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Bipolar Network News

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Vol. 23, Issue 1, 2019

Risk of Suicide in People with Bipolar Disorder: Lowest with Lithium, Highest with Antidepressants

Researcher Markku Lähteenvuo and colleagues reported in the journal *JAMA Psychiatry* in early 2018 that long-acting injectable antipsychotics and lithium were best at preventing re-hospitalization in 18,018 bipolar patients in Finland who received an average of more than 7 years of follow up. Lähteenvuo and colleagues have now gone on to analyze suicide data from the same cohort of patients with bipolar disorder, and report that **those taking lithium had the lowest rate of suicide, while those taking valproate had the next lowest suicide rate.** Those patients with bipolar disorder who were treated with antidepressants had the greatest suicide rate. The suicide rate was particularly high for those once-hospitalized patients taking the MAO inhibitor antidepressant meclobemide, which is not approved for use in the US. Increased rates of suicide were also seen with use of sedatives and benzodiazepines.

Editor's Note: Evidence continues to mount that lithium should be the definitive first line therapy in bipolar disorder for a multitude of reasons (as this editor Robert M. Post reviewed in an open-access article in the journal Neuropsychopharmacology *in 2017). Still, lithium is not often prescribed for people with bipolar disorder in the US, and this does not seem to be in these patients' best interests.*

Use of antidepressants in bipolar disorder has remained controversial, but it is common in clinical practice despite a lack of evidence that it is effective, and the presence of some evidence that it is actually harmful. Antidepressant use in a person with bipolar disorder may cause switching into mania, cycle acceleration, dysphoria induction, and even suicide.

Clinicians should take these data seriously and overcome the impulse (leftover from treating unipolar depression) to use unimodal antidepressants as first line or adjunctive therapy for bipolar depression. Antidepressants are only effective in the long term in about 15% of patients with bipolar depression, and now it appears antidepressant use also carries an additional risk of suicide.

Family History of Lithium Response A Potent Predictor of Lithium Effectiveness

Researcher Martin Alda and colleagues reported at a 2018 scientific meeting that a family history of good response to lithium is highly predictive of response to lithium in a current bipolar patient. **A good prospective response to lithium was seen in 68.6% of patients with a family member who responded well to lithium. Only 22% of those without a family member with a positive lithium response responded well to lithium.**

Editor's Note: Other predictors of a good response to lithium include: a family history of mood disorder, classical euphoric mania with clear-cut well intervals between episodes, lack of a simultaneous anxiety or substance abuse disorder, starting lithium early rather than late in the course of illness after many episodes or rapid cycling has occurred, and a sequential pattern of episodes of mania followed by depression, and then an interval of wellness (i.e. M-D-I rather than D-M-I). Even in those without these characteristics, lithium has many benefits including neuroprotection, reduction of suicide risk, and improved medical health (perhaps through its ability to increase the length of telomeres which are bits of DNA at the end of each chromosome). Longer telomeres are protective, while people with shorter ones may be vulnerable to some medical and psychiatric illnesses.

In This Issue:

Lithium Superior to Other Mood Stabilizers in Study of Bipolar Youth

At a late-2018 scientific meeting, researcher Danella Hafeman and colleagues reported some results of the Course and Outcome of Bipolar Youth (COBY) study. The study includes long-term follow up of 413 youth with bipolar disorder, who ranged in age from 7 to 17 years old. Hafeman and colleagues reported that **taking lithium more than 75% of the time was linked to fewer suicide attempts, fewer depressive symptoms, and fewer psychosocial difficulties than taking another mood stabilizer (such as an atypical antipsychotic, lamotrigine, or valproic acid) more than 75% of the time,** after adjusting for demographic variables.

Despite the limitations of observational studies such as this one, the authors concluded, "Our findings are consistent with studies in adult populations, showing that lithium (compared to other mood stabilizers) is associated with decreased suicidality, less depression, and better psychosocial functioning. Given the paucity of evidence regarding lithium in children and adolescents, these findings have important clinical implications for the pharmacological management of youth with [bipolar disorder]."

Editor's Note: These observations are consistent with several other studies. Researcher Barbara Geller and colleagues observed in eight years of follow up of children diagnosed with bipolar disorder that those who were treated with lithium spent more time in remission than those who took other medicines. A randomized controlled study by researcher Robert Findling and colleagues documented that maintenance lithium treatment was more effective than placebo at preventing bipolar episodes. Together, these data suggest that lithium should be used more often in the long-term treatment of children with bipolar disorder.

Way ahead of his time in about 1993, the renowned child psychiatrist Dennis Cantwell said something like this: "If I had an adolescent child with a first manic episode, I would have him stay on lithium for the rest of his life." He seems to have been prescient, as evidence of the many benefits of lithium over other alternatives in the treatment of both children and adults has been accumulating.

An open-access review article this editor (Robert M. Post) published in the journal Neuropsychopharmacology *in 2017, "The New News about Lithium: An Underutilized Treatment in the United States," argues that lithium's many benefits have been underestimated, while its side effects have been overestimated. It is my view that it would be beneficial if lithium were more often included in the treatment regimen of adults as well as children and adolescents with bipolar disorder.*

Lithium has an astounding range of effectiveness. It prevents recurrent depressions and suicide (even in those with unipolar depression), increases hippocampal and cortical volume, protects memory, and increases the length of telomeres (the end portions of chromosomes that protect them as they replicate). In multiple animal models of neurological diseases, it has also been found to be neuroprotective and to reduce the size of brain lesions.

Bipolar Network News
bipolarnews.org

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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.

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Scientific Mechanisms of Rapid-Acting Antidepressants Such As Ketamine

At a recent symposium, researcher Francis McMahon provided electrophysiological evidence that **several different types of rapid-acting antidepressants—low-dose ketamine, scopolamine, and rapastinel (a partial agonist of the neurotransmitter NMDA)—act by decreasing the inhibitory effects of GABAergic interneurons on excitatory neurons called pyramidal cells, thus increasing synaptic firing.**

Researcher Ronald Duman further dissected these effects, showing that ketamine and its active metabolite norketamine reduce the steady firing rate of GABA interneurons by blocking NMDA receptors, while the partial agonist rapastinel acts on the glutamate neurons directly, and both increase the effects of a type of glutamate receptors known as AMPA. These effects were demonstrated using a virus to selectively knock out GluN2B glutamate

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Inflammation Associated With Duration of Untreated Unipolar Depression

Researcher Sophia Attwells and colleagues reported at a 2018 scientific meeting that the longer the time that a patient went without treatment for depression, the more inflammation they exhibited on positron emission tomography (PET) scans. Attwells and colleagues used the PET scans to assess the total distribution volume of TSPO, which is a marker of brain microglial activation, a form of inflammation.

Strikingly, in participants who had untreated major depressive disorder for 10 years or longer, TSPO distribution volume was 29–33% greater in the prefrontal cortex, anterior cingulate cortex, and insula than in participants who were untreated for 9 years or less. TSPO distribution volume was 31–39% greater in these three important regions of gray matter in participants with long durations of untreated major depressive disorder than in healthy control participants.

Editor's Note: In schizophrenia, the duration of untreated interval (DUI) is associated with a poor prognosis, but not with inflammation. Researcher Yvette Sheline has also reported that less time on antidepressants compared to more time treated with them was associated with greater hippocampal volume loss with aging in patients with major depression.

Given Attwells and colleagues' remarkable finding about the adverse effects of the DUI in depression, including inflammation and brain volume loss, and other findings that associate more episodes with poorer functioning, cognition, and treatment responsiveness, physicians and patients should think hard about committing to long-term antidepressant treatment to prevent episodes, beginning early in the course of illness.

This editor (Robert M. Post) would propose that if a second depressive episode occurs after a first depression that responded well to treatment, this would be an appropriate time to start antidepressant prophylaxis. Most guidelines suggest that prophylaxis be started after a third episode, but these recommendations generally do not account for newer data on the pernicious effects of experiencing repeated depressive episodes. In addition to causing dysfunction and disability, going through four depressive episodes doubles the risk of dementia in old age, and this risk increases further with each successive episode, according to researcher Lars Kessing.

Having too many depressions is bad for the brain. In Kessing's studies, two episodes of unipolar or bipolar depression did not increase the risk of dementia compared to the general population, while four depressions did. One could compare the effects of repeated depressions on the brain to the effects of heart attacks on the heart muscle. A heart might still function well after one or even two heart attacks, but the chances of significant loss of function and the risk of congestive heart failure increase as a function of the number of heart attacks. After even one heart attack, most patients change their lifestyle and/or go on prophylactic medications to reduce risk factors such as elevated blood pressure, cholesterol, triglycerides, weight, blood sugar, and smoking. The benefits of reducing heart attacks are a no brainer. Trying to prevent recurrent depression with pharmacotherapy and adjunctive psychotherapy after a second depressive episode should be a no brainer too.

In addition, if antidepressants are not effective enough in preventing depressions, lithium is an option, even in unipolar depression, for preventing both episodes and suicide. The evidence of efficacy in both instances is very strong according to an article by Mohammed T. Abou-Saleh in the International Journal of Bipolar Disorders *in 2017. The renowned psychiatrist Jules Angst's recommendation as to when to start lithium treatment was that if a patient had had one episode or more in the previous five years in addition to the present episode, then they were likely to have two further episodes in the following five years, and lithium prophylaxis would be recommended.*

Scientific Mechanisms of Rapid-Acting Antidepressants (cont.)

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receptor subunits in either GABA interneurons or glutamate neurons.

Increasing AMPA activity increases synapse number and function and also increases network connectivity, which can reverse the effects of stress. Duman and colleagues further showed that when light is used to modulate pyramidal cells (a process called optogenetic stimulation) in the medial prefrontal cortex, different effects could be produced. Stimulating medial prefrontal cortex cells that contained dopamine D1 receptors, but not D2 receptors, produced rapid and sustained antidepressant effects. Conversely, inhibiting these neurons blocked the antidepressant effects of ketamine. Stimulating the terminals of these D1-containing neurons in the basolateral nucleus of the amygdala was sufficient to reproduce the antidepressant effects. These data suggest that stimulation of glutamate D1 pyramidal neurons from the medial prefrontal cortex to the basolateral nucleus of the amygdala is both necessary and sufficient to produce the antidepressant effects seen with ketamine treatment.

Researcher Hailan Hu reported that NMDA glutamate receptors drive the burst firing of lateral habenula (LHb) neurons, which make up the depressogenic or "anti-reward center" of the brain and appear to mediate anhedonic behavior (loss of interest or enjoyment) in animal models of

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In Study of Mice, Risk Gene for Bipolar Disorder Is Linked to Depressed Behaviors and Abnormal Firing of GABA Neurons

At a 2018 scientific meeting and in a 2017 article in the journal *PNAS*, researcher Shanshan Zhu and colleagues reported that **mice genetically engineered to lack the protein Ankyrin-G in certain neurons showed increases in depression- and mania-like behavior after being exposed to defeat stress (by repeatedly being placed in physical proximity to a larger, more aggressive mouse), which is often used to model human depression.**

The researchers targeted the gene ANK3, which is responsible for the production of Ankyrin-G, and has been linked to bipolar disorder in genome-wide association studies. By manipulating the gene, they could eliminate Ankyrin-G in pyramidal neurons in the forebrain, a region relevant to many psychiatric disorders. Pyramidal neurons perform key brain functions, sending nerve pulses that lead to movement and cognition.

The missing Ankyrin-G affected sodium channels (which allow for the flow of sodium ions in and out of cells) and potassium channels. The neurochemical GABA (which typically inhibits nerve impulses) was also dysregulated, resulting in the kind of disinhibition seen in psychosis. Mice showed dramatic behavioral changes ranging from hyperactivity to depression-like behavior (e.g. giving up in a forced swimming test). The hyperactivity decreased when the mice were given treatments for human mania, lithium or valproic acid.

While mutations in the ANK3 gene may disturb sodium channels, another gene linked to depression and bipolar disorder, CACNA1C, affects calcium channels.

In a related study by researcher Rene Caballero-Florán and colleagues that was also presented at the meeting, mice were genetically engineered in such a way that interactions between Ankyrin-G and GABA Type A Receptor-Associated Protein (GABARAP) were disrupted, leading to deficits in inhibitory signaling. These deficits were partially corrected when the mice were treated with lithium.

The study by Caballero-Florán and colleagues used mice with a mutation known as W1989R in the ANK3 gene. Through a program that examines the genes of people with bipolar disorder, the researchers also identified a family with this genetic mutation, including a patient with type I bipolar disorder with recurrent mania and depression who has responded well to lithium treatment.

In Healthy Subjects, Calcium Channel Blocker Nimodipine Decreased Frontal and Parietal Cortical Activity During A Working Memory Task

At a recent scientific meeting, researcher Kristin Bigos and colleagues described the effects of nimodipine, a treatment for brain hemorrhage, on the brain during working memory tasks. Nimodipine is a dihydropyridine L-type calcium channel blocker. These prevent calcium from entering neurons and cells in the heart and blood vessel walls and are often used to treat high blood pressure.

Nimodipine acts on the CACNA1C calcium influx gene. Certain genetic variations in this gene (particularly the rs1006737 A allele) have been linked to vulnerability to bipolar disorder, schizophrenia, depression, and autism. Carriers of the risk allele also have higher CACNA1C mRNA expression in the dorsolateral prefrontal cortex and exhibit more activity in the frontal and parietal regions of the brain during working memory tasks, suggesting inefficient brain processing in these regions. Bigos and colleagues found that **60mg/day of nimodipine decreased frontal and parietal cortical activity by 39.1% and 42.8%, respectively, during a working memory task, suggesting that nimodipine improved the efficiency of memory processing.** Nimodipine's positive effects were greater in those participants who had the CACNA1C risk allele.

Editor's Note: Using a placebo-controlled off-on-off-on study design (meaning patients took placebo for a period, then nimodipine, then placebo again and nimodipine again), this editor (Robert M. Post), Peggy J. Pazzaglia and colleagues found that nimodipine had positive effects in both mania and depression in patients with bipolar disorder (described in the 2008 book Treatment of Bipolar Disorder: A Casebook for Clinicians and Patients *by Robert M. Post and Gabriele S. Leverich). In a large randomized study of patients with bipolar disorder presented by Haroon R. Chaudhry at the 2010 meeting of the Society of Biological Psychiatry, lithium was associated with about a 50% response rate while the combination of lithium and nimodipine was associated with a 73% response rate.*

It remains to be seen whether people with bipolar disorder who have the CACNA1C risk gene would respond better to nimodipine than those without the risk gene, and whether it would improve working memory more in the subgroup with the risk gene.

Assessing Baseline Levels of Inflammatory Marker CRP Could Help Predict Clinical Response to Different Treatments

C-reactive protein, or CRP, is a marker or inflammation that has been linked to depression and other illnesses. **People with high levels of CRP respond differently to medications than people with lower CRP, so assessing CRP levels may help determine which medications are best to treat a given patient.**

High baseline levels of CRP (3–5pg/ml) predict a poor response to selective serotonin reuptake inhibitor antidepressants (SSRIs) and to psychotherapy, and are associated with increased risk of recurrent depression, heart attack, and stroke.

However, high baseline CRP predicts a better response to the antidepressants nortriptyline and bupropion. High CRP is also associated with better antidepressant response to infliximab (a monoclonal antibody that inhibits the inflammatory cytokine TNF alpha), while low levels of CRP predict worsening depression upon taking infliximab.

High baseline CRP also predicts good antidepressant response to intravenous ketamine (which works rapidly to improve treatment-resistant depression), minocycline (an anti-inflammatory antibiotic that decreases microglial activation), L-methylfolate (a supplement that can treat folate deficiency), N-acetylcysteine (an antioxidant that can improve depression, pathological habits, and addictions), and omega-3 fatty acids (except in people with low levels of DHA).

High baseline CRP also predicts a good response to the antipsychotic drug lurasidone (marketed under the trade name Latuda) in bipolar depression. In people with high baseline CRP, lurasidone's positive results have a huge effect size of 0.85, while in people with low CRP (<3pg/ml) the improvement on lurasidone has a smaller effect size (0.35).

In personal communications with this editor (Robert M. Post) in 2018, experts in the field (Charles L. Raison and Vladimir Maletic) agreed that assessing baseline CRP levels in a given patient could help determine optimal strategies to treat their depression and predict the patient's responsiveness to different treatment approaches.

At a 2018 scientific meeting, researchers Cynthia Shannon, Thomas Weickert, and colleagues reported that high baseline levels of CRP were associated with symptom improvement in patients with schizophrenia when they were treated with the drug canakinumab (marketed under the trade name Ilaris). Canakinumab is a human monoclonal antibody that targets the inflammatory cytokine interleukin-1 beta (Il-1b). Il-1b is elevated in a subgroup of patients with depression, bipolar disorder, or schizophrenia, and CRP levels are an indication of the associated inflammation.

Rapid-Acting Antidepressants

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depression. Ketamine blocks the burst firing of the LHb neurons, which disinhibits monoamine reward centers, enabling ketamine's rapid-onset antidepressant effects. This may occur because inhibitory metabotropic glutamate receptors (mGluR-2) are activated, decreasing the release of glutamate.

MGluR-2 may also help explain the antidepressant effects of acetyl-L-carnitine supplements. Acetyl-L-carnitine is an amino acid that is low in the blood of depressed patients (see research by Carla Nasca described on page 6 of this issue). The supplement acetyl-L-carnitine activates the DNA promoter for mGluR-2, increasing its production and thus decreasing excess glutamate release. The acetyl group of the acetyl-L-carnitine binds to the DNA promoter for mGlur-2 and increases the levels of this receptor.

It's now faster and easier to join the Child Network!

The consent form for the Child Network has been simplified. If you previously tried to sign up and gave up in frustration, please try again. The new consent form is much easier to complete.

The Child Network is a study designed to evaluate how children with mood disorders are being treated for their illness. Parents who enroll in the study complete an online checklist of their child's symptoms once a week using a secure web-based system. Parents of children aged 2–12 who have mood or behavioral problems should consider joining.

See page 11 for more information.

Ketamine May Enhance the Effects of Cognitive Training Therapy

Rebecca B. Price, a professor of Psychiatry and Psychology at the University of Pittsburgh, and colleagues reported at a recent scientific meeting that **the combination of intravenous ketamine treatment and four days of cognitive training to enhance positive self-representations improved depression better than either intervention alone** (IV ketamine plus a sham training or a non-medicated saline drip plus 4 days of cognitive work).

Price and colleagues suggested that priming brain plasticity with ketamine could enhance cognitive training focused on increasing positive self-representations. Psychologists have theorized that self-representations (or assessments of one's strengths and other qualities) can be a resource that helps people cope with life stress.

Low Acetyl-L-Carnitine Associated with Insulin Resistance in Traumatized Children

Researcher Carla Nasca and colleagues from the Rockefeller University reported at a late-2018 scientific meeting that **depressed patients with a history of childhood adversity had low levels of the amino acid acetyl-L-carnitine and also exhibited insulin resistance.** This is noteworthy because in a series of small studies, acetyl-L-carnitine supplements have had antidepressant effects. In laboratory animals, acetyl-L-carnitine also sensitizes insulin receptors. This suggests the possibility that the supplements could provide a two-for-one benefit in depressed patients with a history of adversity in childhood.

Inflammation Linked to Poor Sleep Quality and Worse Executive Functioning

At a recent scientific meeting, researcher Ellen E. Lee and colleagues reported that **compared to healthy volunteers, people with bipolar disorder or schizophrenia had elevated levels of inflammatory markers, which were associated with poor sleep.**

According to self-reports, people in the schizophrenia and bipolar disorder group had worse sleep quality than the control group. Those with schizophrenia or bipolar disorder also had significantly higher levels of the inflammatory markers CRP, IL-6, and TNF alpha compared to the healthy volunteers. Among people with bipolar disorder, executive functioning and sleep quality had a strong inverse association to levels of IL-6, such that lower sleep quality and worse executive functioning were associated with higher levels of IL-6. These findings suggest that sleep disturbance and inflammation may have negative consequences for cognitive functioning.

Il-6 Inhibitor Sirukumab May Improve Anhedonia, But Not General Depression

At a 2018 scientific meeting, researcher Giacomo Salvadore and colleagues reported that the drug sirukumab, a monoclonal antibody that targets the inflammatory marker Il-6 and that was originally developed to treat rheumatoid arthritis, did not have a statistically significant effect on overall depression compared to placebo. However, by the twelfth week of treatment, sirukumab did have a significant effect on anhedonia (loss of interest or pleasure in activities that one previously enjoyed).

The degree of improvement in anhedonia was significantly correlated with patients' baseline levels of the inflammatory marker CRP. Since the inflammatory marker that sirukumab targets, Il-6, is one of those most often elevated in depression, it appears that more study of sirukumab would be warranted.

White Matter Abnormalities Linked to Irritability in Both Bipolar Disorder and DMDD

At a 2018 scientific meeting, researcher Julia Linke of the National Institute of Mental Health reported that **there were white matter tract abnormalities in young people who had irritability associated with either bipolar disorder or disruptive mood dysregulation disorder (DMDD).** Thus, while these two disorders differ in terms of diagnosis, presentation, and family history, they seem to have this neurobiological abnormality in common.

White Matter Abnormalities in Obesity

Researcher Ramiro Reckziegel and colleagues reported at a recent scientific meeting that white matter is abnormal in obese adults with bipolar disorder. In a 2018 article in the journal *Schizophrenia Bulletin*, Reckziegel reported that **body mass index (BMI) was associated with reduced fractional anisotropy, a measure of brain fiber integrity, in the cingulate gyrus in patients with bipolar disorder.** This finding implies that obesity may play a role in white matter microstructure damage in the limbic system.

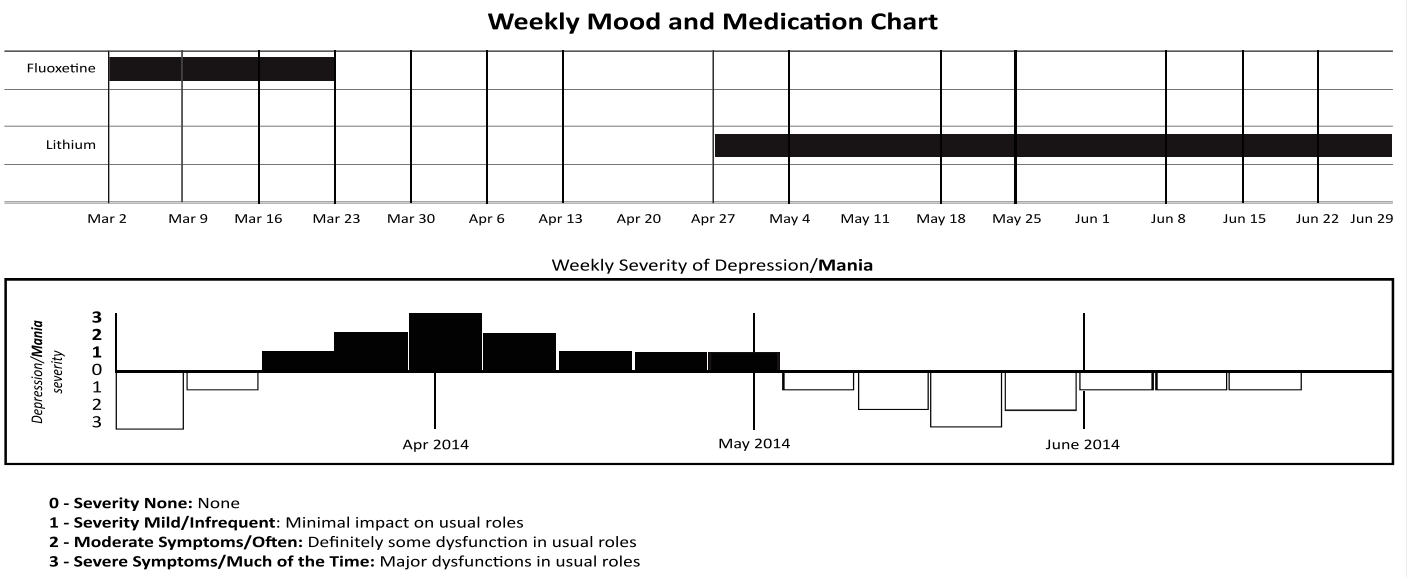
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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

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

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

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



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

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

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

Robert M. Post, MD and Michael Rowe, PhD
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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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