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Bipolar Network News

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Therapy Improves Outcomes for People with Bipolar Disorder

Studies have shown that therapy can be helpful for people with bipolar disorder. In a 2016 article in the *British Journal of Psychiatry*, researchers led by Matthijs Oud described the findings of their systematic review of studies evaluating different types of therapy for bipolar disorder. The research team reviewed the findings of 55 randomized controlled trials of psychotherapeutic interventions that included a total of 6,010 adult participants with bipolar disorder. **The team found moderate-quality evidence that psychological interventions reduced relapses following treatment, and that collaborative care reduced hospital admissions for adults with bipolar disorder.** Oud and colleagues found lower-quality evidence that group interventions reduced depression relapses following treatment, and that family psychoeducation reduced symptoms of depression and mania.

The reseachers concluded that there is evidence that therapy can be helpful for people with bipolar disorder. Since some of the evidence was of low quality, specific implications of the research are limited. More research is needed to identify the most effective therapies for different phases of bipolar disorder.

Editor's Note: The data are clear that therapy is helpful. In particular, one approach worth emulating is that described in an article by Lars V. Kessing and colleagues in the British Journal of Psychiatry *in 2013. They found that comprehensive care in an outpatient mood disorder clinic, which included psychotherapy, psychoeducation, mood monitoring, and drug treatment, reduced relapses significantly compared to treatment as usual.*

Alzheimer's Treatments May Work for Memory Dysfunction in Depression

In a recent *BNN* article on potential drugs for memory loss, we omitted two conventional classes of drugs used to treat Alzheimer's Disease—acetylcholine esterase inhibitors (AChE-Is) and memantine (Namenda), which blocks glutamate NMDA receptors. This was intentional, as we intended to suggest possible approaches prior to the use of these drugs for full-blown dementia. However, we neglected to cite a 1999 study by Fred Jacobsen in the *Journal of Clinical Psychiatry* that indicated that the AChE-I drug **donepezil (Aricept) was effective in improving drug-induced memory dysfunction in patients without dementia.** Side effects included insomnia, nausea, vomiting, and diarrhea.

Jacobsen has used AChE-Is to improve memory in over 80 patients with unipolar or bipolar depression, aged 19-85. In a 2016 personal communication to the *BNN*, he indicated that doses of 5mg/day are typically enough to improve memory. Higher doses of 10mg/day may be more effective, but increase the risk of switching into mania for patients with bipolar depression. Some of Jacobsen's patients have used AChE-I drugs for 10–15 years without the drugs losing effectiveness. For some patients, Jacobsen has switched from prescribing donezepil to prescribing rivastigmine (Exelon or Exelon patch), which he finds they can more easily tolerate.

We should also remind readers of the *BNN* of our previous report on memantine (Namenda) for bipolar depressed patients with cognitive impairment. We wrote, "In an abstract presented at the 67th Annual Meeting of the Society of Biological Psychiatry in 2012, Dan V. Iosifescu reported that in a randomized 12-week study in which the anti-Alzheimer's drug memantine was given to 72 euthymic bipolar subjects experiencing cognitive deficits, the drug was associated with improvement in spatial and working memory, verbal and episodic memory, and other indices that included measurements of attention and language skills. In conjunction with this treatment, a subgroup of subjects had increases in left hippocampal NAA (a measure of neuronal viability) and increases in choline in the right hippocampus. The initial improvements in these neuropsychological test results remained over 12 weeks of open follow-up."

In an earlier proof-of-concept study published in the journal *CNS Neuroscience and Therapeutics* in 2009, Iosifescu also reported that among nineteen subjects with bipolar disorder that was in remission, but who had residual cognitive deficits, open-label treatment with the AChE-I galantamine (extended release) at doses of 8–24 mg/day led to improvement in those cognitive symptoms after 4 months.

Parents with Mood Disorders:

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

Memory Activates Epigenetic Changes in Two Types of Brain Cells

In a 2015 article in *Nature Neuroscience*, Stefan Bonn and André Fischer reported that when mice were prompted to use their long-term memory to recognize a specific environment, two types of epigenetic changes occurred in two types of cells in their brains. Epigenetic changes refer to changes in the ways genes are expressed. Sometimes environmental factors lead to molecules such as methyl or acetyl groups joining a strand of DNA or the histones that give DNA structure, changing the way those strands are replicated.

When the mice used their long-term memory, the main change that occurred was DNA methylation in their neurons. Changes to histones in the neurons also occurred, and both kinds of changes also occurred in non-neuronal brain cells. The histone modifications were linked to memory acquisition, but resulted in few changes in gene expression. The DNA methylation changes, on the other hand, changed neural pathways, leading to "rewiring" of the brain.

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

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

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

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Anti-Viral Treatment Leads to Improvement in Chronic Fatigue Syndrome/SEID

Chronic fatigue syndrome, or Systemic Exertion Intolerance Disease (SEID), as it is now known, is characterized by extreme fatigue that cannot be explained by any underlying illness. Doctors have long disagreed over how it should be treated, particularly about whether or not exercise should be encouraged. A new small study of adolescents suggests that antiviral medications can reduce fatigue.

The 2014 article by Theodore A. Henderson in the journal *Advanced Mind Body Medicine* reports that among 15 adolescents who reported chronic fatigue symptoms, **1000 mg/day of the antiviral valacyclovir (trade name Valtrex) led to improvement in 86% of the patients by 3 months, and 92% of the patients by 5 months.** One patient dropped out due to nausea. Symptoms of fatigue, exertion-induced malaise, excessive sleep, napping, unrefreshing sleep, headaches, cognitive symptoms, and emotional symptoms all improved after treatment with the antiviral. Several previous studies have also shown positive effects of antiviral treatments in patients with chronic fatigue.

Diabetes Drug with Positive Effects in Bipolar Depression Investigated for Cancer Risks

Researchers are working on determining whether the drug pioglitazone, typically used to treat diabetes, increases the risk of developing certain cancers, including bladder, prostate, and pancreatic cancers. A recent study by James D. Lewis and colleagues in the journal *JAMA* found **no statistically significant increase in risk of bladder cancer among patients taking the drug**, but the researchers said they also couldn't rule out that the drug may increase this risk, as has been seen in previous studies. The study by Lewis did show more pancreatic and prostate cancers in patients taking pioglitazone, but the researchers did not determine whether this was caused by the drug.

Pioglitazone has had positive effects in bipolar depression and may one day be used as a treatment for bipolar disorder. For now, it may be worthy of consideration for the treatment of diabetes in patients who also have bipolar depression.

Guanfacine Improves ADHD Symptoms and Academic and Social Functioning in Children

A study by researcher Jeffrey H. Newcorn and colleagues published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2013 found that **eight weeks of treatment with the drug guanfacine (extended release) improved symptoms of attention deficit hyperactivity disorder (ADHD) in North American children compared to placebo.** A 2015 study by M.A. Stein and colleagues in the journal *CNS Drugs* extended this research, determining that **guanfacine also improved academic and social functioning, including family dynamics, in the same group of children.**

Children aged 6–12 who had been diagnosed with ADHD received either placebo or 1 to 4 mg of guanfacine extended release either in the morning or evening. The children in both guanfacine groups showed improvements in family interactions, learning and school, social behavior, and risky behavior compared to those taking placebo. No improvements were seen in life skills or self-concept. The improvements in functioning were linked to the drug's effectiveness in improving ADHD symptoms. Those children whose ADHD symptoms improved on guanfacine were also more likely to see improvements in academic and social functioning.

Stimulants Linked to Psychotic Symptoms in Offspring of Parents with Psychiatric Illness

Stimulants are one of the most common medications prescribed to children and adolescents, typically for attention deficit hyperactivity disorder (ADHD). In children of parents with major depression, bipolar disorder, or schizophrenia, stimulant use may come with a risk of psychotic symptoms. A 2016 study by Lynn E. MacKenzie and colleagues in the journal *Pediatrics* reported that **among children and youth whose parents had one of these psychiatric illnesses, 62.5% of those who had taken stimulants had current psychotic symptoms, compared to only 27.4% of those who had not taken stimulants.** The participants with psychotic symptoms tended to have hallucinations that occurred while they were taking stimulants. Doctors may want to consider whether parents have a history of psychiatric illness when deciding whether to prescribe stimulants to children and adolescents with ADHD. Activation is a common side effect of antidepressants in children who have a parent with bipolar disorder. Young people taking stimulants for ADHD should be monitored for psychotic symptoms, particularly if they have a parent with a history of depression, bipolar disorder, or schizophrenia.

Guanfacine Improves Cognition in Schizophrenia

People with disorders on the schizophrenia spectrum often suffer cognition problems that affect skills such as the processing of information about people and social situations (social cognition) and the execution of plans (executive function). At the 2015 meeting of the Society for Biological Psychiatry, researcher Larry J. Siever reported that **the drug guanfacine improved these types of thinking in people with disorders on the schizophrenic spectrum compared to placebo.** Participants were enrolled in a 7.5-week training program to improve cognition.

Over-Pruning of Synapses May Explain Schizophrenia

A gene that plays a role in the pruning of synapses has been linked to schizophrenia. The gene encodes an immune protein called complement component 4 (C4), which may mediate the pruning of synapses, the connections between neurons. Researchers led by Aswin Sekar found that **in mice, C4 was responsible for the elimination of synapses. The team linked gene variants that lead to more production of C4A proteins to excessive pruning of synapses during adolescence, the period during which schizophrenia symptoms typically appear.** This may explain why the brains of people with schizophrenia have fewer neural connections. The researchers hope that future therapies may target the genetic roots of the illness rather than simply treating its symptoms. The findings were published in the journal *Nature* in 2016.

Statins Reduce Drug-Craving in Mice

Statins are drugs that are typically used to lower cholesterol. Recent research on the drugs has focused on their effects on the brain.

In 2015 Claudia Chauvet and colleagues reported in the journal *Neuropsychopharmacology* that **the brain-penetrating statins simvastatin and atorvastatin reduced cocaine seeking behaviors in mice that were taught to self-administer cocaine and then were denied access to it for 21 days compared to pravastatin, a statin that does not penetrate the brain as thoroughly.** The researchers found that the brain-penetrating statins also reduced nicotine seeking, but not food reward seeking. The statins also worked in mice that had stopped seeking cocaine but relapsed due to stress, allowing them to abstain from cocaine seeking again.

Statins are considered a very safe treatment in humans. The ability of statins to prevent relapse to addictions in mice may mean that one day they could be used to treat addictions in people as well. A review article by Cassie Redlich and colleagues in the journal *BMC Psychiatry* in 2014 indicated that statins may reduce recurrence of depression in people. The researchers found that simvastatin had a protective effect while atorvastatin was associated with increased risk of depression, so the choice of statins may be important for both depression and addiction.

New Study Suggests RTMS Can Reduce Cocaine Use and Cocaine Cravings

Repeated transcranial magnetic stimulation, or rTMS, is a non-invasive treatment in which a magnetic coil placed near the skull transmits electrical signals to the brain. It is an effective treatment for depression, and now it appears it may also be useful in the treatment of addictions.

A pilot study by Alberto Terraneo and colleagues published in the journal European Neuropsychopharmacology in 2016 compared rTMS treatment delivered to the dorsolateral prefrontal cortex to pharmacological treatment in 32 patients who wanted to stop using cocaine. Those in the rTMS group received one session of the treatment per day for five days, followed by one session per week for three weeks. **Those who received rTMS had a higher number of cocaine-free urine tests than those using pharmacological treatments.** Among those who received rTMS, 69% had a positive outcome, compared to 19% of the control group. RTMS also reduced cravings for cocaine. Both treatments improved depression.

Antonello Bonci, another author of the study who is also scientific director at the US National Institute on Drug Abuse, suggested that rTMS may work by "scrambling" the pattern of neural activity that leads to cocaine craving.

Now that there is some evidence suggesting that rTMS may be useful in the treatment of addictions, the researchers are planning a placebo-controlled study of rTMS treatment for cocaine use, in which they will give some patients a sham treatment instead of real rTMS.

Other studies are examining whether rTMS can be used to treat smoking and alcohol use disorders in addition to depression.

More Evidence that Statins Can Reduce Depression

Many studies have linked depression and cardiovascular problems. The solutions may also be linked. A new study found that **patients with depression and acute coronary syndrome saw their depression improve most when they took the selective-serotonin reuptake inhibitor (SSRI) antidepressant escitalopram and statins (used to lower cholesterol), while depression improved least among patients who took neither type of drug.** Statin use was linked to improvement in depression after one year, while escitalopram was not. In a subset of the study, use of lipophilic statins in particular was linked to improvement in depression.

The study, published in 2015 by Sung Wan Kim and colleagues in the journal *Translational Psychiatry*, suggests that statins can improve depression regardless of antidepressant use, but combining statins with an SSRI may have an even more powerful effect on depression.

Treating Prenatal Depression Improves Outcomes for Mothers and Babies

A recent study confirms that **women who are depressed during pregnancy are more likely to experience adverse pregnancy outcomes such as preterm or cesaerean delivery and small or underweight babies.** However, antidepressant treatment improved outcomes for pregnant women with depression.

The 2016 study by Kartik K. Venkatesh and colleagues in the journal *Obstetrics & Gynecology* included 7,267 women who gave birth after at least 20 weeks of pregnancy. About 11% of the women screened positive for depression during their pregnancy. Depressed mothers-to-be were more likely to give birth before 37 weeks and before 32 weeks compared to nondepressed mothers-to-be. The depressed women were also more likely to deliver small babies or babies weighing under 2500g.

About 7% of the women in the study received antidepressant medication. Compared to nondepressed women, the women taking antidepressants did not have greater rates of early delivery or small babies. However, the authors caution that because so few women received antidepressants, the study does not reveal whether antidepressants improve outcomes for depressed pregnant women.

Very Low Doses of Opioid Buprenorphine May Reduce Suicidal Ideation

There is no perfect treatment to reduce the risk of suicide in someone who is considering it. Antidepressants can reduce suicidal ideation, but they take several weeks to start working. Intravenous ketamine is used at higher doses as an anesthetic, but in low doses works quickly to reduce suicidal thoughts. However, it requires repeated infusions to keep working. Researchers led by Yoram Yovell are exploring another option: ultra-low doses of the opioid buprenorphine.

In a study published in the *American Journal of Psychiatry* in 2015, Yovell and colleagues compared low-dose buprenorphine to placebo in 62 patients with no history of substance abuse who had been contemplating suicide for a week or more. Many had attempted suicide before, and more than half met the criteria for borderline personality disorder.

Buprenorphine was administered under the tongue, in doses of 0.1 mg once or twice a day. The researchers used these low doses to minimize the side effects of a drug that could potentially be addictive. **Those randomized to receive buprenorphine saw greater reductions in suicidal ideation compared to those who received placebo both after two weeks and after four weeks.**

Use of antidepressants did not affect the likelihood that patients would respond to buprenorphine. The researchers suggest that buprenorphine specifically treats suicidal thoughts, rather than improving depression in general.

Patients with borderline personality disorder, who are often unresponsive to medication, also saw improvement in suicidal ideation after taking buprenorphine, suggesting that the opioid treated a particular symptom of their disorder—sensitivity to feelings of separation from the people with whom they are close.

Patients did not experience withdrawal when they discontinued buprenorphine. Side effects included fatigue, nausea, dry mouth, and constipation. Patients who started out taking 0.2 mg per day were much more likely to drop out than those who started at 0.1 mg per day.

There is another reason the researchers used very low doses. A potential benefit to ultra-low–dose buprenorphine is that even a week's supply of the drug would not produce a dangerous overdose, so patients could potentially be prescribed a week's worth of medication to take at home instead of in an inpatient setting.

Buprenorphine is not recommended for patients with a history of substance abuse. The study only explored short-term use of the drug, and replication studies are needed to clarify its effects.

Drug Reduces Agitation in Patients with Alzheimer's

Agitation is common among people with Alzheimer's dementia. A 2015 phase 2 clinical trial by Jeffrey L. Cummings and colleagues, which was published in the journal *JAMA*, found that **a combination of the drugs dextromethorphan hydrobromide and quinidine sulfate called Nuedexta reduced agitation significantly compared to placebo in patients with probable Alzheimer's disease over a period of 10 weeks.** Dextromethorphan-quinidine was dosed at 20mg/10mg in the morning for one week, then twice daily in weeks 2 and 3, then increased to 30mg/10mg twice daily for weeks 4 and 5. Side effects included falls, diarrhea, and urinary tract infections. Dextromethorphan-quinidine did not cause cognitive impairment, sedation, or irregularities in heart rate.

Changes in Sense of Humor May Be Warning Sign of Dementia

A change in a person's sense of humor could be an early indicator of dementia, according to a 2015 article by Jason Warren and colleagues in the *Journal of Alzheimer's Disease*. The changes can appear as early as 10 years before a diagnosis of dementia. **Almost all participants who would go on to be diagnosed with frontotemporal dementia showed an increased preference for slapstick humor over satirical or absurdist compared with those who would not.** In contrast, changes in sense of humor appeared in less than half of those who would go on to be diagnosed with Alzheimer's disease, indicating that changes in sense of humor may allow doctors to distinguish between different types of dementia.

The study has some limitations. It was small (48 patients) and relied on patients' memory of what kind of humor they enjoyed 15 years earlier. More research is needed to clarify the link between changes in humor preferences and dementia.

Warren suggests that changes in humor appear before other warning signs of dementia, such as memory loss. He called humor a type of "stress test" for the brain, since getting a joke can require a quick shift in perspective.

Depression and Resilience Linked to Activity of Neurotransmitter Norepinephrine

Scientists have known for some time that heightened activity of dopaminergic neurons (neurons in the midbrain that contain the neurotransmitter dopamine) can make people vulnerable to depression. New research in animals suggests for the first time that noradrenergic neurons (those that contain the neurotransmitter norepinephrine) control the activity of dopaminergic neurons and that these noradrenergic neurons can make the difference between vulnerability to depression or resilience to stress. The research, published by Elsa Isingrini and colleagues in the journal *Nature Neuroscience* in 2015, showed that **animals that cannot release norepinephrine are vulnerable to depression following chronic stress, but increasing the production of norepinephrine increases the animals' resilience and reduces depression.**

These findings may open up new avenues to treatment that target norepinephrine rather than or in addition to dopamine or serotonin, which is targeted by SSRI antidepressants, or selective serotonin reuptake inhibitors.

Chemicals in E-Cigarettes (Even Nicotine-Free Ones) Cause Cell Damage

E-cigarettes are not regulated to the same extent that cigarettes are by the US Food and Drug Administration, so their contents remain a bit of a mystery. A 2016 study by Vicky Yu and colleagues in the journal *Oral Oncology* determined that even e-cigarettes without nicotine cause cell damage.

The researchers created an extract from two different brands of e-cigarettes. When they added the extract to human cells in a Petri dish, the cells showed signs of damage (including broken DNA strands) and death compared to untreated cells.

The researchers tested e-cigarettes both with and without nicotine, and those that contained nicotine showed even more signs of cell damage and death after exposure to the contents of the e-cigarette.

Other ingredients that have been identified in e-cigarettes include formaldehyde, which is known to be a carcinogen, and diacetyl, a flavoring agent.

Yu and colleagues suggest that e-cigarettes are not as safe as their marketing would suggest. The researchers hope to identify more of the ingredients in e-cigarettes.

See page right for information about a new study of children at risk for mood disorders.

Tests of Generic Lamotrigine Are Successful

Studies published in 2015 and 2016 have established that generic versions of the anti-convulsant lamotrigine are bioequivalent to the name-brand drug (Lamictal) and to each other. Lamotrigine is used to treat epilepsy and is also prescribed for the prevention of bipolar depression.

An article by Tricia Y. Ting and colleagues in the journal *Epilepsia* in 2015 established that **generic lamotrigine works similarly enough to the name brand drug that patients with epilepsy could be switched from one drug to the other without worsening seizures.** More recently, Michael D. Privitera and colleagues reported in the journal *Lancet Neurology* that **different generic versions of lamotrigine were bioequivalent.** No significant changes in seizure frequency or other negative outcomes were reported.

These studies show that generic versions of lamotrigine have the same anticonvulsant effectiveness as the original drug. The same should also be true for lamotrigine's effectiveness in preventing bipolar depression.

Long-Acting Injectable Aripiprazole Approved for Schizophrenia

In October, the US Food and Drug Administration (FDA) approved an injectable, long-acting version of the atypical antipsychotic aripiprazole for the treatment of adults with schizophrenia.

The long-acting drug is administered every 4 to 6 weeks as an injection in the arm or buttocks. The company announced that it would begin releasing the drug immediately.

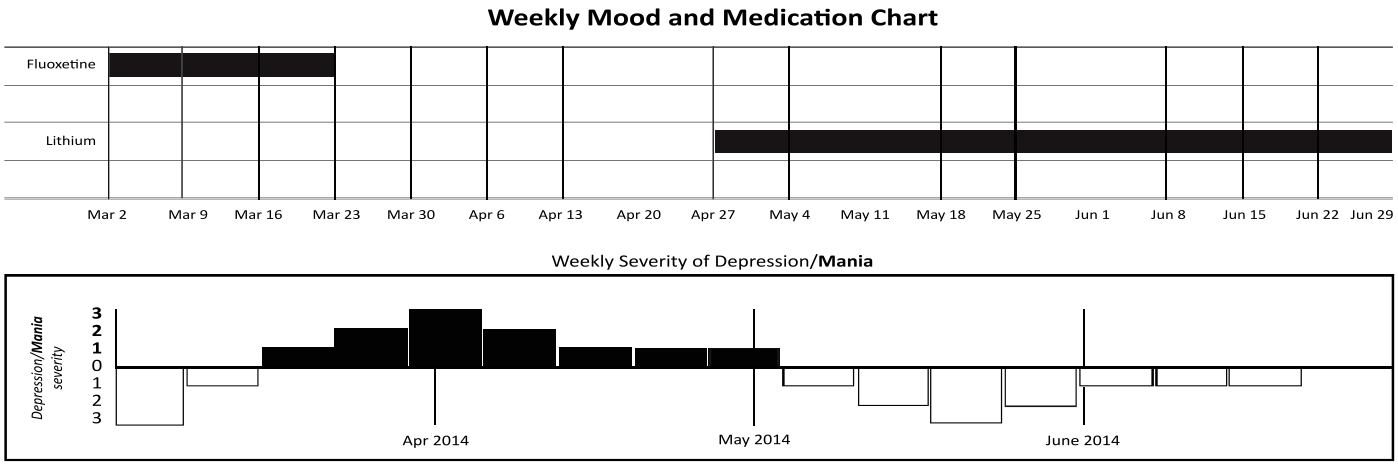
Additional Information about the Child Network:

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

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

The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographics questionnaire and a more detailed symptom checklist to be filled out once a year. The network will collect information about which treatments children are already taking, how effective they are, and for which children.

We believe that this network will be helpful to its participants. Parents will be able to print out the ongoing weekly ratings in a graphic form so that the child's symptoms and responses to any treatments they receive over time can easily be visualized (as illustrated below).



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

We hope that this brief description of the Child Network study helps to orient you to its purpose. Please urge parents to use this new tool. Visit http://bipolarnews.org and click on the tab for the Child Network or http://bipolarnews.org/?page_id=2630 to learn more about the Child Network and to access the informed consent documents.

Thank you for your time and interest in the Child Network.

Robert M. Post, MD and Michael Rowe, PhD
Bipolar Collaborative Network, and
Robert L. Findling, MD, MBA, Principal Investigator
This research study is IRB approved by the Johns Hopkins University School of Medicine
Research Study, Principal Investigator: Robert L. Findling, MD, MBA , IRB Study #00026940

BNN
PO Box 18
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED