

Bipolar Network News

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A Calculator of Risk for Bipolar Disorder in Youth

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Daniella Hafeman of the University of Pittsburgh described a risk calculator for predicting an individual's risk for bipolar disorder, which is available at www.pediatricbipolar.pitt.edu. Possible factors included in the risk calculation include a parent's early age of onset of bipolar disorder, mood shifts early in life, a child's anxiety or depression symptoms, later affective mood shifts, and new onset of subthreshold mania.

Editor's Note: A "poor man's" assessment of risk can also be of help to a family or clinician. There are four components. The first is genetic. Having one parent with bipolar disorder is a potent risk factor, and can be further magnified if the other parent also has a mood disorder. If three or more first degree relatives or three or more generations of first degree relatives have a mood disorder, this further increases risk four- to six-fold.

Perinatal vulnerability is another factor. Beyond these genetic vulnerabilities, a history of maternal toxoplasmosis or a viral infection during pregnancy, or the infant being noticeably underweight at birth can contribute to bipolar risk.

Childhood adversity also contributes to vulnerability to early onset of bipolar illness. A history of psychosocial stress in the child's early years, such as abuse or abandonment, can be an added risk factor.

Prodromal or preliminary symptoms are also a risk factor. The development of an anxiety or depressive disorder, a disruptive behavioral disorder, or a bipolar not-otherwise-specified diagnosis (BP-NOS, used to describe manic symptoms of short duration) further increases risk. In studies by David Axelson and Boris Birmaher, 50% of children with an initial diagnosis of BP-NOS developed full-blown bipolar I or II illness upon several years of followup if there was a family history

of bipolar disorder. About one-third converted to full bipolar disorder if there was no family history of bipolar disorder.

Thus, if a child has three or all four types of risk factors, their risk would be substantial. In this case, one might consider attempts at prevention. This could include a good diet rich in omega-3 fatty acids, regular exercise, joining a school sports team, developing good sleep habits, playing a musical instrument, and engaging in something akin to family focused therapy. Family focused therapy emphasizes psychoeducation, good communication skills, and problem solving. Attending to and treating parents' symptoms and building a support system for both parents and the child can also help.

While these endeavors are not a guarantee to prevent the onset of more severe illness, they are all health-promoting in general and have few downsides.

An Inflammatory State Impedes Treatment for Bipolar Disorder

A 2017 study by in the *Journal of Clinical Psychiatry* links inflammation to a poor antidepressant response in bipolar disorder. Many previous studies have found that elevated inflammatory markers are common in mood disorders, and that an inflammatory state seems to prevent response to certain therapies.

Researcher Francesco Benedetti and colleagues report that **high levels of inflammatory cytokines (a type of small proteins) predicted a worse response to treatment with sleep deprivation and light therapy for bipolar depression.** This treatment typically brings about a rapid antidepressant response.

Benedetti and colleagues measured 15 immune-regulating compounds in

37 patients who were experiencing an episode of bipolar depression and 24 healthy volunteers. Among those participants with bipolar disorder, 84% had a history of non-response to medication. Twenty-three of the 37 patients, or 62%, responded to the sleep deprivation/light therapy combination. Those who did not had higher levels of five cytokines: interleukin-8, monocyte chemoattractant protein-1, interferon-gamma, interleukin-6, and tumor necrosis factor-alpha.

Body mass index was correlated with cytokine levels and also reduced response to the treatment.

The finding supports a link between the immune system and mood disorders. Evaluating a patient's level

of inflammation may, in the future, allow doctors to predict the patient's response to a given therapy. Patients with high levels of inflammation might benefit most from treatments that target their immune system.

In This Issue:

Exercise, Obesity, PTSD, ADHD, Omega-3 Fatty Acids, Cognition, Opiate Use ...and more!

Minimizing Cardiovascular Risk in Bipolar Disorder

At the 2017 meeting of the American Association of Child and Adolescent Psychopharmacology, researcher Ben Goldstein gave an overview on cardiovascular risk and bipolar disorder. He noted a study by Nicole Kozloff and colleagues in the *Journal of Affective Disorders* in 2010 that indicated that **onset of cardiovascular disorder occurred an average of 17 years earlier in those with BPI (at age 40-45 years) compared to controls (at age 55-60 years)**. Several risk factors made onset of cardiovascular disorder more likely, including diabetes, obesity, and the metabolic syndrome (which consists of any three of the

five following symptoms: high cholesterol, triglycerides, blood sugar, blood pressure, and waist circumference).

Risk factors include pathophysiological and behavioral mechanisms and certain medications. Pathophysiological mechanisms include inflammation, oxidative stress, and autonomic and endothelial dysfunction.

Behavioral mechanisms include poor diet, exercise, sleep, and increases in tobacco and alcohol use.

Medications could also contribute, with the most to least problematic for weight gain including, among atypical antipsychotics: clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, and lurasidone. Among mood stabilizers, worst to best for avoiding weight gain are: valproate, lithium, carbamazepine, oxcarbazepine, and lamotrigine.

Goldstein has data on retinal vascular photography (RVP), whereby blood vessels can be observed directly. As opposed to in adults, in youth large vessels are more problematic and arteriolar to venous ratio is abnormally higher in bipolar children compared to normal controls. This ratio is lower in bipolar adults, also reflecting increased cardiovascular risk.

Given the huge loss of life expectancy in bipolar disorder, primarily from

cardiovascular disorders, Goldstein urges greater and earlier attention to reducing the pathophysiological, behavioral, and pharmacological mechanisms for poor health. These should be pursued in parallel with attempts at mood stabilization. Goldstein endorses the position of researcher James J. Hudziak that "all health begins with emotional health."

Editor's Note: One way to conceptualize good medical and emotional health is to consider the benefits of preserving telomere length. Telomeres are bits of genetic material that sit at the ends of DNA strands and protect the DNA during cell replication. Shorter telomeres are associated with aging and a host of medical and psychiatric illnesses.

Stress and numbers of depressive episodes shorten telomeres so that mitigating stressors and preventing depressions is a good place to start. A good diet, exercise, and practicing mindfulness or meditation are associated with longer telomeres, so adopting these lifestyle changes from an early age is ideal. It is noteworthy that lithium directly activates the enzyme telomerase that lengthens telomeres, and lithium normalizes their length in those with affective illness as a function of the duration of lithium treatment.

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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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Exercise in Childhood Decreases Depression Symptoms Two Years Later

A 2017 study in the journal *Pediatrics* found that **higher rates of moderate to vigorous physical activity at ages six and eight was linked to fewer symptoms of depression at age 10**.

The study included 795 six-year-olds who were tracked for four years. Their physical activity was measured by accelerometry, the same type of

technology found in smartphones and other consumer products that can track a person's daily steps. Depression symptoms were assessed via interviews with the children and their parents.

While exercise seemed to reduce depression symptoms, sedentary behavior did not predict later depression.

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Adipokines May Be the Link Between Mood Disorders and Obesity

Researchers David J. Bond and Lakshmi Yatham think they may have identified why bipolar disorder and obesity occur so often together. In North America, more than 60% of people with bipolar disorder are overweight or obese, and obesity rates are 60% higher in people with bipolar disorder than in people without bipolar disorder.

Bond and Yatham hypothesized that adipokines might be responsible for both bipolar disorder and obesity. **Adipokines are cell signaling proteins that regulate both mood and appetite. Abnormal levels of adipokines in blood could cause both mood episodes and weight gain.**

The researchers measured blood levels of five adipokines (leptin,

adiponectin, resistin, adipon, and lipocalin-2) in 53 young people with bipolar disorder. They found three interesting links between adipokines, mood, weight, and medications, which they reported in the *Journal of Clinical Psychiatry* in 2017.

The first finding was that low levels of leptin and adiponectin (adipokines with antidepressant properties) predicted a greater risk of depressive relapse over a 12-month period. The second finding was that high levels of leptin and adipon predicted greater weight gain over a 12-month period. The third finding was that treatment with second-generation antipsychotics, which often leads to weight gain and other metabolic side effects, was as-

sociated with higher levels of resistin, an adipokine linked to type 2 diabetes.

The findings about leptin were particularly interesting, because leptin's appetite-regulating effects change with a person's weight. In the study, low leptin predicted depression, while high leptin predicted weight gain. In people of normal weight, low leptin predicts weight gain, while in overweight or obese people, high leptin predicts weight gain. Bond and Yatham suggest that leptin's mood-regulating effects may be more consistent, with low leptin increasing depression risk regardless of weight.

These findings may help researchers find ways of treating mood episodes that do not encourage weight gain.

Diet Drinks May Worsen Glucose Control, Making Type 2 Diabetes More Likely

Many people substitute diet drinks containing artificial sweeteners for sugary drinks in the hopes of reducing their diabetes risk. However, new research suggests that **artificial sweeteners alter the gut's response to glucose in a way that could actually worsen diabetes risk.**

At the 2017 meeting of the European Association for the Study of Diabetes, researcher Richard Young described a small study in which he and his colleagues compared the effects of artificial sweeteners to those of placebo in healthy adults. Seventeen participants consumed an amount of artificial sweetener equivalent to what would be found in 1.2 to 1.5 liters of diet beverage per day for two weeks, while 16 participants received placebo.

Young and colleagues determined that glucose absorption and glycemic response increased in the participants who consumed the artificial sweetener. Those who consumed the sweetener absorbed 20% more glucose than those in the placebo group. While before the

study the two groups had similar blood glucose levels, these rose by 24% in those who consumed the artificial sweetener.

Consuming artificial sweetener also seemed to affect the gut peptide GLP-1, which limits the rise in blood glucose after meals. The two groups had similar GLP-1 responses before the study, but after consuming artificial sweetener, participants showed a 34% reduction in GLP-1 response to glucose absorbed in the intestines.

Changes like these could increase the risk of type 2 diabetes. Young explained that artificial sweeteners may reduce the body's ability to control blood sugar levels, leading to high glucose, and possibly predisposing those who consume artificial sweeteners to type 2 diabetes. Young and colleagues have previously found that switching from sugar to artificial sweeteners does not predict a lower risk of type 2 diabetes.

This study was the first of its kind in humans. Larger studies will help to clarify the effects of artificial sweeteners on glucose control.

Proton Pump Inhibitors Linked to Gastric Cancer

Proton pump inhibitors (PPIs), a type of medication used to reduce gastric acid, have been linked to gastric cancer in a new study by Ka Shing Cheung and colleagues. A 2017 article in *Gut*, the journal of the British Society of Gastroenterology, reports that receiving PPIs to treat stomach infections from the bacterium *Helicobacter pylori* increases the risk of later gastric cancer.

The study relied on a territory-wide health database in Hong Kong. Out of 63,397 subjects, 153 developed gastric cancer after being treated for *Helicobacter pylori*. PPI treatment was associated with a 2.4-fold increase in risk of gastric cancer, while treatment with histamine-2 receptor agonist drugs did not increase cancer risk.

Editor's Note: PPIs are widely used in psychiatric patients. Care should be taken with their long-term use.

Eye Movement Desensitization and Reprocessing Can Improve PTSD

A 2014 meta-analysis of clinical trials showed that the therapeutic technique known as eye movement desensitization and reprocessing (EMDR) can reduce symptoms of post-traumatic stress disorder (PTSD). The meta-analysis also established that longer durations of EMDR treatment correlated with better outcomes.

The meta-analysis by Ying-Ren Chen and colleagues in the journal *PLOS One* evaluated 26 randomized controlled trials of EMDR in people with PTSD. Chen and colleagues found that **EMDR reduced PTSD symptoms, depression, anxiety, and subjective distress.**

EMDR is a psychotherapeutic technique intended to reduce the distress that a patient feels about a traumatic memory. The patient is encouraged to recall the traumatic event while focus-

ing on an external stimulus. Typically this would mean using their eyes to track the therapist's hand moving back and forth from left to right. This process can help patients reprocess the trauma and alleviate the stress that they feel upon recalling the traumatic memory.

Chen and colleagues found that **EMDR sessions that lasted longer than one hour were more effective than those that lasted less than an hour. Another finding that was that groups led by therapists who were experienced in PTSD group therapy were more effective than groups led by therapists without that experience.**

Other more recent research has established that traumatic memories can be reprocessed or even extinguished by making use of the memory reconsolidation window. Five

minutes to one hour after a patient engages in active emotional recall of a traumatic memory, a window of time opens in which that memory is subject to reinterpretation and revision.

An experienced therapist can create a safe environment for a patient to recall traumatic events and find alternative ways of interpreting the experience—for example, by focusing on their strength in surviving the experience. This process resembles EMDR in many ways, but without the eye movements.

In a 2017 article in the journal *Psychiatry Research*, BNN Editor-in-Chief Robert M. Post and colleague Robert Kegan discuss the possibility of using the reconsolidation window to reprocess stressors that led to a depressive episode.

Type of Trauma Affects Gene Transcription Effects in PTSD

In a 2017 article in the journal *Neuropsychopharmacology*, researcher Michael S. Breen and colleagues analyzed five separate studies of post-traumatic stress disorder (PTSD) and found that sex and type of trauma affected the immunological pathways that changed with PTSD. People with PTSD showed disruptions in gene expression in specific immunological pathways depending on what type of trauma they had experienced.

Men exposed to combat traumas showed downregulation in a pathway related to wound healing, while men who were exposed to interpersonal traumas had upregulation in a signaling pathway mediated by the inflammatory marker IL-12. Women exposed to interpersonal traumas showed upregulation of two pathways—one related to lipid metabolism and the other related to MAPK (or mitogen-activated protein kinase) activity.

The participants with PTSD also showed a lot of the same disruptions across all types of trauma, including disruptions that affected cytokine, innate immune, and type 1 interferon pathways.

These data show that **immune dysregulation and inflammatory pathways play a role in the pathophysiology of PTSD.**

PTSD Increases Risk of Lupus

A new large 2017 study in the journal *Arthritis and Rheumatology* reports that post-traumatic stress disorder (PTSD) in women triples their risk of developing the autoimmune disease lupus. The study included 54,763 civilian women whose health data was tracked over a period of 24 years.

Not only did PTSD increase lupus risk, but any traumatic event doubled lupus risk compared to women who were not exposed to trauma.

The researchers, led by Andrea L. Roberts, were taken by surprise at the strong links between trauma and lupus. Trauma was more of a risk factor for lupus than smoking.

Omega-3 Fatty Acids Improve ADHD

A 2017 systematic review and meta-analysis found that omega-3 fatty acid supplementation improves symptoms of attention-deficit hyperactivity disorder (ADHD) in children and adolescents. The article by Jane Pei-Chen Chang and colleagues in the journal *Neuropsychopharmacology* identified seven randomized controlled trials in which omega-3 fatty acids improved clinical symptoms of ADHD, and three trials in which omega-3s improved cognitive measures associated with attention.

The meta-analysis also found that children and adolescents with ADHD have lower than normal levels of the omega-3s DHA and EPA, in addition to lower total levels of omega-3s measured in blood and cheek tissues.

Chang and colleagues suggest that omega-3 fatty acid supplementation is a potentially helpful and largely risk-free treatment option for ADHD in children and adolescents.

Gabapentin May Increase Opioid-Related Deaths

The anticonvulsant gabapentin is sometimes prescribed for chronic pain conditions along with opioids. A 2017 article by researcher Tara Gomes in the journal *PLOS Medicine* reports that compared to opioid prescriptions alone, co-prescription of gabapentin increases the risk of an opioid-related death by 49%. The risk was increased by 60% for those receiving moderate or high doses of gabapentin (those above 900 mg/day).

The increased risk when the drugs are taken together may be because both gabapentin and opioids depress the respiratory system. Opioids also slow the gastrointestinal system, meaning that more gabapentin is absorbed by the intestines than occurs when gabapentin is prescribed alone.

Gomes and colleagues looked at cases of patients who were prescribed opioids and had opioid-related deaths, and matched these with similar patients who had not died while taking prescription opioids during the same time period. The researchers found that **having taken gabapentin in the previous 120 days dramatically increased the risk of death from opioid-related causes.**

Gomes and colleagues suggest that caution should be used when prescribing gabapentin and opioid drugs at the same time.

Omega-3 Fatty Acids Improve Executive Function in Youth with Mood Disorders

A 2017 study by Anthony T. Vesco and colleagues in *The Journal of Child Psychology and Psychiatry* suggests that in youth with depression or bipolar not otherwise specified (BP-NOS), omega-3 fatty acid supplements improve executive functioning and behavior regulation compared to placebo.

Ninety-five participants aged 7–14 years received two capsules daily of either omega-3 fatty acids (1.87g total per day, mostly consisting of EPA) or placebo for 12 weeks. **Those who received omega-3s showed improvement in executive functioning (which can include planning and decision-making), behavioral regulation, and metacognition, as rated by their parents.**

Editor's Note: Since omega-3 fatty acids have no known side effects, there is little reason not to try them in youth with depression or bipolar disorder.

In Rats, Weight-Loss Drug Lorcaserin Reduces Opiate Use

The serotonin 5HT-2c agonist drug lorcaserin (Belviq) was approved by the US Food and Drug Administration in 2012 for the treatment of obesity and weight-related conditions (such as high blood pressure, type 2 diabetes, or high cholesterol) in adults. A 2017 article by researcher Harshini Neelakantan and colleagues in the journal *ACS Chemical Neuroscience* reports that in rats, lorcaserin may also reduce opiate use.

The rats had been self-administering the opiate oxycodone. **After receiving lorcaserin, the rats were less likely to consume oxycodone and less likely to seek it out.** The rats were also less responsive to cues that had previously led them to consume oxycodone, such as lights or sounds that occurred when oxycodone was available.

Serotonin 5HT-2c receptors both regulate psychostimulant reward in the brain and play a role in reactivity to cues like the lights and sounds the rats associated with oxycodone. Lorcaserin's effect on these serotonin receptors explains how it could reduce the rats' drug use.

Clinical trials are expected to examine whether lorcaserin can reduce opiate use in humans in addition to assisting with weight loss.

Grape Extract May Improve Cognition

Polyphenolic compounds in colored fruits and vegetables are thought to improve memory and cognition. Extracts from *Vitis vinifera*, the grape species that includes almost all well-known varieties of wine, have been found to have many beneficial effects: antioxidant, antibacterial, anti-inflammatory, anticancer, antidiabetic effects, in addition to protective effects on skin, the heart, the liver, and neurons. For about a decade, researchers have known that polyphenolic compounds from grapes could improve cognitive impairment and reduce neuropathological lesions in the brain in animals with a model of Alzheimer's disease. New research suggests that the same compounds that protect the plant against damage, fungus, or UV rays may also protect the human brain against damage.

Researchers led by Gioacchino Calapai tested a trademarked nutritional supplement called Cognigrape, which includes extracts from *Vitis vinifera*, in healthy adults between the ages of 55 and 75 in Italy. One group of 57 participants received 250mg of Cognigrape per day while the other group of 54 received placebo once a day for twelve weeks. Several weeks after the supplementation period, **the group taking Cognigrape showed significant improvement in cognitive function** compared to baseline and compared to the group taking placebo. The Cognigrape group also showed significant reductions in depression symptoms, improvements in somatic symptoms, and improvements in attention, language, immediate memory, and delayed memory. This is the first study to find an improvement in cognitive performance in humans after supplementation with a *Vitis vinifera* extract.

The study by Calapai and colleagues was published in the journal *Frontiers in Pharmacology* in 2017.

Exercise May Improve Memory

A recent study suggests that exercising vigorously 20 minutes per day may improve “interference memory,” a type of memory that involves reconciling new learning with information one already knows. (Sometimes older information “interferes” with new learning.) In a 2017 article in the *Journal of Cognitive Neuroscience*, researcher Jennifer Heisz and colleagues report that **performance on a high-interference memory task improved when participants engaged in 20-minute daily sessions of interval training for six weeks.**

Heisz and colleagues compared three groups of students: one did interval training, another did both interval training and cognitive training, and a control group did no special training. Both exercise groups performed better on the high-interference memory task than the control group. Those who exercised also had higher levels of brain-derived neurotrophic factor (BDNF), which promotes the growth of new synapses and is crucial for long-term memory.

The researchers suggest that this finding could be useful to seniors facing memory deficits, since only six weeks of exercise improved memory performance. Interference memory tends to decline with age.

Previous research has linked aerobic exercise to better academic performance.

Link Clarified Between Gut Microbes and Emotions

A 2017 article in the journal *Microbiome* suggests that **gene-regulating molecules called microRNAs in the brain may be the link between microbes in the gut and emotions.**

The research by Alan E. Hoban and colleagues looked at mice raised in a sterile, microbe-free environment. These mice had fewer anxiety-like behaviors than mice raised among the usual bacteria, viruses, and fungi. This finding implies that the microbiome—the trillions of microbes that live in and around our bodies— affects brain functions. In this case, the affected regions were the prefrontal cortex and the amygdala, which both play a role in the detection and response to fearful stimuli. These regions showed alterations in the level of microRNAs present.

When Hoban and colleagues introduced microbes into the animal’s systems, some microRNAs did not bounce back, suggesting that there may be a crucial window early in life when the presence of microbes is needed for the brain to develop normally.

In general, this research shows that microRNAs are key to understanding the link between the microbiome and the brain.

Exercise May Protect Against Breast Cancer

Epidemiological evidence suggests that exercise reduces breast cancer rates and rates of breast cancer recurrence. However, it is not well understood why this is true.

Exercise that is intense enough to increase the heart rate and induce heavy breathing can increase the hormone epinephrine in the blood. A 2017 article by researcher Christine Dethlefsen and colleagues in the journal *Cancer Research* reported that **this elevated level of epinephrine in the blood of breast cancer patients after one intense exercise session stopped their breast cancer cells from growing in vitro and reduced tumor growth by half.**

Senior author Pernille Hojman told *Reuters* that while exercise could not be expected to replace anti-cancer treatments, it is a great supportive strategy that has the added benefits of increasing patients’ quality of life and sense of empowerment.

The study looked at human breast cancer tumor cells in test tubes, and the same type of tumor cells implanted into mice. Only 45 percent of the mice implanted with the cancer cells collected after vigorous exercise developed tumors, compared to 90 percent of the mice who received cancer cells collected before exercise or with no exercise.

Depression and Suicidal Thoughts Linked to Brain Inflammation

A 2017 article by Sophie E. Holmes and colleagues in the journal *Biological Psychiatry* reports that people with major unipolar depression, especially those with suicidal thoughts, have higher levels of the inflammatory marker translocator protein than do healthy individuals.

The participants with depression and suicidal thinking had high levels of translocator protein in the anterior cingulate cortex, which suggests that inflammation is affecting microglia.

Many studies have found links between different indicators of inflammation and mood disorders, leading researchers to speculate whether targeting the immune system could be an effective way to treat mood disorders. Patients with high levels of inflammation often fail to respond to typical treatments for depression.

Some previous research has found evidence of microglial activation in the brains of people who died from suicide.

The small study by Holmes and colleagues used positron-emission tomography, or PET scans, to observe evidence of translocator protein levels in the brain in 14 medication-free participants in a major depressive episode and 13 healthy volunteers. Those with depression, and particularly those with suicidal thoughts, showed more evidence of neuroinflammation.

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