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Meta-Analysis Shows Anti-Inflammatory Treatments Improve Bipolar Depression

It has been clear for some time that depression and inflammation are linked. This has led researchers to explore a variety of anti-inflammatory agents to treat depression. A meta-analysis of studies examining anti-inflammatory treatments for bipolar depression was published in the journal *Bipolar Disorders* in 2016.

Researcher Joshua D. Rosenblat and colleagues identified eight randomized controlled trials that met their criteria for anti-inflammatory treatments of bipolar disorder. **These treatments included nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen and aspirin), omega-3 fatty acids, the antioxidant N-acetylcysteine, and pioglitazone (used to treat diabetes).** Overall, the anti-inflammatory treatments had a moderate and statistically significant antidepressant effects. No serious side effects were reported, and the anti-inflammatory treatments did not cause a switch into mania in any of the participants.

The diversity of the anti-inflammatory treatments reviewed in this meta-analysis limit the extent to which it can be interpreted, but it is clear that more research on anti-inflammatory treatments for bipolar depression is needed. An open question is whether patients with particularly elevated levels of inflammatory markers in their blood would respond better to these anti-inflammatory treatments.

Inflammation Linked to Non-Response to Antidepressants

In a symposium on inflammation's role in psychiatric disorders at the 2016 meeting of the Society of Biological Psychiatry, researcher Carmine Pariante reviewed the considerable literature indicating that major depression is often associated with measures of inflammation. **Depression has been linked to elevated blood levels of the inflammatory proteins interleukin-1, interleukin-6, TNF alpha, and c-reactive protein,** with about one-third of depressed patients having an elevated level of at least one of these proteins. **People with elevated inflammatory markers are also less likely to respond to traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs).**

Pariante reported that in depressed people, interleukin-6 is also elevated in cerebrospinal fluid in addition to blood, suggesting that inflammation in depression extends to the central nervous system. Increased secretion of interleukin-6 has been linked to depressive behaviors in mice exposed to stress.

There is some hope that anti-inflammatory treatments can help patients who do not respond to traditional antidepressant treatment. Some anti-inflammatory medications that may eventually be used to treat depression with inflammation include the COX-1 inhibitor aspirin, the COX-2 inhibitor celecoxib (Celebrex), or the antibiotic minocycline. Each of these approaches gained some support in preliminary clinical trials, but it has not yet been established that these anti-inflammatory treatments produce a better response in people with elevated inflammatory markers.

Supportive-Expressive Therapy Improved Depression, Reduced Inflammation

A recent study shows that psychotherapy can not only improve depression symptoms, but may also reduce the inflammation that often accompanies them.

Researcher Jean Pierre Oses and colleagues randomly assigned participants with depression to receive Supportive-Expressive psychodynamic therapy, which is designed to help patients understand conflictual relationship patterns, or an alternative therapy. **Among the 47 participants who received Supportive-Expressive therapy, depression improved significantly after 16 sessions, and blood levels of the inflammatory markers interleukin-6 and TNF alpha also dropped.**

The research was presented at the 2016 meeting of the Society of Biological Psychiatry.

In This Issue:

Kynurenine Pathway Suggests How Inflammation is Linked to Schizophrenia

The kynurenine pathway describes the steps that turn the amino acid tryptophan (the ingredient in turkey that might make you sleepy) into nicotinamide adenine dinucleotide. This pathway might be a connection between the immune system and neurotransmitters involved in schizophrenia.

A recent autopsy study by researcher Thomas Weickert and colleagues explored this link by determining that in the brains of people with schizophrenia and high levels of inflammation, messenger RNA for Kynurenine Aminotransferase II (KATII, a step on the kynurenine pathway) was elevated in the dorsolateral prefrontal cortex compared to the brains of people who died healthy and those with schizophrenia but low levels of inflammation.

The KATII mRNA levels also correlated with mRNA levels of inflammatory markers such as glial fibrillary acidic protein and interleukin-6.

Blood measures related to the kynurenine pathway also differentiated people with schizophrenia from healthy controls. **People with schizophrenia had lower levels of tryptophan, kynurenine, and kynurenic acid in their blood. The low levels of kynurenic acid in the blood were correlated with deficits in working memory and smaller volume of the dorsolateral prefrontal cortex.**

Weickert and colleagues suggest that blood levels of kynurenic acid might provide a measurable indicator of the degree to which people with schizophrenia are experiencing problems with executive functioning (planning and decision-making) and loss of brain volume.

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Meta-Analysis Shows Inflammation is Common in Illnesses Such As Unipolar Depression, Bipolar Depression, and Schizophrenia

In a symposium at the 2016 meeting of the Society of Biological Psychiatry, Mark Hyman Rapaport described the results of his research group's meta-analysis of studies comparing levels of inflammation in the blood of people with unipolar depression, bipolar depression, and schizophrenia. Rapaport and colleagues determined that **people acutely ill with any of the three illnesses showed abnormally high levels of certain inflammatory proteins. These included: interleukin-1beta, interleukin-6, TNF alpha, and c-reactive protein. Those who were chronically ill showed elevations in interleukin-6.**

These data are consistent with increasing evidence that inflammation also occurs in the brain. Brain inflammation can be observed by measuring translocator protein binding, a measure of brain microglial activation, using positron emission tomography (PET) scans.

Inflammation Predicts Depression and Anxiety Four Years Later in Older Americans

A large study of retired Americans found that those with high levels of the inflammatory marker C-reactive protein in the blood had more depression and anxiety. **Higher CRP also predicted severity of depression and anxiety four years later.**

The study, by researchers Joy E. Lin and Aoife O'Donovan, included 18,603 people over age 50 from the Health and Retirement Study. It was presented at the 2016 meeting of the Society of Biological Psychiatry.

Lin and O'Donovan hope that treating or preventing inflammation may be the key to preventing symptoms of depression and anxiety.

Fluctuations in White Matter in Adolescents with Bipolar Disorder May Indicate Cardiovascular Risks

During functional magnetic resonance imaging (fMRI) of the brain, data on physiological fluctuations in white matter are collected. These fluctuations are caused by cardiac pulses, cerebrovascular dysfunction, and other factors. Increasing fluctuations have been linked to cognitive impairment with age.

Vascular problems in adults with bipolar disorder have been linked to cerebrovascular disease, a group of conditions that affect bloodflow to the brain. In a recent study, researcher Arron W. S. Metcalfe and colleagues used data on physiological fluctuations in white matter (usually a nuisance variable) to assess the vascular health of teens with bipolar disorder. **Compared to 32 age-, IQ-, and sex-matched controls, 32 adolescents with bipolar disorder had more fluctuations in white matter in three different clusters in the brain.**

These white matter fluctuations are a possible early indicator of susceptibility to cerebrovascular disease in teens with bipolar disorder. Patients with depression and bipolar disorder are at increased risk for cardiovascular disease, so maintaining a good diet, exercising regularly, and assessing blood pressure, cholesterol, and lipid levels is recommended. See article at above right where we describe research showing teens with bipolar disorder have stiffer artery walls.

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Teens with Bipolar Disorder Have More Inflammation, Cardiovascular Risks

Bipolar disorder has been linked to cardiovascular disease. New research by Jessica Hatch and colleagues shows that inflammation may be at the root of this connection. At the 2016 meeting of the Society of Biological Psychiatry, the researchers showed that teens with bipolar disorder have higher levels of inflammatory marker interleukin 6.

Hatch and colleagues assessed the blood of 60 teens with bipolar I or II disorder and 20 healthy controls for a variety of biomarkers, including the inflammatory proteins interleukin 6, interleukin 10, and TNF alpha; VEGF, which is responsible for the production of new blood vessels; and brain-derived neurotrophic factor (BDNF), which protects neurons. The researchers also assessed the participants' cardiovascular health, performing the carotid intima media thickness test to estimate how much plaque is in the arteries, and measuring how well the patients' arteries dilate in response to changes in bloodflow.

Participants with bipolar disorder had higher levels of interleukin 6 than healthy controls, regardless of whether their bipolar illness was symptomatic. Low BDNF was linked to greater carotid intima thickness in participants with symptomatic bipolar disorder, and vascular measurements suggest a possible mechanism by which bipolar disorder increases cardiovascular risk.

Brain Inflammation Found in Autopsy Studies of Teen and Adult Suicides

Suicide and depression have both been linked to elevated levels of inflammatory cytokines in the blood and cerebrospinal fluid. A recent study finds that these inflammatory markers are also elevated in the brains of teens and depressed adults who died from suicide.

In autopsy studies, researcher Ghanshyam N. Pandey measured levels of the inflammatory cytokines interleukin-1beta, interleukin 6, and TNF-alpha in the brains of teen suicide victims, and compared these to the brains of teens who died from other causes. Pandey also measured levels of interleukin-1beta, interleukin 6, interleukin 8, interleukin 10, interleukin 13, and TNF-alpha in the prefrontal cortex of depressed adult suicide victims and compared them to levels in adults who died of other causes.

There were abnormalities in the inflammatory markers in the brains of those who died from suicide compared to their matched controls. **The suicide victims had higher levels of interleukin-1beta, interleukin 6, and TNF-alpha than the controls.** Among the adults, levels of the anti-inflammatory cytokine interleukin 10 were low in the suicide victims while levels of Toll-like receptors (TLR3 and TLR4), which are involved in immune mechanisms, were high.

Brain inflammation has also been observed in positron emission tomography (PET) scans of depressed patients, where signs of microglial activation can be observed. Elevated inflammatory cytokines are also found in the blood of some people with bipolar disorder, depression, and schizophrenia.

Pandey presented this research at the 2016 meeting of the Society of Biological Psychiatry.

Brain Volumes Affected by Type and Timing of Childhood Abuse

Maltreatment during childhood has been linked to brain changes and mental illness. In a study by researcher Carl M. Anderson and colleagues that was presented at the 2016 meeting of the Society of Biological Psychiatry, maltreatment at particular ages was statistically linked to deficits in the size of certain brain areas in young adulthood.

The brain areas under examination are critical for the regulation of emotion and behavior, and this research suggests that early experiences can stunt their development, perhaps through altered production of synapses or via the synaptic pruning process that occurs during preadolescence. The details, summarized below, are perhaps less important than the overall finding that maltreatment in childhood affects brain volume, and this effect varies based on the timing and type of maltreatment. **Abuse and neglect earlier in life affected the left side of the brain, while later maltreatment affected the right side.**

Severity of physical abuse at age 3 affected the volume of the ventromedial prefrontal cortex in women. Physical abuse at ages 3 and 8 in men affected left ventromedial prefrontal cortical volume, while later abuse at ages 7 and 12 predicted volume of the right side.

In women, dorsal anterior cingulate area on the left was predicted by physical abuse at age 5 and by emotional neglect at ages 7 and 11. Later emotional neglect at ages 15 and 16 and physical abuse by a peer at age 10 was associated with smaller right dorsal anterior cingulate. In men, smaller left dorsal anterior cingulate area was predicted by physical neglect at age 2 and emotional abuse by a peer and witnessing abuse of a sibling at ages 5 and 10, and right area by physical neglect at age 12.

Early Life Stress Affects Volume of the Hippocampus

New research shows that there are crucial periods of early life in which a stressful event can reduce hippocampal volume in adolescence. In a study presented at the 2016 meeting of the Society of Biological Psychiatry, Kathryn L. Humphreys and colleagues found that children who experienced a significant stressor before age 8 had smaller hippocampi in early adolescence than children who did not have a significant stressor early in life.

The severity of the stressors that occurred when children were between the ages of 0 and 2 predicted the volume of the hippocampus later in life. This was true to a lesser extent for stressful events that occurred between the ages of 3 and 5. No effect was seen for stressful events that took place between the ages of 6 and 8.

The period of sensitivity to stressful events between ages 0 and 2 and its effects on hippocampal volume could influence a variety of psychiatric outcomes in conditions such as depression and post-traumatic stress disorder (PTSD).

Amygdala Hyperactivity Linked to Family History of Depression

In new research presented at the 2016 meeting of the Society of Biological Psychiatry, researcher Tracy Barbour and colleagues revealed that youth with a family history of depression showed more amygdala activation in response to a threat than people without a family history of depression. **This amygdala hyperactivity was linked to low resilience to stress and predicted worsening depressive symptoms over the following year.**

In the study, 72 non-depressed youth were shown images of cars or human faces or cars that seemed to loom in a threatening way. Brain scans showed increased amygdala activity in participants with a family history of depression compared to those without such a history.

The amygdala is an almond-shaped part of the brain in the temporal lobe that has been linked to emotional reactions and memory, decision-making, and anxiety.

IL-6 in Blood and Bone Marrow Linked to Lack of Resilience to Stress

Rodents who are repeatedly defeated by larger animals often exhibit depression-like behaviors. In new research that researcher Georgia E. Hodes presented at the 2016 meeting of the Society of Biological Psychiatry, animals who are susceptible to these social defeat stress behaviors showed immune irregularities, including high levels of the inflammatory marker interleukin-6.

An intervention to prevent the mice from secreting interleukin-6 in blood and bone marrow took away their susceptibility to social defeat stress. When bone marrow from rodents with no interleukin-6 was transplanted into susceptible mice, the recipients showed resilience to social defeat stress. Conversely, a transplant from susceptible mice to those mice without IL-6 led to social defeat stress in the previously "immune" mice.

This research shows that the peripheral immune system, including blood and bone marrow, plays an important role in depression-like behaviors in mice.

Child Abuse Linked to Adolescent Obesity

New research clarifies how trauma in early life can lead to obesity in adolescence. In a study of 160 young people between the ages of 9 and 15, researcher Janitza Montalvo-Ortiz and colleagues identified seven sites in the genome where DNA methylation predicted body mass index (BMI) in adolescence. The researchers also collected information on family traumas that occurred during the participants' childhoods and found that DNA methylation and family trauma such as child abuse interacted to predict BMI.

Epigenetics describes the ways life experiences can change how easily DNA is turned on or off. While the genes coded by DNA sequences one inherits from one's parents never change, the structure of DNA can change. DNA methylation is one type of epigenetic change that refers to the addition of methyl groups to promoter regions of DNA in response to life events.

In this research, which was presented at the 2016 meeting of the Society of Biological Psychiatry, Montalvo-Ortiz and colleagues found that the site of DNA methylation with the strongest link to BMI in adolescence was a gene called MAP2K3. This gene had previously been linked to obesity, but **this is the first time DNA methylation at this site has been linked to both obesity and childhood trauma.** Other relevant gene sites where DNA methylation occurred include ANKRD2, CPXM2, NUBPL, and RFK.

Certain Types of Inflammation and Body Weight Predict Depression

At the 2016 meeting of the Society of Biological Psychiatry, researcher Femke Lamers and colleagues presented findings from the Netherlands Study of Depression and Anxiety. **The inflammatory markers interleukin-6 and CRP were elevated in people with current major depression. These measures were correlated with BMI, a measure of body weight. High levels of interleukin-6 at the beginning of the study predicted who would have a chronic course of illness.**

Editor's Note: Previous studies have found that elevated levels of CRP predicted a future mood episode in people at high risk for bipolar disorder due to a family history of the illness.

These studies suggest that it might be useful to assess levels of these inflammatory markers (CRP, interleukin-1, interleukin-6, and TNF-alpha) in young people who are at high risk for bipolar disorder. Factors that put someone at high risk include a family history of depression or bipolar disorder, a history of adversity in childhood (abuse, neglect, loss of a parent, etc.), and preliminary symptoms.

Several interventions are available that may reduce the likelihood that someone at risk for bipolar disorder will go on to develop the illness. Family interventions such as the Family Focused Therapy developed by researcher David Miklowitz are helpful. In a 2013 study in the Journal of the American Academy of Child and Adolescent Psychiatry, *Miklowitz reported that Family Focused Therapy outperformed treatment as usual for youth at risk for bipolar disorder.*

Measures of inflammation might provide additional rationale for beginning interventions in youth at high risk for mood disorders. In addition to family interventions, omega-3 fatty acid supplementation is a low-risk option that is supported by some positive data. Since BMI was implicated in the study by Lamers and colleagues, keeping weight under control might also have some benefit.

For adults with depression who want to keep their weight under control, the combination of the antidepressant bupropion XR (150–300mg/day) and naltrexone (50mg/day), an opiate antagonist medication normally used to fight addictions, has been effective.

Emotional Abuse Increases Inflammation

Trauma in childhood is a risk factor for depression, and both childhood trauma and depression have been linked to increased inflammation. In a study presented at the 2016 meeting of the Society of Biological Psychiatry, Sarah R. Horn and colleagues found that emotional abuse in childhood predicted high levels of inflammation measured in the blood in adulthood.

Horn and colleagues took blood samples from 35 people with treatment-resistant depression and 28 healthy control subjects. The researchers measured inflammatory markers in the blood and also interviewed the participants about any physical, sexual, or emotional abuse they experienced in childhood. Among all the participants, **emotional abuse was linked to elevated levels of several inflammatory markers, including interleukin-6, interleukin-10, interleukin-1a, interleukin-15, and fractalkine.**

The researchers suggest that more research is needed to clarify the link between early trauma, depression, and inflammation. How elevated inflammation in people with a history of abuse may influence the effectiveness of different psychotherapies and medications for depression remains to be determined.

Mothers Who Were Abused in Childhood Secrete Less Oxytocin While Breastfeeding

A recent study suggests that women who experienced moderate or severe abuse in childhood secrete less oxytocin while breastfeeding their own children. Oxytocin is a hormone that promotes emotional bonding. The study included 53 women. They breastfed their newborn children while blood samples were collected from the women via IV. **Those women with a history of moderate or severe abuse (emotional, physical, or sexual) or neglect (emotional or physical) had lower measures of oxytocin in their blood during breastfeeding than women with no history or abuse in childhood or a history of mild abuse.**

A history of abuse or neglect was more common among women with current depression compared to women with a history of depression or anxiety. Women who had never experienced depression or anxiety were least likely to have a history of abuse or neglect.

The study by Alison Steube and colleagues, presented at the 2016 meeting of the Society of Biological Psychiatry, suggests that traumatic events that occur during childhood may have long-lasting effects. These experiences may modulate the secretion of oxytocin in adulthood. Low oxytocin has been linked to depression.

Intranasal Oxytocin Soon After a Trauma May Prevent Worsening PTSD

Oxytocin, a hormone that promotes emotional bonding, also benefits people having trouble dealing with stress. A new study suggests that giving oxytocin for a week shortly following a traumatic experience reduces the risk that the recipient will develop post-traumatic stress disorder (PTSD).

In the study by researcher Mirjam van Zuiden and colleagues, people who visited an emergency room following some kind of trauma were randomized to receive either a placebo nasal spray or intranasal oxytocin twice daily for 7.5 days beginning within 12 days after the trauma. The dosage was 40 IU twice daily.

For those participants with severe PTSD symptoms at baseline, repeated oxytocin administration prevented worsening PTSD. The research was presented at the 2016 meeting of the Society of Biological Psychiatry.

Oxytocin Improves Facial Expressiveness in People with Autism

In a new study by Keiho Owada and colleagues, 18 people with autism spectrum disorders had more neutral facial expressions and fewer surprised expressions than 17 typically developing people while interacting socially. **Oxytocin, a hormone that promotes social bonding, was delivered to the autism group via a nasal spray for six weeks, and made the faces of the people with autism more expressive.** Oxytocin also improved their reciprocity in social interactions and increased activity in the dorsomedial prefrontal cortex, as observed via functional magnetic resonance imaging (fMRI).

The study suggests not only that oxytocin can normalize facial expressions, but also that the counting of facial expressions on videos of social interactions can be used as a measure of social symptoms of autism. The research was presented at the 2016 meeting of the Society of Biological Psychiatry.

Animal Studies Suggest That Oxytocin May Treat Addictions

Oxytocin, the hormone that promotes emotional bonding, also regulates a variety of behaviors. Two recent studies suggest that in rats, an injection of oxytocin can prevent drug-seeking behavior.

In the first study, researcher Gary Aston-Jones found that **oxytocin reduced the rats' interest in methamphetamine.** The effect was strongest in the rats that started out with the strongest interest in the methamphetamine.

In the second study, researcher Luyi Zhou and colleagues determined that **oxytocin also reduced cocaine-seeking behavior in rats.** In addition, the oxytocin reversed changes in the brain's glutamate signaling pathway that were caused by cocaine use.

Both studies, which were presented at the 2016 meeting of the Society of Biological Psychiatry, suggest that oxytocin is a promising potential treatment for drug addictions.

Azithromycin Antibiotic May Improve PANS

PANS is a neuropsychiatric syndrome affecting children. A child with PANS begins exhibiting obsessive compulsive and other abnormal behaviors, tics, and mood changes directly following a bacterial or viral infection. PANS refers to any pediatric acute-onset neuropsychiatric syndrome of this type, while PANDAS refers more specifically to such a syndrome that occurs after a streptococcal infection.

New research suggests that treatment with the antibiotic azithromycin can treat PANS. In a study presented at the 2016 meeting of the Society of Biological Psychiatry, Tanya K. Murphy and colleagues found that **among 32 children aged 4–14 who showed obsessive compulsive symptoms following an infection, those who were given a 4-week course of azithromycin (10mg/kg of body weight, up to 500 mg/day) saw a 26% drop in symptoms, compared to a 1% drop in symptoms in those who received placebo instead.**

At the end of the four weeks, 38.9% of the azithromycin group were classified as much improved or very much improved, while no one in the placebo group achieved this level of improvement. Azithromycin treatment increased the QTc interval (a measure of heart rate) and pulse in the study participants, but did not have any other notable side effects.

PANS is thought to arise from an immune response to infection that goes awry and begins attacking neurons in the brain, particularly in the thalamus. For a more complete review of PANS, see a relevant case study in *BNN* Volume 19, Issue 6 from 2015 and an excellent review article by researcher Kiki Chang and colleagues in the *Journal of Child and Adolescent Psychopharmacology* in 2015.

It is important to work up a child suspected of having PANS, as the syndrome does not usually respond to conventional psychiatric treatment and often requires anti-inflammatory drugs (steroids or immunosuppressants), intravenous immunoglobulin (IVIG), plasma exchange, the TNF alpha blocker infliximab, or antibiotics.

Allopregnanolone Injection Eliminated Post-Partum Depression in Four Women

In a small proof-of-concept study, researcher Stephen J. Kanes and colleagues showed that injections of allopregnanolone could nearly eliminate symptoms of post-partum depression. Allopregnanolone is the main metabolite of the hormone progesterone. Rapid changes in hormone levels following delivery are thought to cause post-partum depression.

In the study, four women with post-partum depression were given injections of SAGE-547, a proprietary solution of allopregnanolone. The dose was adjusted over 12 hours until it approximated prenatal levels of allopregnanolone. This level was maintained for 36 hours, and then the women were weaned off the SAGE-547 over another 12 hours. **As soon as the women began injections of SAGE-547, their depression began to improve, and this lasted after they stopped receiving the injections.** By 84 hours after beginning treatment, depression scores had improved by 81%.

Kanes and colleagues, who presented this research at the 2016 meeting of the Society of Biological Psychiatry, will follow up this study with placebo-controlled trials of SAGE-547.

Lithium Increases Cortical Thickness in People with Bipolar Disorder

Recent studies have indicated that bipolar disorder is associated with changes to brain volume, including thinning of the cortex. In research presented at the 2016 meeting of the Society of Biological Psychiatry, researcher Noha Abdel Gawad reported that **four weeks of lithium treatment increased cortical thickness in the left superior frontal gyrus.** This is the third replication of this finding.

Other research has established that lithium treatment also increases the volume of the hippocampus in people with bipolar disorder. Together the findings provide strong evidence that lithium treatment protects neurons and can reverse brain changes associated with bipolar disorder.

Lithium Lengthens Telomeres

Telomeres are repeated DNA sequences that sit at the end of chromosomes and protect the DNA as it is replicated. Depressive episodes and age can reduce the length of telomeres. Lithium treatment increases telomere length. At the 2016 meeting of the Society of Biological Psychiatry, researcher Martin Schalling reported that **the longer a patient takes lithium, the more their telomere length increases.**

According to Schalling, people who respond well to lithium treatment show greater increases in telomere length than those who respond poorly to lithium.

While some cancers are associated with long telomeres, lithium use has not been found to increase cancer risk. In fact, lithium treatment can decrease the risk of certain cancers of the gastrointestinal, respiratory, and endocrine systems.

Treatment with Hormone EPO Improved Cognition in People with Unipolar and Bipolar Disorder

People with unipolar depression and bipolar disorder may experience cognitive difficulties, even when they're not currently depressed. In a study published in the journal *European Neuropsychopharmacology* in 2016, researchers led by Caroline Vintergaard Ott determined that treatment with the hormone erythropoietin (EPO) may help. EPO is produced in the kidney and increases the production of hemoglobin and red cells.

Seventy-nine participants with unipolar or bipolar disorder were randomized to receive infusions of either EPO or a saline solution once a week for eight weeks. By the end of the study, those who received EPO showed significant improvements in the speed of their complex cognitive processing compared to those who received saline. EPO is known to induce the production of red blood cells. The improvements in processing speed lasted for at least another six weeks after red blood cell production would have normalized.

Those participants who received EPO not only had improved scores on tests of processing speed, they also reported fewer cognitive complaints. The EPO treatment was most likely to be effective in participants who had more impaired cognition at the beginning of the study.

In previous research by the same research group presented by Kamilla W. Miskowiak at the 2014 meeting of the International Society of Bipolar Disorders, EPO also improved sustained attention and recognition of happy faces.

Galantamine Did Not Improve Cognitive Deficits in People with Bipolar Disorder

In a recent study by researcher Dan V. Iosifescu and colleagues, the drug galantamine, which is used to treat dementia, did not improve cognitive function in euthymic people with bipolar disorder. The drug had done so in earlier studies. Seventy-two participants with bipolar disorder that was in remission were randomized to receive either a placebo or galantamine extended release for a period of two weeks. Doses of galantamine ranged from 8 to 24 mg/day.

The participants took several tests of attention and memory over the course of the study. After 16 weeks of treatment, those taking galantamine did not show significant improvements in functioning compared to those who received placebo.

This research was presented at the 2016 meeting of the Society of Biological Psychiatry.

Just 2 minutes per week could improve your child's health!

Parents of children aged 2–12 who have mood or behavioral problems should consider joining the Child Network, 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.

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.

Note: Don't be discouraged by the initial consent form, which takes 10 minutes to complete, and the intake form (including demographic data and an initial symptom checklist), which takes another 15 minutes. These are a one-time task, while ongoing weekly ratings take only 2 minutes.

TO PARTICIPATE: Go to **bipolarnews.org** and click on the tab for Child Network. For more information, see page 11 of this issue, call 301-530-8245, or email questions to childnetworkbnn@gmail.com.

Research Study
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IRB Study #00026940

Microdoses of Lithium May Stabilize Cognition in People with Alzheimer's

Several researchers have found that lithium has some value in fighting dementia. The researcher Lars Kessing has published several studies showing that people taking clinical doses of lithium for bipolar disorder have a lower incidence of dementia in old age.

In 2011, another researcher, Oreste Vicentes Forlenza, reported that a year of low-dose lithium (typically around 300mg/day) slowed deterioration in people with mild cognitive impairment compared to placebo.

In an article published in the journal *Current Alzheimer Research* in 2013, researchers led by Marielza Andrade Nunes reported that **very small doses of lithium (more than a thousand times lower than doses used to treat mood disorders) also improved mild cognitive impairment in people with Alzheimer's disease.**

In Nunes' study, participants with Alzheimer's disease were randomly assigned to receive either 300 *micrograms* of lithium daily or a placebo. Beginning at three months of treatment, those receiving the microdoses of lithium showed stable performance on a common Alzheimer's evaluation tool that measures how well patients remember, recall information, and follow directions; while those taking placebo got worse. This continued over the 15 months of the study, with the difference between the two groups intensifying over time—those taking placebo got worse, while those getting the microdoses of lithium remained stable.

There were no complaints of side effects from the microdoses of lithium, and participants showed no sign of impairment to their kidney or thyroid function (a risk with the higher doses of lithium used to treat bipolar disorder).

In 2015, Nunes and colleagues reported in the journal *PLOS ONE* that in a mouse model of Alzheimer's disease, mice treated with chronic low doses of lithium in their water had less memory disruption, fewer plaques in the brain, and fewer reductions in cortex and hippocampus size compared to mice given plain water.

These studies suggest that low or micro doses of lithium may be a promising treatment for Alzheimer's disease. Much more research is needed to determine appropriate lithium dosing for the treatment of dementia or cognition problems.

Medical Device May Treat Alzheimer's Disease

A recently completed clinical trial suggests that **NeuroAD, a treatment system that combines transcranial magnetic stimulation and cognitive training targeted at brain regions affected by Alzheimer's disease, may be effective at treating mild to moderate cases of the illness.**

Neuronix Ltd, the company that produces the device used to deliver transcranial magnetic stimulation in the trial, plans to seek Food and Drug Administration approval for NeuroAD. It would be the first device approved for the treatment of Alzheimer's in the US. The device is already in use in Europe and Asia.

In the clinical trial, 131 patients received six weeks of the NeuroAD treatment or a sham treatment used as a comparison. Those participants who received the real intervention performed better on an assessment of Alzheimer's and experienced minimal side effects.

In transcranial magnetic stimulation, a non-invasive procedure, magnets placed near the skull stimulate electrical impulses in the brain. This activates neurons, releasing excitatory transmitters and brain-derived neurotrophic factor (BDNF), which is important for new synapse formation and long-term learning and memory.

Editor's Note: This editor (Robert Post) has long advocated the use of repeated transcranial magnetic stimulation (rTMS) with simultaneous cognitive behavioral or other positive therapy to activate and enhance specific neural circuits and relieve depression. The trial of NeuroAD adds evidence of the positive effects of this approach in domains other than depression. Cognitive training enhanced by rTMS may be helpful with a variety of cognitive difficulties.

Folate Fortification in Processed Foods Led to Greater Cortical Thickness

In 1996, the US began to require that enriched cereal grain products be fortified with folate, a vitamin that is particularly important to fetal brain development. A new study of children born before and after this policy change suggests that **the increased folate in commercial foods after 1996 led to increases in cortical thickness in the children born after the change.**

At the 2016 meeting of the Society of Biological Psychiatry, Joshua L. Roffman and colleagues described their research into the effects of folate fortification. The researchers identified 3,309 children born between 1993 and 2001 who had had a magnetic resonance imaging (MRI) brain scan. Analysis of the scans showed that children born after folate fortification began had thicker cortices than those born before the change. The frontal and temporal regions of the brain were particularly affected.

A thin cortex is a risk factor for schizophrenia and other cognitive problems.

Editor's Note: Folate supplementation has also been shown to enhance the effects of selective serotonin reuptake inhibitor (SSRI) antidepressants in adults with lingering symptoms of depression.

Up to a third of the population may have a deficit of MTHFR, an enzyme important for folate metabolism, and for these people, l-methylfolate is recommended rather than folate itself.

Omega-3 Fatty Acids May Be Helpful Early in Schizophrenia, But Not Later

Some studies have suggested that omega-3 fatty acids may be helpful in the treatment of schizophrenia, but data to support this idea have been inconsistent. A recent meta-analysis of research on omega-3s and schizophrenia suggests that this nutritional supplement might be more useful in early-stage schizophrenia than in later illness.

At the 2016 meeting of the Society of Biological Psychiatry, researchers led by Alexander T. Chen presented the findings of their meta-analysis. First they analyzed six studies that shared a common scale for measuring schizophrenia symptoms. In these studies, omega-3 fatty acids did not outperform placebo when used as an add-on treatment to antipsychotics for people with schizophrenia.

In four remaining studies of omega-3 fatty acids and schizophrenia, **the omega-3s were associated with improvement only in patients in the early stages of schizophrenia. Compared to placebo, the supplements decreased non-psychotic symptoms, decreased the dosage of antipsychotic medication patients required, and improved early treatment response (but not late treatment response) in patients in their first episode of schizophrenia.**

In the same study, omega-3 fatty acids also reduced conversion to full-blown schizophrenia and psychotic symptom severity in patients at high risk for schizophrenia who were having preliminary symptoms of the illness.

Editor's Note: Researcher Paul E. Keck has also found that omega-3 fatty acids may be more effective early in bipolar disorder rather than later. He reported that younger patients with bipolar depression and rapid cycling showed more improvement when taking the omega-3 fatty acid EPA than when taking placebo. In contrast, patients with bipolar depression who were over the age of 45 did worse on EPA than on placebo.

Part of the ambiguity about whether omega-3 fatty acids can help treat or prevent mental illness may be explained by the supplements working better in younger people or earlier in the course of an illness.

Vitamin D Supplementation Not Effective in Bipolar Depression, But Still Worth Doing

In some studies, vitamin D supplementation (1,500 IU/day) has been found to improve unipolar depression. Recently, researchers led by Wendy K. Marsh found that compared to placebo, 12 weeks of vitamin D3 supplementation (5,000 IU/day) did not produce greater improvement in depressive symptoms. The study, presented at the 2016 meeting of the Society of Biological Psychiatry, included 33 adult participants whose vitamin D levels remained deficient throughout the study.

Editor's Note: Caution is urged in interpreting this small study, especially because the participants did not achieve healthy levels of vitamin D.

Low levels of vitamin D are common in children and adults with bipolar disorder. Future research may explore whether raising vitamin D levels to healthy levels has a beneficial effect on mood. There are many other benefits to vitamin D supplementation. It can improve cognition, regulate calcium and phosphorus absorption, and maintain healthy bones and teeth. It may also protect against diseases such as cancer, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn's disease. Improved cardiovascular health is also a possible benefit of vitamin D supplementation.

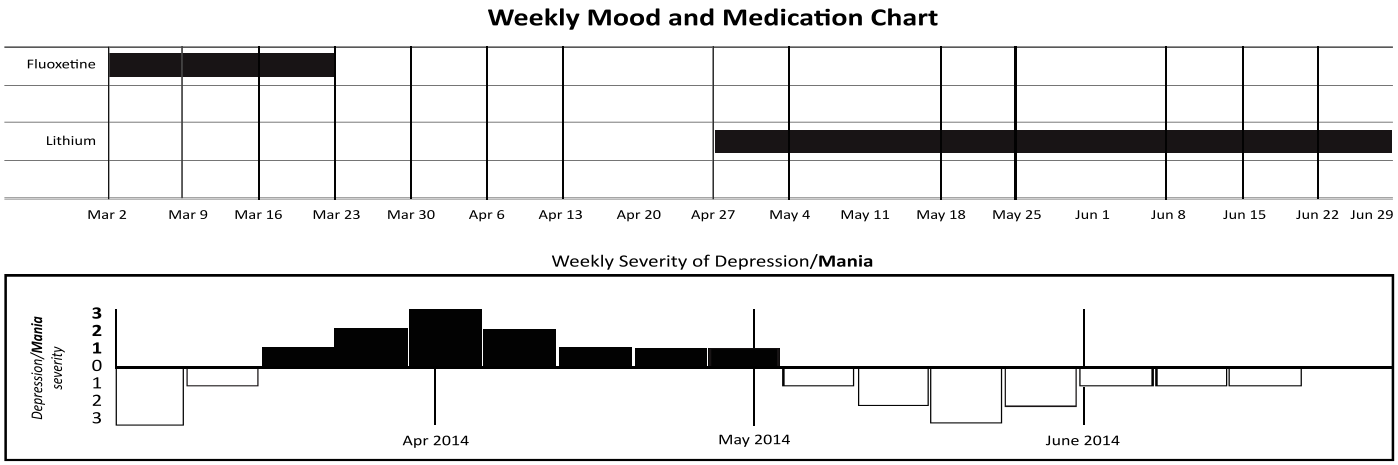
Is Your Child at Risk for a Mood Disorder? Join the Child Network

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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