

# Bipolar Network News

Published since 1995

The latest news on bipolar disorder research from around the world

bipolarnews.org

## “De Novo” Mutations in Dozens of Genes Cause Autism

Vol. 19, Issue 4, 2015

Two studies that incorporated data from more than 50 labs worldwide have linked mutations in more than 100 different genes to autism. Scientists have a high level of statistical confidence that mutations in about 60 of those genes are responsible for autism. So-called *de novo* (Latin for “afresh”) mutations do not appear in the genes of parents without autism, but arise newly in the affected child. The mutations can alter whether or not the genes get “turned on” or transcribed, leading to disturbances in the brain’s communication networks.

The studies led by Stephan Sanders and Matthew W. State appeared in the journal *Nature* in late 2014. The identi-

fied genes fall into three categories. Some affect the formation and function of synapses, where messages between neurons are relayed. Others affect transcription, the process by which genes instruct cells to produce proteins. Genes in the third category affect chromatin, a sort of packaging for DNA in cells.

Before the new studies, only 11 genes had been linked to autism, and the researchers involved expect to find that hundreds more are related to the illness.

*Editor’s Note: This new research explains how autism could be increasing in the general population even as most adults with autism do not have children. It should also put to rest the idea, now totally*

*discredited, that ingredients in childhood immunizations cause autism. It is clearer than ever that kids who will be diagnosed with autism are born with these mutations.*

*With these genetic findings, the search for new medications to treat this devastating illness should accelerate even faster.*

*Bottom line: Childhood immunizations don’t cause autism, newly arising mutations in the DNA of parents’ eggs or sperm do. However, parental behavior could put their children and others at risk for the measles and other serious diseases if they do not allow immunizations. The original data linking autism to immunization were fraudulent, and these new data on the genetic origins of autism provides the best hope for future treatments or prevention.*

## More Evidence N-Acetylcysteine Added to Risperidone Improves Irritability in Autism

We reported in 2014 that researchers Ahmad Ghanizadeh and Ebrahim Moghimi-Sarani had found that the over-the-counter nutritional supplement n-acetylcysteine (NAC) added to the atypical antipsychotic risperidone reduced irritability in autism more than placebo added to risperidone.

A randomized, double-blind, placebo-controlled clinical trial published by M. Nikoo and colleagues in the journal *Clinical Neuropharmacology* in 2015 replicated these results. Forty children with autism disorders aged 4–12 years were randomized to receive either risperidone plus NAC or risperidone plus placebo. Risperidone doses were between 1 and 2 mg/day, and NAC doses were 600 to 900 mg/day. **By the end of the 10-week study, those children who received NAC had significantly greater reductions in irritability and hyperactivity/noncompliance than those who received placebo.**

*Editor’s Note: Three placebo-controlled studies have supported the efficacy of NAC in autism. One 2012 study, by A.Y. Hardan in *Biological Psychiatry*, evaluated monotherapy with oral NAC. In the other two, NAC was added to treatment with risperidone.*

## No Evidence Chelation Therapy Can Treat Autism

Some children with autism have been subjected to chelation therapy, which is used to remove heavy metals from the blood after poisoning. The rationale for using this therapy in autism was the discredited theory that autism resulted from mercury poisoning. A recent review of research on chelation therapy for autism by the Cochrane Collaboration, a nonprofit health research organization, found only one randomized controlled trial of chelation therapy, which had a flawed methodology and also found no evidence of a reduction in autism symptoms. This means **there is no evidence that chelation therapy, which can lead to kidney failure or death, has any effect on autism symptoms.** Based on the lack of evidence that the therapy has benefits for children with autism spectrum disorders, its great expense, and the dangers it poses, chelation therapy should not be prescribed as a treatment for autism.

### Rate Children at Risk for Mood Disorders

See our last page for information on the Child Network. Enrolled parents can rate the symptoms of children (ages 2–12) on a weekly basis and print out charts of the results to show physicians.

# Long-Term Lithium Treatment Still Has Risks for Kidney Function

Long-term lithium use has long been associated with decreased renal function. But some Swedish researchers noticed that most long-term studies of patients with renal failure had begun in the 1960s and 1970s. In the 1980s, when it became clear that lithium could reduce renal function, doctors began to institute new safety measures for lithium users, including monitoring of blood levels of the drug and of creatinine, a substance that is excreted by the kidneys as part of normal muscle metabolism. So the researchers undertook a new study to examine whether the protocols instituted in the 1980s had

reduced the renal risks of long-term lithium use. Unfortunately, they found that **some reduced renal function is still common among people who use lithium for longer than 10 years, and this risk does not necessarily decrease when patients stop taking lithium.**

The researchers, led by Harald Aiff, published the study in the *Journal of Psychopharmacology* in 2015. They identified 4,879 patients who had been prescribed lithium, and narrowed this list down to 630 adult patients who had taken lithium for at least 10 cumulative years, who had normal levels of creatinine when they began taking lithium, and on whom good

data existed. About one-third of these patients had evidence of chronic renal impairment, and in 5% of these the impairment was severe or very severe.

Aiff and colleagues' findings show that lithium treatment requires careful monitoring, especially over the long term. Patients must consider the risk/benefit ratio of lithium treatment. Since prevention of mood episodes can preserve an average ten years of life expectancy, and lithium has the best data for efficacy in preventing manic and depressive episodes, patients must weigh the risks of insufficiently treated bipolar illness against the possibility for long-term decreases in kidney function.

## Bipolar Network News

**Editor-in-Chief:** Robert M. Post, MD  
**Managing Editor:** Moira McCauley

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

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact or omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

As per recent journal disclosure requirements, Dr. Post has consulted to or spoken for Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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

Send any comments or suggestions to:  
mccauleybcn@gmail.com

**BNN**  
5415 W. Cedar Lane  
Suite 201B  
Bethesda, MD 20814

To subscribe or unsubscribe, see our website or email us at:

**info@bipolarnews.org.**

Note that we do not accept requests to subscribe friends or family members. Please have them contact us directly.

bipolarnews.org

## Lithium May Slow or Prevent Dementia

Lithium inhibits the enzyme glycogen synthase kinase 3, which has been implicated in dementia. To study whether lithium may prevent cognitive decline, researchers led by Tobias Gerhard looked at the medication histories of patients with bipolar disorder who were 50 years of age or older. In their article published in the *British Journal of Psychiatry*, **those patients who had taken lithium 301-365 days out of the previous year had substantially lower risk of dementia** than those who had not taken lithium during that time. Patients who had 300 or fewer days of lithium use did

not have a significant reduction in dementia risk, nor did patients who were prescribed anticonvulsant drugs.

*Editor's Note: These data are consistent with those of Lars Kessing and colleagues, which suggest that patients in Denmark who renewed their lithium prescriptions were less likely to receive a diagnosis of dementia in old age.*

In 2011, Orestes V. Forlenza and colleagues also reported in the *British Journal of Psychiatry* that compared to placebo, a very small dose of lithium, 150 mg/day, slowed the progression of mild cognitive impairment over one year.

## Mental Illness Linked to Loss in Life Expectancy

Severe mental illness is one of the leading causes of death worldwide. Recently researchers led by E.R. Walker performed a meta-analysis of all cohort studies comparing people with mental illness to non-ill populations. They used five databases to find 203 eligible studies from 29 countries. Their findings, published in the journal *JAMA Psychiatry* in 2015, show that people with mental illness have a mortality rate 2.22 times higher than people without mental illness. **People with mental**

**illness lose a potential 10 years of life compared to those without severe mental disorders.** The researchers estimated that 14.3% of deaths worldwide are attributable to mental illness.

*Editor's Note: Comorbid cardiovascular illness accounts for a large part of the disparity in life expectancy between people with and without mental illness. Those at risk for serious mental illness should pay close attention to their cardiovascular as well as psychiatric risk factors.*

## Genetic Variation Predicts Which Type of Antidepressant Will Work

In a six-month study of Caucasian patients, normal variations in the gene that is responsible for brain-derived neurotrophic factor (BDNF) predicted whether patients would respond better to a selective serotonin reuptake inhibitor (SSRI) antidepressant versus a serotonin and norepinephrine reuptake inhibitor (SNRI) or a tricyclic antidepressant. **There are several common variants of the BDNF gene**, depending on which types of amino acids appear in its coding – valine or methionine. **Patients with the most common version, two valines (or Val66Val),**

**responded better to SSRIs.** About two-thirds of the population has this version of the gene, which functions most efficiently. The remaining third have at least one methionine in the BDNF gene. **Patients with a Met variation responded better to SNRIs and tricyclic antidepressants.**

The study by R. Colle and colleagues was published in the *Journal of Affective Disorders* in 2015. Of the patients who were prescribed SSRIs, 68.1% of patients with the Val/Val version responded to the medication after three months, compared to 44%

of the patients with a Met version. Of patients prescribed SNRIs or tricyclics, 60.9% of the Met patients reached remission by six months, compared to only 33.3% of the Val/Val patients.

*Editor's Note: In an earlier BNN we reported that according to research published by Gonzalo Laje and colleagues in the journal Biological Psychiatry in 2012, depressed patients with the better functioning Val66Val allele of BDNF respond better to ketamine, while those with the intermediate functioning Val66Met allele respond less well.*

## Verbal Abuse in Childhood, Like Physical and Sexual Abuse, Linked to Earlier Onset and More Difficult Course of Bipolar Disorder

Earlier research has shown that childhood adversity is linked to earlier age of onset of bipolar disorder and more difficult course of illness. Physical and sexual abuse are associated with both earlier age of onset and more difficulties such as anxiety disorders and substance abuse. Now, new research by this editor (Robert M. Post) and colleagues links verbal abuse (even in the absence of physical and sexual abuse) to earlier onset of bipolar disorder and to more severe and complicated course of illness.

The study, published in the journal *Bipolar Disorders*, was based on the self-reports of 634 adult outpatients with bipolar disorder at four sites in the US. These participants were interviewed about their history of illness and the frequency of adverse events they experienced in childhood, adolescence, and adulthood, including physical, sexual, and verbal abuse. Twenty-four percent of these participants reported having experienced verbal abuse occasionally or frequently in childhood, but not other forms of abuse, while another 35% had a history of verbal abuse as well

as physical or sexual abuse, for a total of 59% with a history of verbal abuse.

The greater the frequency of verbal abuse in childhood, the earlier the average age of onset of bipolar disorder. Participants with no history of abuse had a mean age of onset of 20.6 years, but verbal abuse by itself reduced the mean age of onset to 16.5 years, and verbal abuse plus sexual abuse reduced the mean age of onset to 15.3 years. (The mean age of onset for participants who experienced sexual abuse alone was 17.5 years.) It was impossible to determine the combined effect of verbal and physical abuse because verbal abuse was almost always present when physical abuse occurred. For the 14% of the participants who had experienced verbal, physical, and sexual abuse in childhood, the mean age of onset of bipolar disorder was 13.1 years.

**Those who were verbally (but not physically or sexually) abused in childhood had more anxiety disorders, drug abuse, and rapid cycling than those who were not abused**, but not more alcohol abuse. Those who were verbally abused also showed

increasing severity of illness, including increased frequency of cycling.

Genetics can also play a role. Having a parent with a mood disorder also contributed to an earlier age of onset of bipolar disorder.

*Editor's Note: Researcher David J. Miklowitz and colleagues have shown that family focused therapy (FFT), which emphasizes illness education and communication enhancement within the family, is more effective than treatment as usual for children with a family history of bipolar disorder and a diagnosis of depression, cyclothymia, or bipolar not otherwise specified (BP NOS).*

*FFT was particularly effective in reducing symptoms in children from families with high expressed emotion, suggesting that this kind of family-based intervention could reduce levels of verbal abuse.*

Have you  
visited us online?  
**bipolarnews.org**



## Placebo-Controlled Trial Shows Diabetes Drug Pioglitazone May Improve Bipolar Depression

The hypoglycemic drug pioglitazone is typically used to treat diabetes, but a 2015 study by A. Zeinoddini and colleagues shows that it may improve depressive symptoms in patients with bipolar disorder who do not have type 2 diabetes or the metabolic syndrome (characterized by high weight, cholesterol, triglycerides, and blood pressure).

Forty-four patients with bipolar disorder and a major depressive episode were randomized to receive either 30 mg/day of pioglitazone or placebo as an adjunctive treatment to lithium. **Depressive symptoms were lower in the pioglitazone group at weeks 2, 4, and 6 of the six-week study.**

No serious side effect occurred in the study, but pioglitazone use is associated with some risks in those using it for diabetes treatment. People taking pioglitazone for longer than a year have shown increased rates of bladder cancer. There is an increased risk of fractures of the upper arms, hands, and feet in female patients. The drug also lowers blood sugar, but not enough to be a problem in people not taking other drugs that lower blood sugar. Pioglitazone can also cause fluid retention, worsening congestive heart failure, and it can cause mild weight gain, anemia, and sinus problems.

## Deep Transcranial Magnetic Stimulation Safe and Effective in Major Depression

Repeated transcranial magnetic stimulation is a non-invasive procedure that has been approved for the treatment of severe depression since 2008. In rTMS treatment, a figure-8-shaped electromagnetic coil is placed against the forehead and magnetic pulses that can penetrate the scalp are converted into small electrical currents that stimulate neurons in the brain up to 1.5 cm deep. More recently, in 2013, the Federal Drug Administration approved a device with an H-shaped coil that delivers deep transcranial magnetic stimulation (dTMS). It can stimulate a wider area, and up to 8 cm deep.

Y. Levkovitz and colleagues have published the first double-blind randomized controlled multicenter trial of dTMS, reporting in the journal *World Psychiatry* that the intervention was effective and safe in patients who had not responded to antidepressant medication.

The study included 212 patients aged 22–68 years. All participants had

failed to respond to one to four antidepressants or had not been able to tolerate the side effects of at least two antidepressants during their current episode of depression. The patients were randomized to receive either a sham treatment or 18 Hz dTMS over the prefrontal cortex acutely for four weeks and biweekly for 12 weeks for a total of 20 sessions.

The patients who received dTMS showed significantly greater improvement in symptoms than those who received the sham treatment, with a moderately large effect size of 0.76. Response and remission rates were also better in those who received dTMS. **Response rates were 38.4% for the dTMS group versus 21.4% in the sham group. Remission rates were 32.6% for the dTMS group and 14.6% for the sham group.** These differences in response remained stable during the three months of the study.

Side effects were minor except for a seizure that occurred when the protocol for the treatment was breached.

## Vagal Nerve Stimulation Successful for Severe Depression

Vagal nerve stimulation (VNS) is an FDA-approved treatment for both seizures and depression that has resisted other treatments. It requires an operation for the insertion of a stimulator in the chest wall and electrodes on the left vagus nerve in the neck. A new study by Scott T. Aaronson and colleagues presented at the 2015 meeting of the Society of Biological Psychiatry observed severely depressed patients, 494 who received VNS and 301 who received treatment as usual in the community, over a period of five years. **The patients who received VNS had greater response rates, they were more likely to have experienced remission, and their remissions lasted longer than those who received treatment as usual.** Overall the patients who received VNS had lower mortality rates and suicide rates as well. VNS might be a good option for patients with depression that has not responded to most other treatments.

## Laughing Gas Briefly Reduces Depression

In a proof-of-concept study presented at the 2015 meeting of the Society of Biological Psychiatry, Charles R. Conway and Peter Nagele showed that an hour of 50% oxygen/50% nitrous oxide reduced depression more than placebo as measured 2 hours and 24 hours later. Twenty patients were randomized to receive the laughing gas combination or a placebo combination made up of 50% oxygen/50% nitrogen. **In the laughing gas group, four patients responded to the treatment and three patients achieved remission, compared to only one patient responding in the placebo group.**

Like the anesthetic ketamine, which can bring about rapid but temporary antidepressant effects when delivered intravenously, nitrous oxide is an NMDA receptor antagonist.

## Cognitive Behavioral Therapy: An Effective Follow-up to ECT

While electroconvulsive therapy (ECT) is very effective treating acute depression, especially among patients who have not responded to antidepressants, relapse rates following ECT are high. Researchers have been exploring treatments that may extend the effectiveness of ECT and reduce relapses, including antidepressant medication and continuation ECT. A new study by Eva-Lotta Brakemeier and colleagues in the journal *Biological Psychiatry* finds that cognitive-behavioral therapy combined with medication was most effective at sustaining response to ECT.

In the study, 60 patients who responded well to three-times-per-week right unilateral ultra-brief ECT then were prescribed antidepressant medication following current guidelines for ECT followup. Of these patients, one-third were randomly assigned to receive the medications only. Another third were randomly assigned to receive the medications and continuation ECT, and the final

third were randomly assigned to receive medication and participate in 15 weeks of cognitive-behavioral therapy in a group setting. Each group was observed at six months, and then at one year. The group who received medication and cognitive behavioral therapy had significantly higher response rates than the other groups at both follow-up evaluations.

After the initial treatment with ECT, 70% of the patients had responded and 47% had achieved remission. Following the six months of continuation treatment, **77% of the group that received medication and cognitive behavioral therapy responded, while only 40% of the group receiving medication and continuation ECT responded, and 44% of those receiving medication alone responded.**

After one year (six months after the end of treatment), response rates were 65% for those who had received medication and therapy, 28% for those who had received medication

and ECT, and 33% for those who had received medication alone.

*Editor's Note: These results are striking for several reasons. As has been found in most studies, continuation ECT is not very effective at sustaining remission. Cognitive behavioral therapy with medication beats the other options hands-down. These results are in accord with others that show that cognitive behavioral therapy also helps prevent relapses in patients who responded well to medications. The take-home message is that people who respond well to antidepressant medication or ECT would do well to add cognitive behavioral therapy to their other preventive treatments.*

The current study did not replicate parameters for continuation ECT that were successful in a study by Axel Nordenskjöld and colleagues in the *Journal of ECT* in 2013. Nordenskjöld used weekly ECT for six weeks and every two weeks thereafter, for a total of 29 ECT treatments in one year, and found this more intense regimen was more effective at preventing relapse than medication alone.

## Another Antidepressant Fails in Bipolar Depression

Despite repeated studies, including meta-analyses, showing that antidepressants that work in unipolar depression do not work in bipolar depression as adjuncts to mood stabilizers, antidepressants remain widely used for the treatment of bipolar depression. **A recent study of the antidepressant agomelatine has shown that it is not effective in bipolar depression.** In patients taking lithium or valproate but still depressed, agomelatine was no better than placebo at reducing depression.

**Agomelatine has an unusual mechanism of action (blockade of 5HT-2C receptors and activation of melatonin M1 and M2 receptors) that helps normalize sleep and circadian**

**rhythms, but only in unipolar depression.** Until this study by Lakshmi Yatham and colleagues in the *British Journal of Psychiatry*, it was thought that these properties would make the drug ideal for bipolar depression.

Three atypical antipsychotics have been approved by the Federal Drug Administration for bipolar depression: quetiapine (Seroquel), lurasidone (Latuda), and the olanzapine-fluoxetine combination Symbyax. These, used alongside mood stabilizers (lithium, valproate, carbamazepine, and lamotrigine) are more effective treatments for bipolar depression. There are other adjunctive treatments that may be helpful, such as the antioxidant N-acetylcysteine, vitamin D3, and folate.

**Bipolar Network  
News is available  
as an email  
newsletter!**

**Make the  
switch now!**



**<http://bipolarnews.org>**

## Substance Abuse Is a Treatable Brain Disorder

Depression and bipolar disorder come with a high incidence of substance abuse. **It is important to realize that there are now good medicines to treat the addictions as well as the primary mood disorders they accompany.** At the 2015 meeting of the American Psychiatric Association, Nora Volkow, director of the National Institute of Drug Abuse, encouraged psychiatrists to think of addiction as a “disease of the brain that disrupts the systems that allow people to exert self-control,” saying that this would help reduce stigma both for insurance companies and for the wider public.

Most treatment of substance abuse in bipolar disorder is off-label. Doctors must infer indirect evidence of the possible efficacy of each drug in bipolar disorder from studies in those with only the primary addiction, for example, cocaine abuse without bipolar disorder.

The table on the right is a preliminary rating of 1) the strength of the evidence for the efficacy of each drug in the primary addiction and 2) the likely utility of the drug for the treatment of addictions in people with bipolar disorder. For example, the drug baclofen has excellent evidence of efficacy in cocaine addiction, but gets a D for utility in bipolar disorder because baclofen can exacerbate depression.

This list is provisional, and the subjective grades for each drug are likely to change as more research is collected on these treatments. Consult a doctor if you are seeking treatment for bipolar disorder and/or substance abuse.

## Mindfulness Interventions May Reduce Substance Use and Cravings

A 2014 meta-analysis of the literature to date on mindfulness-based interventions (MBIs) for substance use disorders suggests that **these interventions can reduce consumption of alcohol, cocaine, amphetamines, marijuana, cigarettes, and opiates, compared to several types of controls.** The research by Alberto Chiesa and Alessandro Serretti, published in the journal *Substance Use and Misuse*, includes 24 studies published before 2012. The authors also found some evidence that MBIs are associated with reduced craving and increased mindfulness. Most of the studies included in the meta-analysis were small, so their generalizability is limited.

A 2014 article by S. Bowen and colleagues in the journal *JAMA Psychiatry* compared mindfulness-based relapse prevention with standard relapse prevention and treatment as usual for people recovering from substance abuse. Mindfulness-based relapse prevention combines the cognitive behavioral approach of standard relapse prevention with MBIs that have been successful in other studies.

Bowen et al. found that **both standard relapse prevention and mindfulness-based relapse prevention lowered the risk of relapse and reduced days of substance use at 6 months, compared to treatment as usual.** The standard treatment delayed first drug use, but the mindfulness intervention decreased use at the 12-month mark compared to both standard relapse prevention and treatment as usual.

## Treatments for Substance Use/Abuse in People with Bipolar Disorder

Of drugs that can treat addictions, some are more appropriate than others for use in people with bipolar disorder. This table rates 1) the evidence for the efficacy of each drug in the primary addiction and 2) the likely utility of the drug for the treatment of addictions in people with bipolar disorder.

	1) Strength of Evidence for Drug's Effectiveness in Primary Addiction	2) Usefulness For Addictions in Patients with Bipolar Disorder
--	---	--

### Alcohol (Abstinence)

Naltrexone	A	A
Topiramate	A	A
12-Step Programs	A	A
Valproate	A	A
N-Acetylcysteine	A	A
Acamprosate	A	B
Lamotrigine	C	C
Disulfiram	A	D

### (Withdrawal)

Benzodiazepines	A	A
Carbamazepine	A	A
Gabapentin	A	A
Valproate	B	B

### Cocaine

Topiramate	A	A
Modafinil	A	A
12-Step Programs	A	A
N-Acetylcysteine	A	A
Carbamazepine	C	C
Disulfiram	A	D
Baclofen	A	D

### Nicotine

Bupropion	A	A
Nicotine Patch	A	A
Alpha7 Agonist	A	B

### Food/Bulimia

Topiramate	A	A
Zonisamide	A	A
Dexamfedamine	A	C



## Inability to Balance on One Leg May Indicate Stroke Risk

A balance test may indicate declining cognitive health and risk for stroke. Researchers led by Yasuharu Tabara had previously found that balancing on one leg became more difficult for people with age. Now the same team has found that this type of postural instability is associated with decreases in cognitive functioning and with risk of stroke. Fourteen hundred participants with an average age of 67 were challenged to balance on one leg for up to 60 seconds. They also completed computer surveys, magnetic resonance imaging (MRI) scans, and a procedure to measure the thickness of their carotid artery. **Those who could not balance on one leg for 20 seconds or longer were more likely to have cerebral small vessel disease.**

*Editor's Note: Whether exercise would reverse this vulnerability remains to be seen, but lots of other data suggest the benefit of regular (even light) exercise on general health.*

## Inflammation Can Differentiate Apathy From Depression in Older Patients

In a new study by ESM Eurelings and colleague in the journal *International Psychogeriatrics*, the inflammatory marker C-reactive protein differentiated between older people with symptoms of apathy versus symptoms of depression. **Higher levels of C-reactive protein were found in those with symptoms of apathy.** The researchers concluded that apathy may be a manifestation of mild inflammation in elderly people.

## Transcranial Direct Current Stimulation Reduces Depression Following Strokes

One-third of people who have strokes face depression afterward. New research is looking to expand the safe options for the treatment of depression following strokes. At the 2015 meeting of the Society of Biological Psychiatry, researchers led by Leandro Valiengo presented their successful randomized, sham-controlled double-blind study of transcranial direct current stimulation (tDCS) for post-stroke depression. Forty-eight people who had depression following a stroke were randomized to receive either a sham procedure or tDCS in twelve 30-minute sessions over a period of six weeks. After the six weeks, **those who received tDCS had fewer symptoms of depression, more remission, and better response.** There were no serious side effects.

TDCS consists of very low-level electrical current that has a positive (anode) or negative (cathode) electrode. Anodal stimulation of the cortex is usually associated with positive effects on mood and cognition. TDCS sessions in this study consisted of 2-mA anodal left/cathodal right dorsolateral prefrontal stimulation.

*Editor's Note: Placebo-controlled studies have repeatedly indicated that patients who have a stroke show better neurological and psychiatric response afterward when they are given an selective serotonin reuptake inhibitor (SSRI) antidepressant, whether or not they have depression or a prior history of depression. If a neurologist does not suggest treatment with an SSRI after a stroke, ask why not. Since antidepressants increase brain levels of brain-derived neurotrophic factor (BDNF) and increase neurogenesis, they could help with post-stroke recovery.*

## Anti-TNF Alpha Antibody Improves Depression and Anhedonia in Patients with Rheumatoid Arthritis

Patients with rheumatoid arthritis have high levels of the inflammatory proteins known as interleukin-6 (IL-6), which have been implicated in depression and stress. Rheumatoid arthritis is sometimes characterized by depressive symptoms as well. New research by Dai Wang and colleagues presented at the 2015 meeting of the Society of Biological Psychiatry suggests that **treating the high levels of IL-6 in rheumatoid arthritis with the human anti-interleukin-6 antibody sirukumab can reduce symptoms of depression and anhedonia (loss of capacity to experience pleasure).**

In the study, patients with rheumatoid arthritis and symptoms of depression or anhedonia were randomized to receive either placebo or sirukumab. After 12 weeks, those who received sirukumab had significantly reduced depression.

*Editor's Note: These data are consistent with meta-analyses showing that IL-6 is elevated in depression and with a study by Scott Russo showing that in animals, interfering with IL-6 blocks the development of depression-like behaviors that typically occur after repeated defeat stress (when an animal is subjected to attacks from a larger, more dominant animal).*

## More Evidence Vortioxetine Improves Depression and Cognitive Function

Vortioxetine (Brintellix) is a relatively new antidepressant that has a range of effects on serotonin receptors, making it different from selective serotonin reuptake inhibitors (SSRIs), which work only on the serotonin transporter. In multiple studies, it has treated not only depression but also cognitive dysfunction. In a new study led by Atul Mahableshwarkar and published in the journal *Neuropsychopharmacology*, **10-20 mg/day of vortioxetine reduced symptoms of depression more than placebo and improved performance on tests of cognitive ability more than placebo and another antidepressant, duloxetine.**

While depression is often accompanied by cognitive dysfunction, in this study vortioxetine seemed to directly treat the cognitive deficits rather than reducing them by alleviating the depression. The participants were aged 18-65.

## Vitamin B6 May Reduce Restless Legs in Patients Taking Antipsychotics

The atypical antipsychotic lurasidone (Latuda) is one of only a few drugs effective at treating bipolar depression. But 5-10% of patients who take lurasidone experience akathisia, or restless legs.

At a recent meeting, psychiatrist Cynthia Turner-Graham told this editor (Robert Post) of her success in treating a patient with lurasidone-related akathisia that had been resistant to all the standard treatments, including dose reduction, anticholinergic drugs, benzodiazepines, beta-blockers, etc. **Vitamin B6 at a dose of 600mg twice a day gave the patient complete relief.**

Dr. Turner-Graham was kind enough to direct me to a small double-blind study supporting this clinical observation in patients with schizophrenia who experienced akathisia from treatment with antipsychotics. The study by V. Lerner and colleagues was published in the *Journal of Clinical Psychiatry* in 2004.

## Clozapine-Induced Myocarditis More Common Than Previously Thought

**New research indicates that myocarditis, inflammation of the middle layer of the heart wall, occurs in about 3% of patients who begin taking clozapine (Clozaril).** Researcher Kathlyn J. Ronaldson and colleagues recently published research to this effect in the journal *Acta Psychiatrica Scandinavica*. Many cases of myocarditis, which can be fatal, begin with fever. Other symptoms include rapid or abnormal heart rhythms, shortness of breath, fluid retention, and fatigue. Because the illness resembles a viral infection, it may be misdiagnosed.

In 2010 Ronaldson and colleagues reported in the *Journal of Clinical Psychiatry* that tachycardia (rapid resting heart rate) and elevated levels of a group of proteins known as troponin in the blood are almost always present during the first 45 days of treatment in patients who develop myocarditis. The researchers found that the time to onset of myocarditis was 14 to 22 days in almost all cases. Eosinophilia (high levels of a certain type of white blood cell) may occur in the week after peak troponin levels, and high levels of the inflammatory protein CRP (above 100mg/L) occurred in 79% of cases.

Ronaldson and colleagues suggest that patients who are prescribed clozapine be monitored for myocarditis during the first four weeks of treatment, particularly during the third week.

## Solutions for Clozapine-Induced Drooling

Clozapine is a treatment for schizophrenia and treatment-resistant bipolar disorder. Drooling is a side effect for about one-third of people taking clozapine. Here are some treatments that may help reduce it:

- 1) Botox injected into each salivary (parotid) gland in doses of 50 IU.
- 2) Ipratropium, either sprayed under the tongue or intranasally. A 2004 case series by Oliver Freudenreich in the *Journal of Clinical Psychiatry* described sublingual administration.
- 3) Glycopyrrolate. In a 2011 article in the *Annals of Pharmacotherapy*, AM Bird described some treatments for clozapine-induced drooling, including glycopyrrolate.
- 4) The blood pressure drugs clonidine (50-100 mg) or terazosin.
- 5) Transdermal scopolamine patch. This is typically placed behind the ear to reduce motion sickness, but it also reduces saliva production.



## Serotonin 5-HT7 Receptors: Why Should We Care About Them?

5-HT7 is a type of nervous system receptor that is activated by the neurotransmitter serotonin. Some of the most potent effects of lurasidone (Latuda), an atypical antipsychotic with antidepressant effects in bipolar depression, and vortioxetine (Brintellix), a unique antidepressant for unipolar depression that also has positive effects on cognition, occur through the blockade of 5-HT7 receptors. The atypical antipsychotics aripiprazole and sulpiride also act on 5-HT7 receptors.

Researcher Agnieszka Nikiforuk summarized the research to date on 5-HT7 receptors in the journal *CNS Drugs* in 2015.

**The receptors play a role in regulating sleep and circadian rhythms, which may explain why drugs that target them can be helpful in depression. Drugs that target 5-HT7 receptors have also improved learning and memory.**

One subject of research into 5-HT7 receptors is whether better results come from blocking the receptors or stimulating them.

Blockade of 5-HT7 receptors has improved depression-like symptoms in animals and enhances the effects of sub-therapeutic doses of antidepressants. In other animal studies, stimulation of the receptors has appeared promising for the prevention of age-related cognitive decline.

## Bright Light Therapy Adds to Venlafaxine's Antidepressant Effects

A study by Pinar Güzel Özdemir and colleagues in the *Journal of Clinical Psychiatry* indicates that bright light therapy may improve the effects of antidepressant venlafaxine (Effexor) in patients diagnosed with major depression for the first time. In the study of 50 inpatients, half received 150mg of venlafaxine at 7am each morning, while half received 150mg of venlafaxine plus 60 minutes of 7000 lux bright light therapy at 7am each morning. Beginning after the first week of treatment, both groups showed significant improvement in depression and negative mood states throughout

the eight-week study. However, at weeks 2 and 4, **the patients who received bright light therapy showed greater reductions in depression, with 76% reaching the target goal of treatment after four weeks compared to 44% of the venlafaxine-only group.**

Both venlafaxine and combined treatment with venlafaxine and bright light therapy reversed symptoms of depression, but adding bright light therapy may produce more rapid, stronger effects. Larger studies are needed to replicate these effects and determine whether they are long-lasting.

## Surprisingly, Adult ADHD Is Distinct From Childhood ADHD

In a longitudinal study of 1,037 people born in Dunedin, New Zealand in 1972 and 1973, most participants with attention deficit hyperactivity disorder (ADHD) in adulthood did not have the disorder as children. The study by Terrie E. Moffitt and colleagues in the *American Journal of Psychiatry* is the first prospective longitudinal study to describe the childhood of adults with ADHD.

When the study participants were children, about 6% were diagnosed with ADHD (mostly males). These children also had comorbid disorders, neurocognitive deficits, multiple genes associated with risk for ADHD, and some life impairment when they reached adulthood.

**In adulthood, about 3% of the participants had ADHD (roughly equal between men and women), and 90% of these participants had no history of ADHD in childhood.** The participants with ADHD in adulthood also had substance dependence and life impairment, and had sought treatment

for the disorder. The researchers were surprised to find that these participants with adult ADHD did not show neuropsychological deficits in childhood, nor did they have the genetic risk factors associated with childhood ADHD.

If the findings of this study are replicated, researchers will have to rethink the current classification of ADHD as a neurodevelopment disorder that begins in childhood, and begin to determine how adult ADHD develops.

*Editor's Note: Before the publication of this article, most investigators (including this editor Robert M. Post) thought that virtually all ADHD in adulthood evolved from the childhood disorder, and if it did not begin in childhood, the diagnosis was suspect. I still believe the ADHD that appears in adulthood in patients with bipolar disorder is likely attributable to residual depression and anxiety or hypomania and that more concerted treatment of the patient to full remission will often result in much better attention, concentration, and ability to follow through and stay on task.*

Have you  
visited us online?

**bipolarnews.org**

## White Matter Abnormalities and Impaired Functioning Follow Concussions

Many people suffer problems with mental functioning after an apparent concussion (otherwise known as mild traumatic brain injury, or mTBI) that does not show abnormalities on traditional brain imaging measures such as the MRI. **New technology called diffusion tensor imaging (DTI) shows that the integrity of white matter tracts may be disturbed by concussions.** White matter comprises parts of the brain where myelin wraps around axons, as opposed to grey matter, which reflects the presence of neuronal cell bodies.

In a longitudinal study published in the *Journal of Neurotrauma*, Vigneswaran Veeramuthu and colleagues compared 61 people with an mTBI to 19 healthy controls. The mTBI participants had their neuropsychological faculties assessed an average of 4.35 hours after their trauma, and participated in DTI scans an average of 10 hours

after the trauma. Both the neuropsychological assessment and the DTI scan were repeated six months later. When the acute and follow-up assessments were compared to the same assessments in control participants, the two groups showed differences in numerous white matter tracts at the six-month mark. **There was also an association between the degree of abnormality observed on the DTI scans and decrements in performance on the tests of neuropsychological functioning both immediately after the trauma and six months later.**

The researchers concluded that their results “provide new evidence for the use of DTI as an imaging biomarker and indicator of [white matter] damage occurring in the context of mTBI, and [the results] underscore the dynamic nature of brain injury

and possible biological basis of chronic neurocognitive alterations.”

*Editor's Note: People should be aware of these findings, which confirm earlier studies, and begin rehabilitative treatment as soon as possible after a concussion. New research should target white matter tract changes, with the goal of secondary prevention, i.e. limiting damage to the brain after a traumatic injury has occurred. There are several promising drugs that can prevent damage if administered immediately after an mTBI, including the antioxidant supplement N-acetylcysteine (NAC), which has shown promise in preliminary clinical and laboratory studies, and many others, including lithium and valproate, as reported by De-Maw Chuang and this editor Robert M. Post in a 2015 article in the Journal of Neurology and Stroke titled “Preventing the Sequelae of Concussions and Traumatic Brain Injury.”*

## New Name and New Treatment for Chronic Fatigue Syndrome

People with chronic fatigue syndrome, or myalgic encephalomyelitis, as it has also been called, suffer from extreme exhaustion and unrefreshing sleep. The condition has been considered mysterious, but new research is clarifying its symptoms and leading to more useful treatments. In 2015, **a committee convened by the Institute of Medicine at the National Academy of Sciences decided to change the name of the condition to systemic exertion intolerance disease (SEID)** to better reflect its symptoms and reduce stigma around the illness.

**In recent years it had been determined that exercise regimens and cognitive behavioral therapy helped up to 60% of patients. Some new small studies show good results when patients are treated with anti-viral medications such as valacyclovir (Valtrex).** Researcher Theodore Henderson reports that he has seen response rates as high as 85% in adults and 92% in adolescents.

Researchers now believe that some patients diagnosed with depression may actually have SEID. Symptoms like fatigue, exertion-induced malaise, brain fog, and impaired academic performance could be the result of the body's reaction to a virus.

## New Injectable Treatment for Obesity

Liraglutide, an injectable drug used to treat Type 2 diabetes, has been approved by the Federal Drug Administration for the treatment of obesity. The drug is newly formulated in recommended doses of 3mg/day under the brand name Saxenda. Liraglutide is suggested for adults with a body mass of 30 or above, or 27 and above with other weight-related conditions such as hypertension, diabetes, or high cholesterol.

**In clinical trials, out of 3,731 participants without weight-related comorbid conditions, 62% of those who received liraglutide lost at least 5% of their body weight, compared to 34% of those who received placebo.** Of the 635 participants with Type 2 diabetes, 49% of those who received liraglutide lost at least 5% of their body weight, compared to 16% of those who received placebo. In the 422 participants with other weight-related comorbidities, 42% of those taking liraglutide lost 5% or more of their body weight compared to 21.7% of those on placebo.

There were also some improvements in risk factors for cardiovascular disease in people taking liraglutide.

Liraglutide affects appetite regulation, leading to reduced calorie intake that produces weight loss. The treatment is delivered in a pre-filled multidose pen that can be injected in the abdomen, thigh, or arm. Dosing begins at 0.6 mg/day to minimize unwanted gastrointestinal effects.

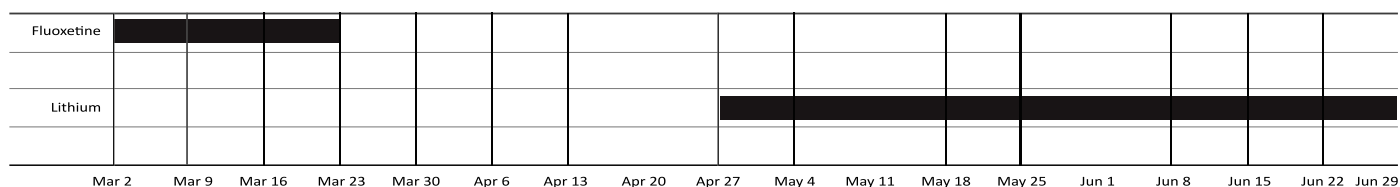
## Parents with Mood Disorders and Their Clinicians,

We are reaching out to you to let you know about a new study that the Bipolar Collaborative Network is implementing called the Child Network. Our goal is to **foster collective knowledge about childhood mood and behavioral disorders by acquiring data about children who have or may be vulnerable to childhood-onset depression and bipolar disorders and associated conditions**. Depressive, oppositional, and bipolar disorders as well as anxiety in very young children have not been well studied for their course and for treatment effectiveness and tolerability. Our goal is to compile and analyze the varied treatments for children with these disorders. How well a child responds to a specific treatment may provide new preliminary information of use to others, and assist parents and physicians in assessing treatment options.

The Child Network is specifically for parents of children ages 2 to 12 who have few symptoms, minor (prodromal) symptoms, or the full onset of a psychiatric illness prior to age 13. Participating in the Child Network will primarily involve a confidential, few-minute parental assessment of their child every Sunday evening, the listing of medications, other treatments, and any side effects that occurred in the prior week. There will also be a short demographic questionnaire and a once-a-year more detailed symptom checklist. This study does not involve treatment. The network is only meant to document what is currently being done in the community.

We believe that this network will also benefit its participants. Parents will be able to print out results of the ongoing brief weekly ratings in graphic form so that the course of the child's symptoms and response to treatment can easily be visualized, as illustrated below.

**Weekly Mood and Medication Chart**



**Weekly Severity of Depression/Mania**



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

We encourage you to visit [www.bipolarnews.org](http://www.bipolarnews.org) and click on the tab for Child Network to learn more about the study and to access the informed consent documents.

Robert M. Post, MD and Michael Rowe, PhD, Bipolar Collaborative Network  
 Robert L. Findling, MD, MBA, Principal Investigator  
 IRB Study #00026940, Johns Hopkins University School of Medicine



---

BNN  
PO Box 18  
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED