementia in these elderly individuals. People with diabetes had more brain atrophy on average than others who share their age and gender but did not have diabetes. People with bipolar disorder who also had diabetes and either insulin resistance or glucose intolerance had neurochemical changes in the prefrontal cortex that indicated poor neuronal health. In some cases, these patients also had reduced brain volume in the hippocampus and cortex.

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Statins Have Many Benefits

Patients with mood disorders and elevated lipids, cholesterol, or triglycerides can get several benefits by taking statin drugs. **Patients with depression are at increased risk for cardiovascular disease, heart attack, and stroke, and statins can lower these risks.** Statins lower cholesterol and triglycerides.

Compared to women not taking statins, women taking this class of medications have a lower risk of depression. Men taking statins have a lower incidence of depression following a heart attack than men who are not taking statins.

Several studies over the past two decades have suggested that statins can also decrease the incidence of Alzheimer's disease, though a 2017 article by Julie M. Zissimopoulos and colleagues in the journal *JAMA Neurology* suggested the effectiveness of statins in preventing Alzheimer's may depend on the race and gender of the person taking them. People with depression are at increased risk for Alzheimer's.

Editor's Note: Given these many benefits, it may be a good idea for patients with depression or bipolar disorder and high lipid levels to talk to their physician about whether statins would be a helpful treatment for them.

Some Drugs for Hypertension Come with Greater Risk of Mood Disorders

Depression and bipolar disorder have been linked to atherosclerosis, the accumulation of fats, cholesterol, and plaques on the walls of the arteries. There is some evidence that drugs to treat hypertension may contribute to mood disorders. A large study published in the journal *Hypertension* in 2016 suggests that **certain classes of anti-hypertensive drugs, calcium antagonists and beta blockers, may increase risk of mood disorders compared to other treatments for hypertension.**

The study by researcher Angela H. Boal and colleagues used data from a hospital database to identify 144,066 patients between the ages of 40 and 80 who had taken anti-hypertensive drugs for more than 90 days. There was an independent linear connection between receiving a prescription for hypertenstion and being diagnosed with a mood disorder. Patients who took angiotensin-converting enzyme inhibitors or angiotensin receptor blocking drugs had the lowest rates of mood disorder admissions. Those taking calcium antagonists or beta blockers had an increased risk of a mood disorder, while those taking thiazide diuretics and those not taking anti-hypertensive drugs had no change in risk.

Preventing Metformin Side Effects

Depression is a risk factor for type 2 diabetes, and the drug metformin is a common treatment for diabetes. In a 2016 article in the *Journal of Clinical Psychiatry*, researcher Chittaranjan Andrade suggests ways of minimizing side effects from metformin.

Gastrointestinal side effects such as nausea, vomiting, abdominal discomfort, flatulence, and diarrhea are common on metformin. In the article, Andrade writes, "These are less likely to occur with gradual dose uptitration, administration of the drug with meals, and use of a time-release formulation."

Lactic acidosis, a buildup of lactate in the body that can result in muscle pain, burning, and other symptoms, is a rare side effect of metformin. Avoiding prescribing metformin to people with impaired kidney, liver, or cardiac functioning and other risk factors can prevent lactic acidosis.

Vitamin B12 absorption can also be affected by long-term metformin use. Andrade suggests that rather than waiting for a vitamin deficiency to be identified, a proactive approach should be taken. Long-term metformin users could be given an annual intramuscular shot of vitamin B12.

Marker of Heart Failure May Predict Brain Deterioration

A protein released into the blood in response to heart failure may be able to predict brain deterioration before clinical symptoms appear. The protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP), is released when cardiac walls are under stress. **High levels of NT-proBNP in the blood are a sign of heart disease. A 2016 Dutch study indicated that high levels of NT-proBNP in the blood are also linked to smaller brain volume, particularly small gray matter volume, and to poorer organization of the brain's white matter.** The study by researcher Hazel I. Zonneveld and colleagues, published in the journal *Neuroradiology*, assessed heart and brain health in 2,397 middle-aged and elderly people with no diagnosed heart or cognitive problems.

Researchers are working to clarify the relationship between cardiac dysfunction and preliminary brain disease, but researcher Meike Vernooij says it is likely cardiac dysfunction comes first and leads to brain damage. Measuring biomarkers such as NT-proBNP may help identify brain diseases such as stroke and dementia earlier and allow for earlier treatment and lifestyle changes that can slow or reverse the course of disease.

Antipsychotic Drug Pimavanserin Seems to Reduce Psychosis in People with Alzheimer's

The antipsychotic drug pimavanserin was approved by the US Food and Drug Administration last year as a treatment for hallucinations and delusions in Parkinson's disease. Now it looks as though it may also help people with Alzheimer's disease. Pimavanserin works differently than other antipsychotic medications—a selective serotonin inverse agonist, it acts at serotonin HT2A receptors to produce effects opposite to those that serotonin would produce at the same receptor.

In a trial of 181 patients with Alzheimer's and psychotic symptoms, those who received 34 mg/day of pimavanserin had a significant improvement in psychotic symptoms in six weeks compared to those who received placebo.

Over 12 weeks of treatment, pimavanserin did not impair cognition, as atypical antipsychotics can do.

Pimavanserin was well tolerated. The most common side effects were falls, urinary tract infections, and agitation. Like other atypical antipsychotics, the drug carries a box warning from the FDA that there is an increased risk of death when the drug is used to treat older people with dementia-related psychosis.

The FDA has designated pimavanserin a breakthrough therapy and is giving it priority review. These designations can speed up the development and review of a drug and are granted when a drug looks like it will be substantially better or safer than existing treatments for a serious condition.

Coenzyme NAD+ Postpones Aging in Mice and Worms

Aging cells seem to lose their ability to repair DNA, while the mitochondria that power cells also become less reliable. A coenzyme called NAD+ may be able to postpone these changes. NAD+, which is found in all living cells, naturally decreases with age.

A 2016 article by Evandro Fei Fang and colleagues in the journal *Cell Metabolism* reports that **giving mice and roundworms supplemental NAD+ postponed cell aging and extended the lives of these animals.**

The researchers hope this research might eventually help patients with Alzheimer's and Parkinson's' diseases.

NAD+ Supplements May Not Contain Much NAD+

NAD, or nicotinamide adenine dinucleotide, is found in all living cells. Its oxidized form, NAD+, has become popular as a nutritional supplement following a 2013 Harvard study that suggested it might slow aging in mice. However, commercially available NAD+ supplements may contain less than 100mg of NAD+, when ten times that amount would be required to produce any effect. NAD+ has not been tested in clinical trials.

Vitamin B3 is a better-tested alternative. A 2016 controlled clinical trial of a type of vitamin B3 called nicotinamide riboside (NR) found that this supplement was safe for humans and increased levels of NAD+. In the study by Samuel A.J. Trammell and colleagues in the journal *Nature Communications*, single doses of 100mg, 300mg, and 1000mg were all found to be safe. Larger doses increased NAD+ metabolism by greater amounts.

Check with your doctor before taking an NAD+ or vitamin B supplements.

Transcranial Direct Current Stimulation Improved Picture-Naming in People with Dementia

In a study of 12 people with mild Alzheimer's disease or frontotemporal dementia, transcranial direct current stimulation (tDCS) improved the participants' abilities to name an object in a picture more than did a sham stimulation. TDCS is a treatment in which an anode and a cathode electrode placed on the skull are used to deliver a steady low level of electrical current to the brain. There is currently no treatment available to specifically target symptoms of dementia such as forgetting words.

The research by Howard Chertkow and colleagues was presented at the 2017 meeting of the American Academy of Neurology. In the study, participants received either 30 minutes of anodal tDCS targeting the parietal lobe of the brain or a sham stimulation. They also received training in picture-naming. The participants were evaluated before stimulation, at the final stimulation session, two weeks after stimulation, and two months after stimulation. **Compared to those who received the sham stimulation, those who received real tDCS improved at picture naming, and maintained that improvement for two months.**

Those who received tDCS also performed better at naming new pictures not included in the training, and were better able to remember a string of digits than those who got the sham stimulation.

Caffeine One of Several Compounds That May Protect Against Dementia

A 2017 article by Yousuf O. Ali and colleagues in the journal *Scientific Reports* finds that **24 compounds may boost a brain enzyme that protects against dementia. The enzyme, NMNAT2, protects neurons from stress and combats misfolded proteins called tau that form plaques in the brain as people age.**

Ali and colleagues screened 1280 compounds to identify those that might increase NMNAT2 production. Twenty-four of these looked promising, including caffeine and rolipram, an "orphaned drug" once studied as an antidepressant but discontinued in the 1990s. Others with weaker effects on NMNAT2 production included the atypical antipsychotic ziprasidone, cantharidin (a wart-removing substance secreted by blister beetles), fungal metabolite wortmannin, and retinoic acid, a vitamin A derivative. Thirteen of the compounds tested decreased NMNAT2 production.

The researchers followed up the caffeine finding by testing caffeine in mice genetically engineered to produce less NMNAT2. The caffeine administration normalized NMNAT2 production levels in these mice.

Senior researcher Hui-Chen Lu hopes this research will lead to the development of new drugs that can create a chemical blockade against the effects of neurodegenerative illnesses.

TDCS May Improve ADHD Symptoms

Transcranial direct current stimulation (tDCS) is a therapy in which electrodes placed on the skull deliver a steady, low level current to the brain, changing its threshold for electrical activity. Anodal tDCS to the prefrontal cortex can improve working memory. In a small 2017 study in the Journal of Neural Transmission, Cornelia Soff and colleagues found for the first time that tDCS may improve symptoms of attention-deficit hyperactivity disorder (ADHD).

People with ADHD tend to have underactivation of the prefrontal cortex and deficits in working memory. The study randomized 15 young people aged 12–16 (three girls and twelve boys) to receive either real tDCS or a sham stimulation. The anodal tDCS was delivered at 1 mA targeting the left dorsolateral prefrontal cortex for 5 days. **Those participants who received tDCS showed a reduction in inattention, impulsivity, and hyperactivity compared to those who received the sham stimulation.** The effects were more pronounced 7 days after the stimulation, suggesting that tDCS' effects may be long-term. Larger, more definitive trials are needed to clarify the effects of tDCS on ADHD, but these preliminary findings are promising.

Single Dose of Modafinil Improved Memory in People in Remission from Depression

Modafinil is a wake-promoting medication used to treat narcolepsy, but studies have also shown that it can improve cognition in people with schizophrenia or attention deficit hyperactivity disorder. It may also help people with lingering cognitive difficulties after recovering from a depression. A 2016 article in the journal *Biological Psychiatry* reported that **a single 200mg dose of modafinil improved performance on tests of episodic memory and working memory (but not planning or attention).**

The study by researcher Barbara Sahakian and colleagues included 60 patients who had recently recovered from a depression. They took some cognitive tests to establish a baseline of their performance. A week later, they were given either a placebo or a single dose of modafinil, and two hours later they completed the cognitive tests again. The modafinil group performed better on the memory-related tasks.

While side effects were limited, two participants who received modafinil had sleep disturbances that night.

Longer-term studies are needed to determine whether modafinil is safe and effective if taken over a longer period of time. Cognitive dysfunction can interfere with daily tasks such as work or school and put people at greater risk of relapse, so effective treatments have the potential to greatly improve quality of life for people in remission from depression.

Giving Infants Vitamin D Can Reduce Type 1 Diabetes

A 2001 cohort study in Finland showed that giving vitamin D supplements to infants may reduce their risk for type 1 diabetes. The data for the study, by Elina Hyppönen and colleagues in the journal *The Lancet*, came from 10,366 people born in 1966. Their mothers were part of a medical registry that collected information on vitamin D given to children during the first year of their lives.

Of the 10,366 people in Hyppönen's study, 81 had been diagnosed with type 1 diabetes by the end of 1997. Those participants who were given vitamin D supplements during their first year of life were less likely to be diagnosed with type 1 diabetes than other participants. **Those who regularly took the recommended dose at the time, 2000 IU daily, during their first year of life had significantly lower diabetes rates 33 years later.**

High-Dose Vitamin D May Improve Cognition More Than Low-Dose Vitamin D

Vitamin D deficiency has been associated with dementia and cognitive decline, but supplements may help. **In a study of 82 healthy individuals with low vitamin D levels, high-dose vitamin D supplements (4000 IU/day) improved visual/nonverbal memory more than did low-dose vitamin D supplements (400 IU/day) over 18 weeks.**

The 2017 study took place in Canada, where short winter days can make it more difficult to get sufficient levels of vitamin D from sunlight. The higher-dose supplements raised blood levels of vitamin D compared with the lower-dose supplements.

Those who received the higher doses performed better at tests of visual memory such as the Pattern Recognition Memory Task and the Paired Associates Learning Task, but their performance on tests of verbal memory was not significantly different from those in the lower-dose group. This suggests that higher vitamin D levels are particularly important to visual/nonverbal memory.

The study by Jacqueline A. Pettersen was published in the journal *Experimental Gerontology*.

Dutch Study Links Low Vitamin D to Bipolar Disorder

A 2016 study in the Netherlands found that **people with bipolar disorder are more likely to have vitamin D deficiency than the general population.** Vitamin D deficiency has been linked to other psychiatric disorders including schizophrenia and unipolar depression. Poor diet and lack of exposure to sunlight can put someone at risk for vitamin D deficiency.

The study, led by Remco Boerman and published in the *Journal of Clinical Psychopharmacology*, included 118 adults with bipolar disorder, 149 with schizophrenia, and 53 with schizoaffective disorder. More than 30% of these participants had deficient levels of vitamin D. Only 15% had optimum levels of the vitamin. More than 22% of the participants with bipolar disorder were deficient in vitamin D, while close to 35% of those with schizophrenia and schizoaffective disorder were deficient.

Study participants had vitamin D levels that were 25% lower than those of the white Dutch population, and vitamin D deficiency was 4.7 times more common in those with psychiatric disorders than the general Dutch population.

The authors suggested screening people with bipolar disorder, schizophrenia, and schizoaffective disorder for low levels of vitamin D.

Vitamin D Deficiency Linked to Depression, But Supplements Helped

A review article in the *Journal of Affective Disorders* in 2017 summarized findings linking vitamin D to depression. Researcher Gordon B. Parker and colleagues found an association between low vitamin D levels and depression. They also found that **vitamin D supplements improved treatment in people with clinical depression and vitamin D deficiency.**

Editor's Note: Vitamin D supplements are an obvious recommendation for people who are deficient. What has not yet been resolved is whether vitamin D is helpful to people who are depressed but not vitamin D deficient.

In a 2013 study in the Australian and New Zealand Journal of Psychiatry, *Nayereh Khoraminya and colleagues suggested that a 1500 IU dose of vitamin D3 combined with the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine was more effective than fluoxetine plus placebo in depressed patients who were not necessarily deficient in vitamin D.*

Parents with Mood Disorders:

See our last page for information on our Child Network. Enrolled parents can rate their children's symptoms on a weekly basis, tracking them over time and sharing with their child's physician.

Concentrated Blueberry Juice Daily Improves Brain Function

A small study in the journal *Applied Physiology, Nutrition, and Metabolism* showed an improvement in cognitive function, bloodflow to the brain, and brain activation in older people who drank concentrated blueberry juice every day for 12 weeks.

The 26 participants were healthy adults between the ages of 65 and 77. People who consumed more than 5 daily servings of fruits and vegetables were excluded from the study. Twelve participants consumed 30mL (less than a quarter cup) of the concentrated juice each day, while the other 14 received a daily placebo instead.

The participants did a variety of cognitive tests before and after the study period. Magnetic resonance imaging (MRI) scans collected information about bloodflow and brain function during these tests.

Participants in the blueberry juice group showed statistically significant increases in brain activity by the end of the study compared to those in the placebo group.

The study was led by researcher Joanna Bowtell.

Eating Fresh Fruits and Veggies Can Improve Feelings of Well-Being

A couple weeks of consuming extra fresh fruits and vegetables can improve well-being, according to a 2017 study of 171 young adults. **Those who were given two extra daily servings of carrots, kiwis, apples, or oranges reported increases in vitality and motivation after only two weeks.**

Interestingly, participants who received text reminders to eat more produce or $10 vouchers to pay for fruits and vegetables did not see the same improvements as those who were given servings of produce directly. Those who got texts or vouchers were more likely to cook extra vegetable servings or mix them into other meals rather than eating additional raw produce.

The authors led by Tamlin Conner suggested that institutional settings such as schools, dormitories, childcare centers, hospitals, and workplaces could make fresh fruits and vegetables easily available to improve general well-being.

In Mice, Vitamin B3 (Niacin) Prevents Glaucoma

A study published in the journal *Science* in 2017 reports that **adding vitamin B3 to the drinking water of mice prevented them from developing glaucoma. Glaucoma is an age-related condition in which pressure inside the eye damages retinal ganglion cells, the neuronal cells that connect the eye to the brain.**

Age contributes both to the buildup of pressure within the eye and to the vulnerability of the neuronal cells to damage. Vitamin B3 seemed to correct the latter problem.

The study by Pete A. Williams and colleagues compared mice with an inherited risk of glaucoma to control mice. Williams and colleagues found that a molecule called NAD that keeps cells functioning normally declined with age, reducing the reliability of the neurons' energy metabolism.

Vitamin B3 boosted the metabolic reliability of the aging neuronal cells. This helped the cells resist damage from mounting pressure in the eye.

Williams and colleagues also found that a single application of gene therapy with the gene NMNAT1 also prevented glaucoma in the mice. NMNAT1 is the gene for an enzyme that makes NAD from vitamin B3. Gene therapy via an injection in the eye has been approved to treat some rare human eye disorders.

The researchers hope to eventually test vitamin B3 treatment in people with glaucoma and other neurodegenerative disorders.

Editor's Note: Vitamin B3 may be beneficial for other conditions as well. High-dose niacin (500 mg and up) is a prescription treatment for high cholesterol, and especially the combination of high cholesterol and high triglycerides (blood fats). Niacin may also prevent hardening of the arteries and second heart attacks in men with heart or circulatory problems, and improve diabetes (type 1 and 2). There is some evidence that vitamin B3 can also improve symptoms of osteoarthritis, such as joint stiffness, pain, and swelling. In addition, people who consume more niacin have a lower risk of Alzheimer's disease, though it is not clear that taking niacin supplements can prevent the illness.

It's now faster and easier to join the Child Network! See page 11

Following Collisions, High School Football Players with No Signs of Concussion May Still Have Neurological Impairment

In a small 2014 study in the *Journal of Neurotrauma*, researcher Thomas M. Talavaga and colleagues reported that repeated head trauma that did not produce concussion symptoms was still associated with neurocognitive and neurophysiological changes to the brain in high school football players.

The longitudinal study tracked 'collision events' experienced by 11 teens who played football at the same high school. The young men also completed neurocognitive testing and magnetic resonance imaging (MRI) scans of their brains over time.

The researchers expected to see the participants fall into two categories: those who had no concussions and normal neurological function, and those who had at least one concussion and subsequent neurological changes. **They ended up observing a third group: young men who had not exhibited concussion symptoms, but nonetheless had measurable changes to their neurological functioning, including impairments to visual working memory and altered activation of the dorsolateral prefrontal cortex.** Young men in this last group had had more collisions that impacted the top front of the head, directly above the dorsolateral prefrontal cortex.

The authors suggest that the discovery of this third category mean that some neurological injuries are going undetected in high school football players. The players who are injured in this way are not likely to seek treatment, and may continue playing football, risking more neurological brain injury or brain damage with subsequent collisions.

Breathing-Focused Yoga and Meditation Improved Depression

A 2016 article in the *Journal of Clinical Psychiatry* reports that Sudarshan Kriya yoga, a breathing-based meditation intervention, improved depression in people who had had an inadequate response to antidepressants.

In the study by researcher Anup Sharma and colleagues, 25 participants were randomized to either receive the breathing-based meditation training right away or be put on a waitlist to receive the training later. **After two months, those who received the intervention showed improvement in depression scores compared to those on the waitlist. The intervention also reduced anxiety.**

Breathing in Through the Nose Enhances Judgment and Memory

A 2016 study published in the *Journal of Neuroscience* reported that the rhythm of breathing changes electrical activity in the brain and can improve emotional judgments and recall. Breathing in through the nose seemed to produce benefits compared to breathing out or to breathing in through the mouth.

Participants more easily identified a fearful face if they viewed it while breathing in. They also had an easier time remembering objects they observed while breathing in. The effects were not seen if the participants breathed through their mouth.

The researchers, led by Christina Zelano, reported that **there was a major difference in brain activity in the amygdala and hippocampus during inhalation versus exhalation.** Breathing in, in addition to stimulating the olfactory cortex responsible for smell perception, seems to activate the entire limbic system, the emotional center of the brain.

Short Telomeres Associated with Family Risk of Bipolar Disorder

Telomeres are bits of genetic material at the end of each strand of DNA that protect chromosomes as they replicate. Short telomeres have been linked to aging and a variety of medical and psychiatric diseases. Stress and depressive episodes can shorten telomeres, while treatment with lithium can lengthen them.

Telomere length is a heritable trait, and a 2017 study by researcher Timothy R. Powell and colleagues suggests that shorter telomeres are a familial risk factor for bipolar disorder.

The study, published in the journal *Neuropsychopharmacology*, compared the telomere lengths of 63 people with bipolar disorder, 74 of their immediate relatives (49 of whom had no lifetime psychiatric illness, while the other 25 had a different mood disorder), and 80 unrelated people with no psychiatric illness. **The well relatives of the people with bipolar disorder had shorter telomeres than the unrelated healthy volunteers.**

Relatives (both well and not) and people with bipolar disorder who were not being treated with lithium both had shorter telomeres than people with bipolar disorder who were being treated with lithium.

Another finding was that longer telomeres were linked to greater volume of the left and right hippocampus, and improved verbal memory on a test of delayed recall. This study provides more evidence that taking lithium increases the volume of the hippocampus and has neuroprotective benefits for people with bipolar disorder.

Traumatic Events in Childhood Linked to Shorter Telomeres

Telomeres are bits of DNA at the end of chromosomes that protect the DNA as it replicates. Shorter telomeres have been linked to aging and increases in multiple types of medical and psychiatric disorders. A 2016 article in *PNAS, the Proceedings of the National Academy of Sciences of the United States of America,* reported that cumulative life adversity and particularly stressful or traumatic events in childhood, predict shorter telomere length.

The study by Eli Puterman and colleagues included 4,590 individuals from the US Health and Retirement Study who reported stressful events that had experienced. A single experience of adversity was not linked to short telomeres, but lifetime cumulative adversity predicted 6% greater odds of having shorter telomeres. This result was mainly explained by adversity that occurred in childhood. **Each stressful or traumatic event in childhood increased the odds of short telomeres by 11%.** These were mostly social or traumatic experiences rather than financial stresses.

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.

Methylphenidate Does Not Cause Mania When Taken with a Mood Stabilizer

Methylphenidate is an effective treatment for attention-deficit hyperactivity disorder (ADHD). Ritalin may be the most commonly recognized trade name for methylphenidate, but it is also sold under the names Concerta, Daytrana, Methylin, and Aptensio. A 2016 article in the *American Journal of Psychiatry* reports that **methylphenidate can safely be taken by people with bipolar disorder and comorbid ADHD as long as it is paired with mood-stabilizing treatment.**

The study was based on data from a Swedish national registry. Researchers led by Alexander Viktorin identified 2,307 adults with bipolar disorder who began taking methylphenidate between 2006 and 2014. Of these, 1,103 were taking mood stabilizers including antipsychotic medications, lithium, or valproate, while 718 were not taking any mood stabilizing medications.

Among those who began taking methylphenidate without mood stabilizers, manic episodes increased over the next six months. In contrast, patients taking mood stabilizers had their risk of mania decrease after beginning treatment with methylphenidate.

Viktorin and colleagues suggest that 20% of patients with bipolar disorder may also have ADHD, so it is not surprising that 8% of patients with bipolar disorder in Sweden receive a methylphenidate prescription.

Mood-stabilizing drugs can worsen attention and concentration, so methylphenidate treatment can be helpful if it can be done without increasing manic episodes. However, Viktorin and colleagues suggest that due to the risk of increasing mania, anyone given a prescription for methylphenidate monotherapy should be carefully screened to rule out bipolar disorder.

The researchers confirmed that taking methylphenidate for ADHD while taking a mood stabilizer for bipolar disorder is a safe combination.

Systematic Review Finds Bupropion is Effective for ADHD in Young People

A 2016 systematic review by Qin Xiang Ng in the *Journal of Child and Adolescent Psychopharmacology* found that the antidepressant bupropion (Wellbutrin) can improve attention deficit hyperactivity disorder (ADHD) in children and adolescents.

The review identified 25,455 studies of bupropion for ADHD, but only six included children. All six studies showed that bupropion improved ADHD symptoms in children and adolescents. Head-to-head trials of bupropion and methylphenidate (one of the most common medications to treat ADHD, which most people know by the name Ritalin) found the drugs had similar efficacy rates, although a large double-blind, placebo-controlled multicenter study found that bupropion had a smaller effect size than methylphenidate.

In terms of side effects, methylphenidate was more likely to cause headaches than bupropion, but otherwise the drugs were similar.

Ng suggests that **bupropion should be considered for the treatment of ADHD in children and adolescents, but more large trials of the drug are needed.** Bupropion may also help children whose ADHD appears alongside conduct, substance abuse, or depressive disorders.

Some Antacids Cause Kidney Damage with No Prior Symptoms

Commonly used antacids such as Prevacid, Nexium, Prilosec, and Protonix can impair kidney function, according to a 2017 article in the journal *Kidney International*. These drugs, known as proton pump inhibitors or PPIs, should not be taken long-term without monitoring of kidney function. Other antacids that work by blocking histamine H2 receptors do not interfere with kidney function but may not work as well as PPIs.

Researcher Yan Xie and colleagues found that **more than half of people who developed chronic kidney damage while taking PPIs showed no earlier acute signs of kidney dysfunction, meaning there may not be signs of kidney function loss until the damage is irreversible.** Xie and colleagues suggest that patients and doctors should be more vigilant about monitoring the use of these medications, since waiting for outward signs of declining kidney function is not a reliable way of detecting damage.

More than 15 million Americans use prescription PPIs to reduce gastric acid, bringing relief to heartburn, ulcers, and acid reflux. Millions more buy PPIs over the counter without consulting a doctor about their use.

The study analyzed Department of Veterans Affairs data from 125,596 new users of PPIs and 18,436 new users of H2 blockers. Acute, reversible symptoms of kidney damage, such as reduction in the urine being cleared from the body, fatigue, and swelling of the legs and ankles were seen in less than 20% of the PPI users. However, more than half of those who developed chronic kidney damage and end-stage renal disease never showed these warning signals beforehand. In contrast, only 7.67% of those taking H2 blockers had chronic kidney disease without acute symptoms, and 1.27% had end-stage renal disease, when kidneys can no longer clear waste from the body, and dialysis or a kidney transplant is required.

Xie and colleagues suggest carefully monitoring kidney function in people taking PPIs, even when there are no outward signs of problems. They also suggest carefully evaluating whether PPIs are necessary, since the risk of kidney damage is serious.

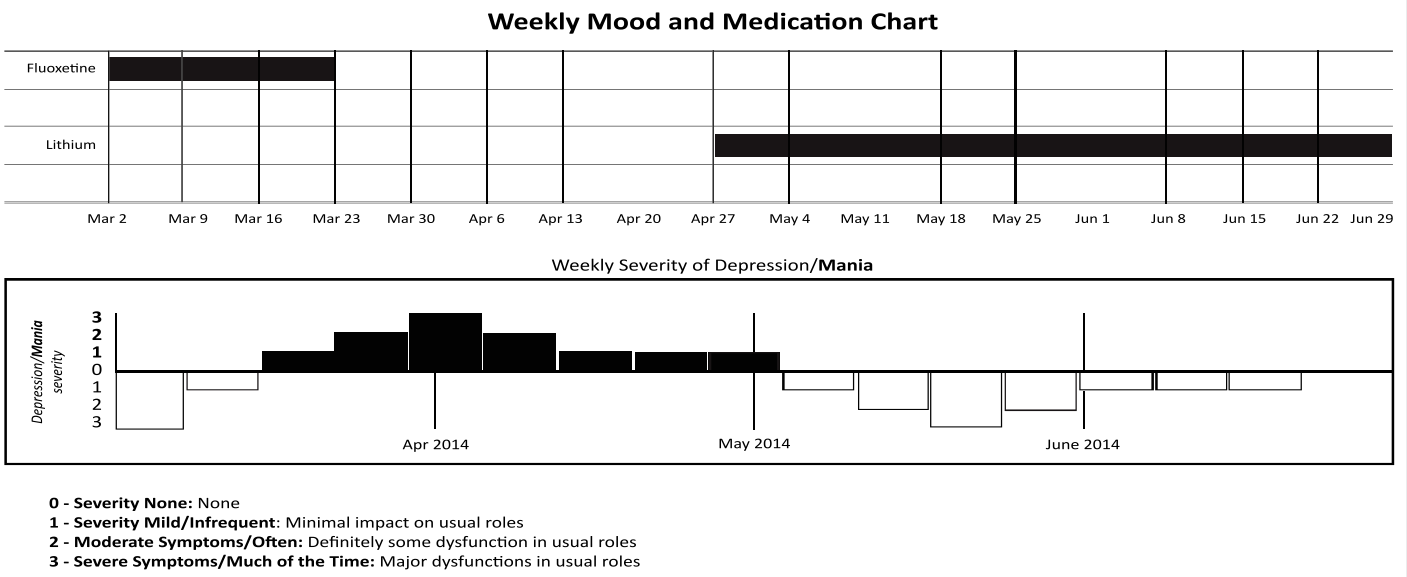
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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).



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 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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