

# Bipolar Network News

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## Probiotics Reduce Re-Hospitalizations for Bipolar Disorder

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In a 2018 article published in the journal *Bipolar Disorders*, researcher Faith Dickerson and colleagues reported that **in a small study of 66 people who had been hospitalized for mania, taking specific probiotic supplements upon their release reduced re-hospitalizations compared to taking placebo.**

The study followed patients for 24 weeks after their hospitalization. **They were randomized to receive either the combination of *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* strain Bb12 or placebo in addition to their regular medications.** While 17 of the 33 participants in the placebo group (51.5%) had at least one re-hospitalization during the study period, only eight (24.2%) of the participants taking probiotics had a re-hospitalization. The duration of the re-hospitalizations was also shorter for those taking pro-

biotics (2.8 days on average versus 8.3 days for those taking placebo).

In a personal communication to this editor (Robert M. Post), Chris Aiken, Instructor in Clinical Psychiatry at Wake Forest University School of Medicine, who was not involved in the study, provided some clarifying details to this editor about the use of probiotics to reduce manic relapse. Aiken explained, "Apparently, it's important to get both the right species (e.g. *Bifidobacterium lactis*) and the right strain (e.g. Bb-12) in choosing a probiotic. The study mentions that one of the strains (Bb-12) is patented and only available in Europe, but it has been licensed to a few U.S. companies.

"I found two products that contain the exact strains in the study and wrote this up for patients: In [the] study [noted above], a probiotic capsule containing *Bifidobacterium lactis* Bb-12 and

*Lactobacillus rhamnosus* GG lowered the risk of psychiatric hospitalization threefold. [Both] strains are available in the supplement *Emergen-C* and in a liquid probiotic designed for infants, *Culturelle Baby Grow and Thrive*. The infant serving would suffice for adults as well. You could also get the two strains by combining two separate probiotic capsules: *Align Daily Immune Support* and *Culturelle Digestive Health Daily Probiotic*."

*Editor's Note: We are grateful to Dr. Aiken for this added information. We also found that the USANA brand probiotic contains both strains used in the study.*

*Recent research has found more and more connections between inflammatory processes and mental health. This study contributes to our understanding of the connection between gut health and the brain.*

## Large Finnish Study Finds Lithium is Best at Preventing Re-Hospitalizations in Bipolar Disorder

A 2018 article in the journal *JAMA Psychiatry* reports that lithium and long-acting antipsychotic injections were most effective at preventing re-hospitalizations among people with bipolar disorder.

The study by Markku Lähteenvuo and colleagues included 18,018 Finnish patients with bipolar disorder. A national database contained information on any hospitalizations that occurred among the patients and what medications were dispersed to patients.

Among the participants, 54% (9,721 patients) were re-hospitalized at least once over a study period of 16 years. Medications associated with the smallest risk of re-hospitalization for psychiatric reasons were long-acting injections of risperidone, gabapentin, long-acting injections of perphenazine, and lithium carbonate.

**When the researchers looked at hospitalizations for any cause (not just psychiatric illness), lithium was associated with the least risk of re-hospitalization,** while benzodiazepines had the greatest risk, both for psychiatric re-hospitalization and re-hospitalization for any cause.

Long-acting injectable medications were associated with less risk of re-hospitalization compared to the identical medications delivered orally.

Lähteenvuo and colleagues concluded, "Lithium...should remain as the first line of treatment for bipolar disorder, after decades of underprescription." They

*Continued on Page 2*

### In This Issue:

Treatments for  
Bipolar  
Disorder p. 2–3

Treatments for  
Unipolar  
Depression p. 3–5

Early Intervention  
Leads to Better  
Outcomes in  
Psychosis p. 6

## Lithium (continued)

suggest that long-acting injectable medications may be a good alternative to prevent relapse in patients for whom lithium is unsuitable.

*Editor's Note: In addition to lithium's ability to prevent depressions and manias, it also increases the volume of the hippocampus and protects against a diagnosis of dementia in old age. Lithium decreases the risk for suicide and also increases the length of telomeres, bits on the ends of DNA strands that protect them as they replicate, which are important to the maintenance of both physical and psychiatric health. When lithium is used cautiously to maintain doses below a given patient's side effects threshold, it is very well tolerated by most individuals.*

### Bipolar Network News

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The *BNN* is published 4–6 times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

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

Dr. Post has consulted on behalf of drug companies including Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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

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## Psychoeducation Is a Must for Patients with Bipolar Disorder

In 2018, researcher S.A. Soo and colleagues published a systematic review in the *Journal of Clinical Psychiatry* that analyzed findings from 40 randomized studies of psychoeducation for the management of bipolar disorder and compared the results for different types of psychoeducation: group, family, individual, and internet-based. Most of the randomized controlled trials (28 of 40 studies, 70.0%) assessed group or family psychoeducation, which had many benefits, while studies of individual or internet-based psychoeducation tended to be inconsistent.

The findings: **“Group psychoeducation was associated with reduced illness recurrences, decreased number and duration of hospitalizations, increased time to illness relapse, better treatment adherence, higher therapeutic lithium levels, and reduced stigma.** Family psychoeducation was associated with reductions in illness recurrence, hospitalization rates, and better illness trajectory as well as increased caregiver knowledge, skills, support, and sense of well-being and reduced caregiver burden.”

*Editor's Note: Given these results, it appears that group or family psychoeducation is a critical component to good care. Soo and colleagues suggest that future studies should directly compare different types of psychoeducation to each other to evaluate whether specific benefits are useful at various stages of illness.*

## Third Study Suggests Cariprazine Is Effective in Bipolar Depression As Well as Mania

The atypical antipsychotic drug cariprazine (sold under the name Vraylar in the US) is currently approved by the US Food and Drug Administration for the treatment of schizophrenia and manic or mixed episodes of bipolar disorder. Based on recent successful phase 3 trials in bipolar depression, the pharmaceutical companies that produce cariprazine, Allergan and Gedeon Richter, plan to apply for a change in FDA labeling later this year to reflect the drug's apparent ability to treat bipolar depression as well.

**While many drugs can prevent or treat mania, treating bipolar depression has typically been more of a challenge. The most recent 6-week trial of cariprazine in 493 patients showed that a dose 1.5mg/day was significantly more effective than placebo at reducing depression ratings.** (A dose of 3mg/day did not show superiority over placebo as it had in previous trials of cariprazine.)

Side effects reported in the trial were mild and included restless legs, nausea, and fatigue. Five percent of those who received cariprazine discontinued the drug due to side effects, compared to three percent of those who received placebo.

The mechanism by which cariprazine improves depression is not yet clear. The drug is a dopamine partial agonist, but unlike aripiprazole (Abilify) and brexpiprazole (Rexulti), which have more potent effects on D2 receptors than on D3 receptors, cariprazine is more potent at dopamine D3 receptors. Whether this difference accounts for the positive effects in bipolar depression that aripiprazole and brexpiprazole do not have remains to be seen.

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## Antioxidant N-Acetylcysteine Improves Working Memory in Patients with Psychosis

In a 2017 article in the journal *Psychological Medicine*, researcher Marta Rapado-Castro and colleagues reported that **among 58 patients with bipolar disorder or schizophrenia and symptoms of psychosis, those who took two grams per day of the antioxidant n-acetylcysteine (NAC) showed improvements in working memory after six months compared to those who took placebo over the same study period.**

Antipsychotic medications can typically reduce psychotic symptoms such as delusions or hallucinations, but cognitive symptoms such as problems with learning, memory, or information processing may remain. NAC, which is sold over-the-counter as a nutritional supplement, seemed to improve these symptoms.

The researchers suggest that larger studies of NAC are needed, particularly to determine whether giving NAC to patients during their first episode of psychosis could prevent cognitive decline from occurring at all during the course of their illness.

NAC has been found to have a range of benefits, including reducing substance abuse and interfering with habit-based behaviors such as compulsive hair-pulling, obsessive-compulsive disorder, and gambling.

Researcher Michael Berk, a co-author of the study, reported in the journal *Biological Psychiatry* in 2008 that NAC could also improve depressive symptoms in bipolar disorder and negative symptoms in schizophrenia.

*Editor's Note: Since cognitive deficits are common in both schizophrenia and bipolar disorder, using NAC in addition to antipsychotic medications could be a useful tool to address these types of symptoms.*

## NAD Precursor May Improve Heart Health

NAD, or nicotinamide adenine dinucleotide, is found in all living cells. Its oxidized form, NAD<sup>+</sup>, rose in popularity as a nutritional supplement following a 2013 Harvard study that suggested it might slow aging in mice. A 2018 article by researcher Christopher R. Martens and colleagues in the journal *Nature Communications* reports that **a precursor vitamin to NAD<sup>+</sup> called nicotinamide riboside (NR) can stimulate NAD<sup>+</sup> metabolism in healthy middle-aged and older adults compared to placebo, which might improve cardiovascular health.**

In the crossover study, participants received NR or placebo for six weeks, and then received the other option for a second six-week period. NR was associated with increased NAD<sup>+</sup> metabolism.

The researchers suggest that more research is needed to investigate whether chronic NR supplementation might be able to reduce blood pressure and arterial stiffness.

## Nutritional Supplement ALC Improves Unipolar Depression

**A meta-analysis of 12 studies suggests that the nutrient acetyl-L-carnitine (ALC), when taken as a nutritional supplement, has antidepressant effects.** The meta-analysis by researcher Nicola Veronese and colleagues appeared in the journal *Psychosomatic Medicine* in 2017. Veronese and colleagues found that in nine randomized controlled trials, ALC reduced depressive symptoms significantly compared to placebo. **In three randomized controlled trials that compared ALC with established antidepressants, ALC showed similar effectiveness at reducing depressive symptoms while producing 79% fewer side effects.** Doses of ALC ranged from 1 to 4 grams per day, and higher doses led to greater improvement.

In the comparisons with antidepressants, the other treatments included fluoxetine (Prozac), dulox-

etine (Cymbalta), and amisulpride (which is not approved by the US Food and Drug Administration).

Low ALC has been linked to depression. According to Veronese and colleagues, ALC deficiency can dysregulate the transport of fatty acids across the inner membrane of mitochondria. The researchers suggest several ways that ALC might contribute to an improvement in depression. One is that it seems to promote neuroplasticity in cerebral regions implicated in depression, such as the hippocampus. It could also work by increasing brain-derived neurotrophic factor (BDNF), which protects neurons and is important for learning and memory. ALC decreases release of the neurotransmitter glutamate by increasing the production of the inhibitory metabotropic glutamate receptor (mGluR-2) on presynaptic glutamate neurons. Another way ALC

might work is by normalizing lipid metabolism. Or it could modulate neurotransmitters, increasing serotonin and dopamine and protecting against stress.

In the meta-analysis, ALC produced more improvement in older patients than in younger ones. The researchers stressed the need for better treatments for older people, which may experience falls, cardiovascular disease, or increased mortality from antidepressants.

ALC also seems to improve pain syndromes, making it a good option for patients with both depression and pain symptoms.

Veronese and colleagues cited another meta-analysis that found that taking ALC in addition to an antidepressant led to lower rates of adverse events than the antidepressants alone, which helped patients adhere to their drug regimen.



## Longer Periods of Untreated Depression Linked to More Brain Inflammation

A 2018 study by researchers Elaine Setiawan, Sophia Attwells and colleagues reports that **inflammation seems to increase with duration of untreated unipolar depression**. This implies that depression may be a progressive illness, and later stage depression may require different treatments than early stage depression, such as those that directly target inflammation.

**The study published in the journal *The Lancet Psychiatry* used positron emission tomography (PET scan) to examine levels of translocator protein in the brain. Higher levels of translocator protein indicate activation of microglia, the brain's immune cells, which can respond to trauma or injury.**

The study included 80 participants between the ages of 18 and 75. Ten had a history of more than 10 years of depression, ten had experienced fewer than 10 years of depression, and 30 comprised a healthy comparison group.

The best predictors of high levels of translocator protein were duration of

untreated major depressive disorder, total illness duration, and duration of antidepressant exposure. These three factors explained about half of the variation in translocator protein levels. Those participants whose depression went untreated for 10 years or longer had inflammation levels 29–33% higher than those whose depression was untreated for 9 years or less.

Participants who had received antidepressant treatment appeared to avoid an average yearly increase in the extent of their microglial activation.

The study took place at Canada's Centre for Addiction and Mental Health.

*Editor's Note: Since inflammation is a predictor of poorer response to antidepressants, these data add a further strong clinical rationale for earlier and more sustained antidepressant treatment and prevention. Virtually all treatment guidelines suggest that after two or three prior unipolar depres-*

*sions, patients should receive long-term (lifelong) antidepressant treatment.*

*There is now a large body of data, including a 2012 article by this editor Robert M. Post and colleagues in the Journal of Psychiatric Research that too many episodes can hurt the brain, and the current study adds to this perspective. Avoiding preventive treatment for too long may actually foster the development of more episodes and more treatment resistance. A good mantra is "prevent episodes, protect the brain."*

*Consensus is now also building that comprehensive long-term treatment is indicated after a first manic episode. A 2013 article by Lars Kessing and colleagues in the British Journal of Psychiatry suggested that high quality initial treatment can improve the long-term course of illness. Moreover, a 2016 article by Jan-Marie Kozicky and colleagues and a 2017 article by Christine Demmo and colleagues, both in the journal Bipolar Disorders, suggest that after a first mania, cognition recovers over the next year only if no further episodes occur in that time.*

## 3-Minute 'Theta Burst' RTMS Treatment as Effective as 37-Minute RTMS

A variation on repeated transcranial magnetic stimulation (rTMS) called intermittent theta burst stimulation (iTBS) may be able to deliver the same benefits in a tenth of the time. RTMS is a non-invasive treatment in which a magnetic coil placed near the skull transmits electrical signals to the brain. It is effective in depression and has been shown to improve aspects of schizophrenia, autism, and addictions as well.

A typical rTMS session lasts for 37.5 minutes and consists of high frequency (10 Hz) stimulation. Access to the treatment remains somewhat limited, so the newer form of iTBS treatment may help more people access treatment by allowing clinicians to treat more patients in a day.

The 2018 study, published by Daniel Blumberger and colleagues in the

journal *The Lancet*, compared iTBS to standard rTMS and evaluated the effectiveness, safety, and tolerability of the new treatment compared to the old. 414 patients aged 18–65 with major depression that had persisted despite treatment with several antidepressant options were randomized to receive either iTBS or rTMS delivered to their left dorsolateral prefrontal cortex. They received the given treatment five days/week for four to six weeks.

**Patients who received iTBS showed a nearly identical level of improvement in depression to those who received rTMS.** Self-reports of pain intensity were worse among those who received iTBS, but the dropout rate was not higher for that group. Headaches were the most common side effect reported, and rates were

similar across both groups. The authors judged iTBS to be a comparable, non-inferior alternative to rTMS for people with major depression.

Among participants who received iTBS, depression improved significantly, with 32 percent reporting a remission of depression symptoms. Those who received standard rTMS had a remission rate of 27 percent.

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## Meta-Analysis Finds Antidepressants More Effective Than Placebo

In a 2018 article in the journal *The Lancet*, researchers led by Andrea Cipriani compared the efficacy of 21 different antidepressants and established that antidepressants are more effective than placebo at reducing unipolar depression. **To date, this is the largest meta-analysis of double-blind, randomized controlled studies of antidepressant efficacy, including 522 trials and a total of 116,477 participants. All 21 of the antidepressants were found to be more effective than placebo.**

Looking at head to head studies, Cipriani and colleagues found that the most effective antidepressants were agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine. The least effective antidepressants were fluoxetine, fluvoxamine, reboxetine, and trazodone.

In terms of tolerability, agomelatine, citalopram, escitalopram, fluoxetine,

sertraline, and vortioxetine were most tolerable to patients, while amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine caused the most study dropouts due to side effects. Only agomelatine and fluoxetine had better dropout rates than placebo.

Interestingly, agomelatine, the medication found to be most effective and most tolerable, is unavailable in the US. Pharmaceutical company Novartis, which owns the rights to the drug, was disappointed by some lackluster studies of the drug and never applied for Food and Drug Administration approval to sell it in the US. The studies found potential problems regarding drug interactions related to the metabolic enzyme CYP1A2 and a risk of liver damage with longer-term use.

*Editor's Note: This meta-analysis should end any remaining controversy*

*about the efficacy of antidepressants in the acute treatment of unipolar depression.*

*This study did not address maintenance treatment for the prevention of depressive episodes. Researcher John R. Geddes and colleagues have found robust, statistically significant data that continuation treatment with antidepressants can prevent depressive relapse, suggesting that if patients continue taking effective antidepressants, rather than switching to placebo, the antidepressants can reduce depressive occurrences by about 70%.*

*It is now recommended in most guidelines that patients with two or three prior episodes of depression consider staying on antidepressants indefinitely over their lifetime in order to prevent recurrence. Antidepressants increase the creation of new neurons and brain-derived neurotrophic factor (BDNF), which protects neurons and is important for learning and memory. Antidepressants can also prevent loss of hippocampal volume.*

## Vortioxetine Now FDA-Approved for Improving Processing Speed in Depression

In May 2018, **the US Food and Drug Administration (FDA) approved a label change for the antidepressant vortioxetine (Trintellix), reflecting new data that show the drug can improve processing speed, an aspect of cognitive function that is often impaired in people with depression.** Vortioxetine was first approved by the FDA for the treatment of depression in 2013.

The approval followed eight-week double-blind placebo-controlled studies of vortioxetine's effects on cognitive function in adults aged 18–65 who have depression. The studies were known as FOCUS and CONNECT. Patients received either 10mg/day, 20mg/day, or placebo. Those who took vortioxetine showed improvement on the Digit Symbol Substitution Test, a measure of processing speed, in addition to improvement in their depression.

*Editor's Note: This is the first time the FDA has approved labeling that describes an antidepressant as improving aspects of cognition in depression. Cognition is impaired in many patients with depression, such that this component of the drug's effects could be of clinical importance. Among the 5 serotonin (5HT) receptor effects of the drug (in addition to the traditional blockade of serotonin reuptake shared by all selective serotonin reuptake inhibitor antidepressants (SSRIs)), it is likely that vortioxetine's effects in blocking 5HT-3 and 5HT-7 receptors are important to the drug's effects on processing speed.*

## Hearing Aids May Lessen Cognitive Decline, Memory Loss

A 2018 article by researcher Asri Maharani and colleagues in the *Journal of the American Geriatrics Society* reports that **using a hearing aid was associated with better scores on a test of episodic memory, and that declines in episodic memory slowed after participants began using hearing aids.**

The study included 2,040 adults aged 50 years and up. Maharani and colleagues used data from the Health and Retirement Study, which measured participants' cognitive functioning every two years for 18 years. Participants were asked to recall 10 words both immediately and after some delay.

The authors suggested that improving access to hearing aids earlier in the course of hearing impairment might help to stem the rise of dementia.

## Clinical Vignettes from Psychiatrist Elizabeth Stuller

Dr. Elizabeth Stuller, a staff psychiatrist at the Amen clinics in Washington, DC and CEO of private practice Stuller Resettings in Baltimore, MD, provided this editor (Robert M. Post) with several interesting anecdotal observations based on her wide clinical experience with difficult-to-treat mood disordered patients.

### Asenapine

Stuller has used low-dose asenapine (Saphris), e.g. half a pill placed under the tongue, for depressed patients with alcohol use problems who have trouble getting to sleep. She has also used asenapine for rapid calming of agitated patients in her office.

### Brexpiprazole

Stuller has also had success with the use of the atypical antipsychotic drug brexpiprazole (Rexulti) for patients with bipolar depression and low energy. She typically uses 0.5 mg/day for women and 1 mg/day for men. Stuller finds that there is little weight gain or akathisia with brexpiprazole.

### Neudexta

Stuller has had success with the drug Nuedexta, which is a combination of dextromethorphan and quinidine and is approved for the treatment of sudden uncontrollable bouts of laughing or crying, known as pseudobulbar affect, which can occur as a result of neurological conditions or brain injuries. It is a combination of an NMDA antagonist and a sigma receptor agonist. Stuller starts with the 20mg dextromethorphan/10 mg quinidine dose once a day and increases to twice a day in week two. She finds it useful for behavioral effects of traumatic brain injury (TBI), anxiety resulting from the use of synthetic marijuana (sometimes called spice), and psychosis not otherwise specified. Stuller also finds that some patients appear to respond well to Nuedextra but not minocycline, or vice versa.

*Editor's Note: Note that these are preliminary clinical anecdotes conveyed in a personal communication, and have not been studied in clinical trials, thus should not be relied upon in the making of medical decisions. All decisions about treatment are the responsibility of a treating physician.*

## Early Intervention Improves Outcomes in Early-Stage Schizophrenia

A recent meta-analysis of 10 studies found that early intervention after a first episode of psychosis or in the early stages of a schizophrenia spectrum disorder led to better patient outcomes than treatment as usual.

The meta-analysis by researcher Christoph U. Correll and colleagues appeared in the journal *JAMA Psychiatry* in 2018. **The 10 studies that were included had randomized a total of 2,176 patients to receive either treatment as usual or early intervention services, which typically include efforts at early detection of symptoms, early treatment with low doses of antipsychotic medication, interventions to prevent relapse, and strategies to help patients return to normal work and social activities.**

Those patients who received early intervention services were less likely to discontinue treatment, were less likely to have a psychiatric hospitalization, were more involved in

school or work, and had less severe symptoms, including both positive and negative symptoms of schizophrenia.

The authors called for better funding and implementation of early intervention services in early psychosis or the beginning stages of schizophrenia.

*Editor's Note: This finding with regard to schizophrenia spectrum disorders emphasizes the enormous disparity in allocation of research resources for the study of early psychosis versus early bipolar disorder, where almost no studies of this kind have been done.*

*The mean age of the patients in this psychosis meta-analysis was 27.5 years. Symptoms of bipolar disorder can often begin earlier, in childhood, and early onset of bipolar disorder predicts poor long-term outcomes into adulthood and is associated with a high risk of substance abuse and suicide. This editor (Robert M. Post) and many colleagues have witnessed two*

*decades of scientific literature on early-onset bipolar disorder. We know that early intervention is necessary, but more treatment studies are needed at the early stages of the illness, and calls for funding treatment-focused research have gone unheeded.*

*More advocacy is needed among families affected by bipolar disorder and advocacy groups interested in better treatment of bipolar disorder. We must try to change the abysmal status quo and campaign publicly, privately, and politically for more funds and public health attention to be directed toward early intervention in bipolar disorder.*

**See page right for a study of children at risk for mood disorders.**



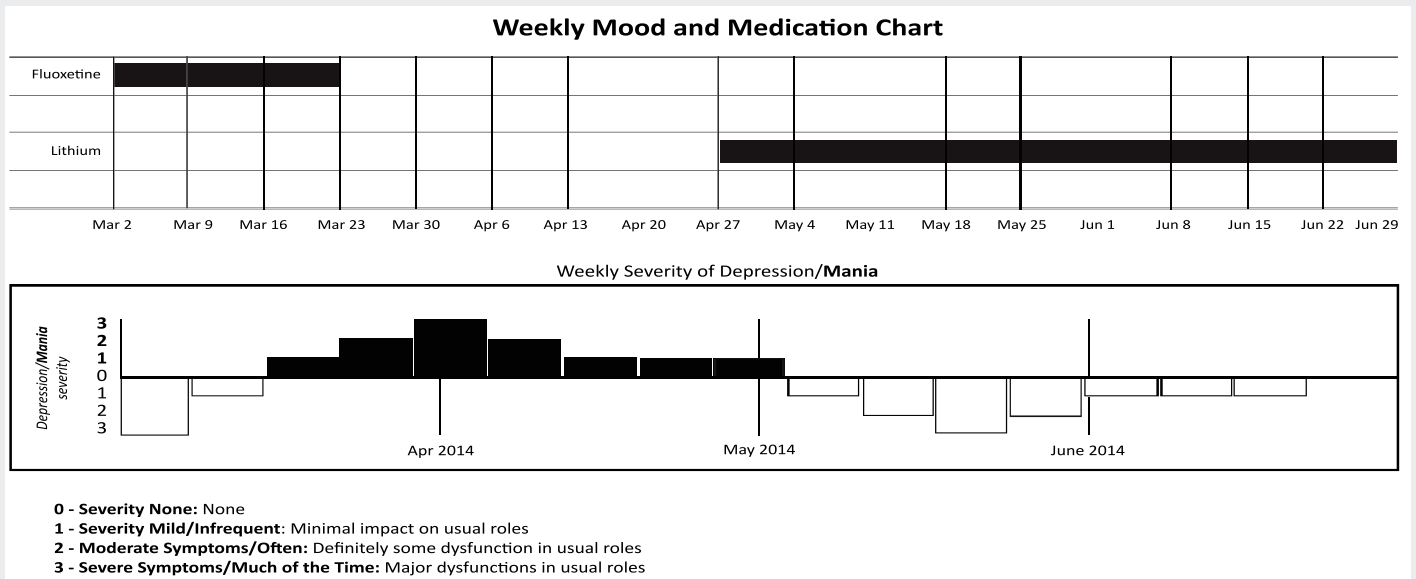
## Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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).



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](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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