

Bipolar Network News

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Lamotrigine Potentiates the Antidepressant Effects of Quetiapine in Bipolar Depression

At the 2015 meeting of the International Society for Bipolar Disorders, researcher John Geddes presented an important study showing in inadequate responders to quetiapine that compared to adding placebo, adding the anticonvulsant lamotrigine to their treatment improved depression rapidly and lastingly. Some psychiatrists have been prescribing this combination to patients for some time, but this is the first formal clinical trial documenting its efficacy. The article was published online in December in the journal *Lancet Psychiatry*.

Researcher Guy Goodwin described details of the study, called CEQUEL, at the meeting. It included 202 patients with bipolar I or II disorder who required treatment for a depressive episode. Participants who did not respond completely to 14 days of treatment with quetiapine were prescribed either an additional dose of lamotrigine or a placebo. Lamotrigine was very slowly titrated up to maximum doses of 200mg/day. Its antidepressant effects were striking. They began early and persisted for 52 weeks. **Response rates for the combination of quetiapine and lamotrigine were 52%, compared to 22% for quetiapine alone.** Remission rates were 35% for quetiapine and lamotrigine and 12% for quetiapine alone.

Folic acid interaction

Another part of the study assessed whether folic acid supplements could improve outcomes, but in fact they did the opposite, reversing the benefits of adding lamotrigine. Geddes did not have an explanation for why this might be the case. Lamotrigine can inhibit

folate metabolism, and it had been thought that adding folate would be useful. **Until further data are gathered on folate augmentation in patients taking the combination of lamotrigine and quetiapine, folate should be used cautiously if at all in these patients.**

Possible combination with lithium

In Goodwin's talk, he also noted lithium's potential to lower suicide rates, premature mortality, and cog-

nitive impairment, and to increase hippocampal and cortical volume.

Since lamotrigine was shown to potentiate the antidepressant effects of lithium in a study by Marc L.M. Van der Loos and colleagues, and quetiapine is approved by the Food and Drug Administration for the prevention of depression as an adjunct to lithium (or valproate), there might be theoretical acute and long-term benefits to combining treatment with the three drugs: lithium, quetiapine, and lamotrigine, but this remains to be seen.

A STUDY ASSESSING YOUR CHILD'S MOOD AND BEHAVIOR

Parents, if your child (aged 2 – 12) has mood or behavioral difficulties, we would like to enlist your participation in a study called the Child Network. Parents who enroll in the study will complete an online rating checklist of your child's symptoms once a week by a secure web-based system.

In addition, adults who have been diagnosed with depression or bipolar disorder and are the biological parent of a child (ages 2-12) who is currently healthy and has no troublesome mood or behavioral symptoms may also be eligible to participate in this study.



If you are interested in participating in this study, go to <http://bipolarnews.org> and click on the tab for Child Network. For more information, call 301-530-8245, or email questions to childnetworkbnn@gmail.com.

Research Study
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IRB Study #00026940

Diagnosing Childhood Bipolar Disorder: Mom Knows Best

In a talk at the 2015 meeting of the International Society for Bipolar Disorders, researcher Eric Youngstrom showed that mothers' evaluation of their children's psychiatric symptoms was more valid than both teacher ratings and the children's own evaluations. **Parents were better at detecting irritability, while children were better at assessing their energy levels and the quality of their sleep.**

Youngstrom reported that about 2% of children worldwide are diagnosed with bipolar disorder. However, when bipolar disorder not otherwise specified (BP NOS), a diagnosis given when symptoms do not meet the diagnostic criteria for Bipolar I or II, is included in the statistics, rates of bipolar disorder among children in the US reach about 6%.

Youngstrom mentioned that an epidemiological study by Kathleen

Merikangas found that among children in the US with a bipolar spectrum diagnosis, only 22% were in treatment, compared to 38% of those with depression and 60% of those with ADHD.

Parents of children (aged 2-12) with mood, anxiety, and behavioral disorders are invited to join the Child Network, our program for tracking weekly symptoms which can then be printed out longitudinally to share with the child's doctor. See page 7 for details.

Bipolar Network News

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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 with drug companies including 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.

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Stem Cell Research May Help Explain Biochemistry of Bipolar Disorder

At the 2015 meeting of the International Society for Bipolar Disorders, researcher Martin McInnis described how stem cells can be used to identify biochemical abnormalities in patients with bipolar disorder. In this research, the stem cells, or iPSCs (for induced pluripotent stem cells), are created when cells from skin fibroblasts, which produce connective tissue, are treated with chemicals that cause them to de-differentiate back into stem cells.

McInnis identified several abnormalities in the stem cells of patients with bipolar disorder. Stem cells with the gene CACNA1C, which is associated with vulnerability to

bipolar disorder, fired more rapidly than non-CACNA1C stem cells. There were other abnormalities at the NMDA glutamate receptor and an imbalance of the neurotransmitter GABA in the cells. When the cells were treated with lithium, some of these abnormalities were reversed. In the cells with the CACNA1C gene, lithium normalized the firing rate. Lithium also re-balanced the distribution of GABA in the cells.

McInnis hopes that this stem cell research will shed light on the abnormalities associated with bipolar disorder, help explain how lithium corrects some of these, and lead to the development of new therapeutic approaches.

Mixed Depression: Risks and Treatments

Mixed depression describes a state of depression accompanied by a few symptoms typically associated with mania. At the 2015 meeting of the International Society for Bipolar Disorders, researcher Roger McIntyre shared some findings about mixed depression.

People with mixed depression have higher levels of MHPG, which is produced as the neurotransmitter norepinephrine breaks down. They also have higher levels of the stress hormone

cortisol and their depressions are more difficult to treat. Those with unipolar mixed depression may respond poorly to traditional antidepressants.

There are also medical risks associated with mixed depression. People with mixed depression are more susceptible to cardiovascular disease than are people with depressive symptoms alone.

The drugs lurasidone, olanzapine, and ziprasidone have each shown efficacy in mixed depression.

Approaches to Restoring Cognition in Unipolar and Bipolar Depression

Many people with bipolar disorder suffer cognitive difficulties, and these may progress as a function of the number of mood episodes they experience. At the 2015 meeting of the International Society for Bipolar Disorders, researcher Eduard Vieta described the importance of directly prescribing diet, exercise, good sleep hygiene, smoking avoidance, and cognitive exercises designed to maintain cognitive reserves in people with bipolar disorder. Vieta stressed that one of the most important approaches to maintaining cognition is to help patients achieve and maintain remission. He also noted that those patients with lithium levels of .6meq/l or greater did not see cognitive deterioration.

Some treatments for bipolar disorder can contribute to cognition problems. Topiramate and benzodiazepines can impair cognition, as can atypical antipsychotic drugs and certain antidepressants that block the neurotransmitter acetylcholine. Avoiding these treatments and those with sedative side effects may also be helpful.

Vieta listed a series of drugs with some promise for improving cognition. (These did not include treatments for dementia, which include memantine and a group of drugs that increase acetylcholine by inhibiting its breakdown.)

This editor (Robert M. Post) has taken the liberty of giving a letter grade (A to D) to each drug on Vieta’s list on the basis of the strength of the data supporting its efficacy, its safety and tolerability, and its overall usefulness for patients with bipolar disorder. These recommendations, like other material in the BNN, are subjective and likely to change as more systematic studies on these treatments are published.

Reduced Cognitive Function and Other Abnormalities in Pediatric Bipolar Disorder

At the 2015 meeting of the International Society for Bipolar Disorders, Ben Goldstein described a study of cognitive dysfunction in pediatric bipolar disorder. **Children with bipolar disorder were three years behind in executive functioning (which covers abilities such as planning and problem-solving) and verbal memory.**

There were other abnormalities. Youth with bipolar disorder had smaller amygdalas, and those with larger amygdalas recovered better. Perception of facial emotion was another area of weakness for children (and adults) with bipolar disorder. Studies show increased activity of the amygdala during facial emotion recognition tasks.

Goldstein reported that nine studies show that youth with bipolar disorder have reduced white matter integrity. This has also been observed in their relatives without bipolar disorder, suggesting that it is a sign of vulnerability to bipolar illness. This could identify children who could benefit from preemptive treatment because they are at high risk for developing bipolar disorder due to a family history of the illness.

There are some indications of increased inflammation in pediatric bipolar disorder. CRP, a protein that is a marker of inflammation, is elevated to a level equivalent to those in kids with juvenile rheumatoid arthritis before treatment (about 3 mg/L). CRP levels may be able to predict onset of depression or mania in those with minor symptoms, and is also associated with depression duration and severity. Goldstein reported that TNF-alpha, another inflammatory marker, may be elevated in children with psychosis.

Goldstein noted a study by Ghanshyam Pandey that showed that improvement in pediatric bipolar disorder was related to increases in BDNF, a protein that protects neurons. Cognitive flexibility interacted with CRP and BDNF – those with low BDNF had more cognitive impairment as their CRP increased than did those with high BDNF.

Drugs that Improve Cognition (see above)

Drug	Strength of Evidence	Safety & Tolerability	Overall Usefulness in Bipolar Disorder
Caffeine	A	A	A (except for anxiety)
Modafinil	A	A	A
Pramipexole	B	B	B
NAC	C	A	A-
Mifepristone	B (in psychotic depression)	C (high cortisol)	C
Lurasidone	A-	A-	A
Vortioxetine	A (in unipolar depression)	B+	B+ (for unipolar depression)
Citicholine	B	A	B

Schizophrenia: The Importance of Catching It Early

By the time psychosis appears in someone with schizophrenia, biological changes associated with the illness may have already been present for years. A 2015 article by R.S. Kahn and I.E. Sommer in the journal *Molecular Psychiatry* describes some of these abnormalities and how treatments might better target them.

One such change is in brain volume. At the time of diagnosis, schizophrenia patients have a lower intracranial volume on average than healthy people. Brain growth stops around age 13, suggesting that reduced brain growth in people with schizophrenia occurs before that age.

At diagnosis, patients with schizophrenia show decrements in both white and grey matter in the brain. Grey matter volume tends to decrease further in these patients over time, while white matter volume remains stable or can even increase.

Overproduction of dopamine in the striatum is another abnormality seen in the brains of schizophrenia patients at the time of diagnosis.

Possibly years before the dopamine abnormalities are observed, under-functioning of the NMDA receptor and low-grade brain inflammation occur. These may be linked to cognitive impairment and negative symptoms of schizophrenia such as social withdrawal or apathy, suggesting that there is an at-risk period before psychosis appears when these symptoms can be identified and addressed. **Psychosocial treatments such as individual, group, or family psychotherapy and omega-3 fatty acid supplementation have both been shown to decrease the rate of conversion from early symptoms to full-blown psychosis.**

Using antipsychotic drugs to treat the dopamine abnormalities is generally successful in patients in their first

episode of schizophrenia. Use of atypical antipsychotics is associated with less brain volume loss than use of the older typical antipsychotics. Treatments to correct the NMDA receptor abnormalities and brain inflammation, however, are only modestly effective. (Though there are data to support the effectiveness of the antioxidant n-acetylcysteine (NAC) on negative symptoms compared to placebo.) Kahn and Sommer suggest that applying treatments when cognitive and social function begin to be impaired (rather than waiting until psychosis appears) could make them more effective.

The authors also suggest that more postmortem brain analyses, neuroimaging studies, animal studies, and studies of treatments' effects on brain abnormalities are all needed to clarify the causes of the early brain changes that occur in schizophrenia and identify ways of treating and preventing them.

Brain Inflammation in People at High Risk for Schizophrenia

A 2016 study by Peter S. Bloomfield and colleagues in the *American Journal of Psychiatry* used PET scans to compare the activity of microglia (immune cells in the central nervous system) in healthy controls, people with schizophrenia, and those at high risk for the illness. The study reports that both people with schizophrenia and those at high risk had greater brain inflammation than the healthy controls.

The study was the first to show that microglial activity was elevated in people at high risk (who showed some preliminary symptoms of schizophrenia). The finding had a large effect size.

Microglial activity was also correlated with symptom severity in the high-risk participants. Increased microglial activity was not linked to depression, suggesting that it is specific to the development of psychosis.

These findings resemble those of other recent studies showing increased inflammation in people at high risk for psychosis.

The study suggests that increased microglial activity occurs before a first episode of psychosis. That means it could help identify people who may develop schizophrenia. The findings also suggest that anti-inflammatory treatment could theoretically be used to prevent psychosis.

Marijuana May Speed Cortical Loss in Boys at Risk for Schizophrenia

In boys, a decrease in the thickness of the cortex is a part of normal maturation. However, according to a recent study, this process is sped up in boys at high risk for schizophrenia when they use marijuana before the age of 16.

Early use of marijuana has been linked to the later development of schizophrenia. Schizophrenia begins about 5 years earlier in males than in females, and the male brain goes through more structural changes during adolescence.

A 2015 article by Tomáš Paus in the journal *JAMA Psychiatry* incorporated data from three studies, which took place in parts of Canada and England and eight European cities. The studies all included magnetic resonance imaging (MRI) scans of the participants, a measure of their genetic risk of developing schizophrenia, and questions about their past marijuana use. **In boys at high risk for schizophrenia based on their genetic profile, cortical thickness dropped more among the ones who used high amounts of marijuana before the age of 16 compared to those who did not.**

Paus hypothesizes that the development of schizophrenia is a "two-hit process." People who develop schizophrenia may have an early risk factor, such as their genetic profile or a problem that occurs in utero, and a later stressor such as drug use in adolescence.

Marijuana Use Worsens PTSD Symptoms in Veterans

A 2015 study by Samuel T. Wilkinson and colleagues in the *Journal of Clinical Psychiatry* reports that among war veterans who completed a special treatment program for post-traumatic stress disorder, **those who continued or began using marijuana after treatment had more severe PTSD symptoms, were more violent, and used drugs and alcohol more often.** Those who stopped using marijuana or never used it had the lowest levels of PTSD symptoms in the study.

Editor's Note: Scientific information about marijuana is almost never reported in the media. Evidence of the adverse effects of heavy marijuana use are robust and consistent.

Some of these include:

1. A doubling of the risk of psychosis compared to non-users. People with a common variation in the enzyme COMT, which metabolizes dopamine, have an even higher rate of psychosis.
2. An increased risk of bipolar disorder onset.
3. A worse course of bipolar disorder.
4. An increased risk of schizophrenia.
5. Memory deficits that remain even after marijuana use has ceased.
6. Loss of motivation (exactly what someone with depression doesn't need).
7. Anatomical changes in brain structures.
8. A worse course of PTSD and increased violence in those with PTSD.

Bottom line: Those who say marijuana is benign may be ill-informed. People with mood disorders, proneness to paranoia, or PTSD should stay away from marijuana.

Antioxidant NAC Improves Symptoms of Schizophrenia and Bipolar Disorder

N-acetylcysteine (NAC), an antioxidant available without a prescription in health food stores, has shown remarkable effectiveness when added to regular treatments for schizophrenia, bipolar disorder, and the substance abuse that often accompanies these illnesses.

A 2008 article by Michael Berk and colleagues in the journal *Biological Psychiatry* reported that compared to placebo, 2g/day of NAC reduced both positive symptoms of schizophrenia (hallucinations, delusions) and negative symptoms (social withdrawal, difficulty planning and problem-solving). A 2013 study by Mehdi Farokhnia found that 2g/day of NAC improved negative symptoms in 42 patients with schizophrenia. Two other studies found that NAC improved deficits in auditory sensory processing in people with schizophrenia.

NAC also improves symptoms of bipolar disorder. A 2008 study by Berk and a 2011 study by Pedro Vieira da

Silva Magalhães showed that NAC improved bipolar depression, and a small 2013 study by Magalhães showed that it improved mania in 15 patients. After 24 weeks, 60% of those who took NAC were in remission, compared to 15% of those taking placebo.

NAC is also effective at reducing habitual behaviors such as substance abuse, which is common in patients with schizophrenia and bipolar disorder. Studies have shown that NAC can reduce patients' use of marijuana, cocaine, alcohol, and nicotine. It is relatively safe with minimal side effects, and fights oxidative stress, which is also common in severe mental illness.

NAC comes in 500mg or 600mg capsules. Dosing typically begins with one capsule twice a day for a week, followed by two tablets twice a day thereafter. As with any recommendations in the BNN, these should not be acted on without guidance from a treating physician.

Emotion Recognition Deficient in Bipolar Disorder

In the past decade, several studies have indicated that people with bipolar disorder have less ability to recognize the emotions expressed on people's faces than do healthy controls. A 2013 meta-analysis by Cecilia Samamé and colleagues concluded that facial emotion recognition was deficient in people with bipolar disorder regardless of their current state. A 2011 quantitative review article by Christian G. Kohler and colleagues revealed that this difficulty distinguishing emotions is general, rather than specific to any one emotion.

A 2015 study by Esther Vierck and colleagues in the journal *Psychiatry Research* showed that **both euthymic patients with bipolar disorder and their first-degree relatives without bipolar disorder performed worse on tests of emotion recognition than did normal controls.** The findings in healthy relatives suggest that the

deficit may be a familial risk factor for the development of bipolar disorder.

These deficits in facial emotion recognition have also been seen in 4 out of 5 studies of children with early-onset bipolar disorder, including those who are euthymic. 2008 studies by Melissa A. Brotman and colleagues showed that even children just at high risk for bipolar disorder due to a family history of the disorder had deficient emotion recognition.

This literature indicates that deficiencies in facial emotion recognition consistently accompany bipolar disorder and may also be a sign that a child or teenager is at risk for bipolar disorder. Since these deficits can create social and interpersonal difficulties, it may be useful to teach better emotion recognition skills to people with bipolar disorder or those at high risk for the illness.

New Atypical Antipsychotic Drug Brexpiprazole Helps Treat Depression

Two studies published in the *Journal of Clinical Psychiatry* in 2015 suggest that the new atypical antipsychotic brexpiprazole (trade name Rexulti) safely improves depression when added to antidepressant treatment. The 6-week studies, both by Michael E. Thase and colleagues, compared brexpiprazole to placebo in people who had not responded adequately to one to three antidepressants and were taking at least one antidepressant at the time of the study.

The studies examined the effectiveness of different doses of brexpiprazole. **Doses of 2mg/day and 3mg/day were more effective than placebo, while a dose of 1mg/day was not.** The drug

was well-tolerated by patients at each of these doses, although those taking the 3mg/day reported more side effects than those taking 2mg/day. The side effects included restless legs, weight gain, and headaches.

Like the atypical antipsychotic aripiprazole (Abilify), brexpiprazole partially blocks and partially stimulates dopamine receptors. While aripiprazole allows 61% activity at dopamine D2 receptors, brexpiprazole allows 43%. It is not yet clear how the new drug's effects may differ from those of aripiprazole.

Another relatively new atypical antipsychotic drug, cariprazine (Vraylar) is approved by the Food and Drug Administration for schizo-

phrenia and mania, but not yet for bipolar depression or as an add-on treatment to antidepressants in unipolar depression, although there are placebo-controlled trials showing that cariprazine can also treat these conditions.

Like aripiprazole and brexpiprazole, cariprazine also partially blocks and partially stimulates dopamine receptors. Unlike them, cariprazine is more potent at dopamine D3 receptors, which are linked to mood, motivation, and drug reward, than at D2 receptors, which are linked to motor control. It is not yet clear how these differences may change treatment outcomes or side effects.

New Drug Cariprazine Approved for Schizophrenia and Bipolar Disorder

In late 2015, the Food and Drug Administration approved the new atypical antipsychotic drug cariprazine for the treatment of schizophrenia and mania in adults. The approval followed a series of clinical trials that showed that the drug reduced symptoms of each illness compared to placebo.

The most common side effects of cariprazine reported in the trials included tremor, slurred speech, and involuntary muscle movements.

Cariprazine is a partial agonist of dopamine. See more above and at right about this class of drugs.

Dopamine Partial Agonists: An Overview

Several atypical antipsychotic drugs are partial agonists of dopamine. They provide weak stimulation of dopamine receptors in the brain and prevent dopamine from overstimulating the receptors by binding to them in its place.

In contrast, most antipsychotic and antimanic drugs are dopamine antagonists, which also bind to dopamine receptors but prevent any stimulation from occurring there.

A. **Aripiprazole** (Abilify) was the first partial dopamine agonist approved by the Food and Drug Administration for the treatment of schizophrenia, and mania, and as an add-on treatment to antidepressants for the treatment of unipolar depression, but not bipolar depression.

B. **Brexpiprazole** (Rexulti) received FDA approval for the treatment of schizophrenia and as an add-on treatment to antidepressants for the treatment of unipolar depression in 2015. It is similar to aripiprazole but has weaker activity at the dopamine D2 receptor. Brexpiprazole is associated with small increases in the hormone prolactin, as opposed to the small decreases in prolactin seen with aripiprazole.

C. **Cariprazine** (Vraylar) is FDA-approved for schizophrenia and mania, and it also has positive placebo-controlled data in bipolar depression and as an adjunct to antidepressants in unipolar depression. It differs from the others in that it is more potent at dopamine D3 receptors than at D2 receptors. It is thought that effects on D3 receptors may provide better antidepressant effects, but this proposition has not yet been tested.

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Additional Information about the Child Network:

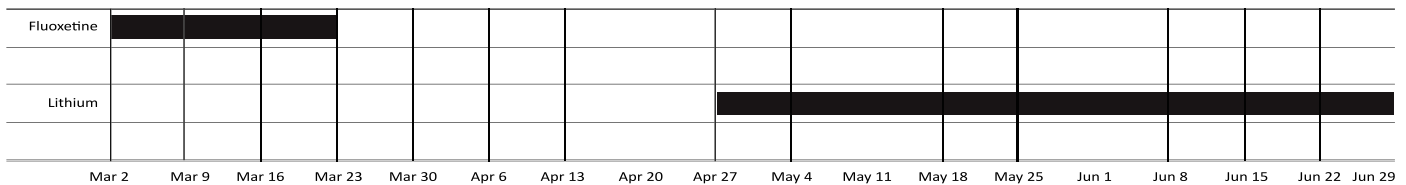
74% of children who have a parent with bipolar disorder (Axelson et al. 2015) and 80% of those who have a parent with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness upon long-term follow up. These illnesses, including depression, anxiety, oppositional behavior, substance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

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

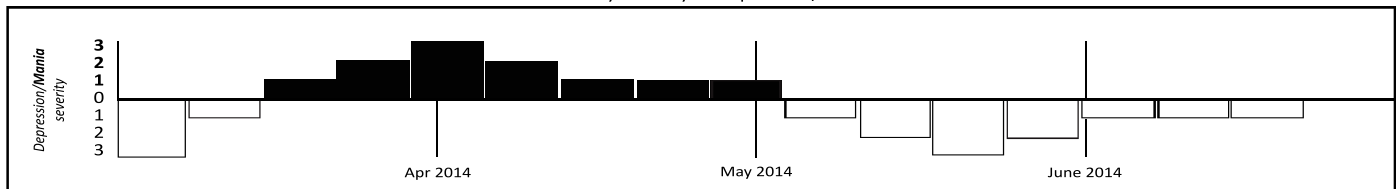
The Child Network is specifically for parents of children ages 2 to 12 who currently have any symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographics questionnaire and a more detailed symptom checklist to be filled out once a year. The 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).

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 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.

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 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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