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Bipolar Network News

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Updates from the 2019 Meeting of the American Academy of Child and Adolescent Psychiatry Vol. 24, Issue 1, 2020

New Research on the Treatment of Childhood Bipolar Disorder

Quetiapine Reduced Childhood Mania, Especially in Those with Thicker Frontal Temporal Regions

In a symposium at the 2019 meeting of the American Academy of Child and Adolescent Psychiatry, researcher Melissa P. Delbello reported that six weeks of treatment with either lithium or quetiapine was effective in childhood mania, but quetiapine had a higher response rate of 71% versus 46% for lithium. Delbello found two types of structural changes on fMRI. **Some children had thicker frontal temporal regions, while others had thinning in these areas. The first group of patients had a 100% response to quetiapine, but only 53% of the second group responded to quetiapine.**

Other researchers including Vivian Kafantaris have shown that patients who respond well to lithium show improvements in white matter abnormalities. Researcher Michael Berk and colleagues found that a year on lithium was superior to quetiapine on all measures including cognition and brain imaging in patients having their first episode of mania.

Potential Problems when Youth at Risk for Bipolar Disorder Receive SSRIs

At the same symposium, researcher Manpreet Singh reported that **in youth at high risk for bipolar disorder, 53% had an adverse event while taking a selective serotonin reuptake inhibitor antidepressant (SSRI), and 26% had a new onset of suicidality while taking an SSRI.** These adverse events were associated with reduced size and increased activation of the amygdala, the brain region responsible for emotion processing. Singh concluded that dysfunction in the prefrontal-limbic network may predict adverse events in children at risk for bipolar disorder when they are given SSRI antidepressants. She urged caution in the use of antidepressants in this population. Researcher Joseph Biederman echoed this caution later in the meeting.

Family Focused Therapy Effective in Youth at Risk for Bipolar Disorder Who Have Early Symptoms

Researcher David Miklowitz developed Family Focused Therapy (FFT), in which families of young people at risk for bipolar disorder take part in therapy, learning about the illness and practicing strategies for communication and coping. At the symposium, Miklowitz reported findings from recent studies of youth who were at high risk for bipolar disorder because of a family history of the illness and the presence of early symptoms such as depression or cyclothymia or bipolar not otherwise specified (BP-NOS). **Family focused therapy reduced symptoms. It also slowed onset of a first episode of mania and slowed the conversion to a diagnosis of bipolar I or bipolar II.** These results converge with a total of 10 other positive studies of family focused therapy in different populations in children and adults. FFT or its equivalent should be made available to all symptomatic children who are at risk for bipolar disorder because of a family history of the disorder.

Positive Effects of a Brief Session of Aerobic Exercise

Also at the symposium, researcher Benjamin I. Goldstein reported that a single 20-minute session of aerobic exercise (achieving 70% of maximal heart rate) was associated with improvement in cognition and in abnormalities seen on brain imaging. **Goldstein urged clinicians to do motivational interviews with sedentary children in their care, emphasizing the positive cardiovascular and cognitive effects of exercise.** He indicated this would be more effective than a focus only on weight loss, which is much more difficult to achieve.

Also In This Issue:

Improvement in Bipolar Depression on Open-Label Lurasidone

Researcher Katherine Burdick and colleagues of Brigham and Women's Faulkner Hospital and Harvard University reported in a poster at the 2019 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) that **youth between the ages of 10 and 17 with bipolar depression who continued taking lurasidone on a non-blind basis following a double-blind placebo-controlled six-week trial of the drug, or those who began taking lurasidone (for those who had been in the placebo group during the trial) saw improvement over a period of one to two years.** All of the patients began the extension portion of the study at a dose of 20 mg/day.

Lurasidone appeared to be effective and well-tolerated. In addition, Burdick and colleagues reported a lack of cognitive difficulties in the youth taking lurasidone. Interestingly, a measure of visual learning substantially and progressively improved over the course of the study.

Lurasidone Highly Effective in Open Continuation in Youth with Schizophrenia

Researcher Michael Tocco and colleagues reported at the 2019 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) that **in adolescents between the ages of 13 and 17 with schizophrenia, taking lurasidone for two years following a double-blind, placebo-controlled study led to steady improvement.** There was a remarkably high 91% response rate and a 66% remission rate. Out of all the participants, 51.3% were rated as recovered.

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 print newsletter is mailed free of charge within the US, and all articles are also published online at bipolarnews.org. A PDF version of the print newsletter is also available on the website.

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Prazosin Effective and Well-Tolerated for Post Traumatic Stress Disorder in Children

In a poster session at the 2019 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), three posters highlighted the efficacy and tolerability of prazosin, a drug typically used to treat high blood pressure, for the treatment of childhood-onset post-traumatic stress disorder (PTSD).

Researchers Samira Khan and Taniya Pradhan of West Virginia University reviewed cases in which 39 patients aged 8–19 received 1–5 mg of prazosin at bedtime. The mean dose was 1.72 mg. **Sleep (including nightmares) improved in 92.3% of the youths, and mood improved in 33.3%. Sleep improved more in patients who received lower doses (1–2 mg) than those who received higher doses.** About 70% of the patients whose data were included in the case series were also receiving psychotherapy while being treated with prazosin.

In another poster, researcher Vladimir Ferrafiat and colleagues from University Hospital of Rouen in France reported on a prospective study of 18 participants under age 15 with severe PTSD who were unresponsive to other medications. The participants were given 1 mg of prazosin at bedtime, which was increased to 3 mg in 20% of the participants. The youth were assessed weekly over a one-month period. Improvement was seen in all domains, including sleep, nightmares and daytime intrusive symptoms. Prazosin was well tolerated, with only one patient experiencing low blood pressure, which did not necessitate withdrawal from the study.

In the final poster, researcher Fatima Motiwala and colleagues reviewed the literature on the treatment of PTSD in children. Motiwala indicated that among the options, prazosin was widely used in her hospital, at doses starting at 1 mg given at bedtime and increasing to a mean of 4 mg at bedtime with excellent results and tolerability.

Editor's Note: Although these were not double-blind controlled studies, the findings are noteworthy in that they provide consistent data on the effectiveness and tolerability of prazosin in low doses in children with PTSD, essentially mirroring controlled data in adults, where higher doses are typically required.

Lithium Better than Other Mood Stabilizers for Youth with Bipolar Disorder

A new study by Danella M. Hafeman and colleagues finds that lithium is superior to other mood stabilizers in young people. The data in this case come from 340 youth aged 7–17 who participated in a study known as Course and Outcome of Bipolar Youth (COBY).

At each visit over an average of 10 years, participants reported medications taken, symptoms they had experienced, etc. during the preceding six-month period. During times that participants had taken lithium (compared to other mood stabilizers) they were older, on fewer antidepressants, and they were less likely to have an anxiety disorder.

Those participants who took lithium had half as many suicide attempts, fewer depressive symptoms, less psychosocial impairment, and less aggression than those who took other mood stabilizers.

The researchers concluded, "Findings are consistent with adult studies, showing that lithium 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: Lithium should especially be considered in those with a family history of mood disorders, and in particular in those with a family history of good response to lithium. Lithium is under-prescribed in both adults and children and should be given much higher consideration in light of the multiple benefits it provides in addition to mood stabilization. These include maintenance of memory, increases in longevity (perhaps based in its ability to increase the length of telomeres, the bits of protective material at the end of DNA strands that deteriorate with age and illness), and neuroprotection against loss of gray and white matter volume in the brain, which often occurs in mood disorders.

Study Finds Lithium Is Effective for Maintenance Treatment of Childhood-Onset Bipolar Disorder

Evidence has been accumulating that lithium is effective in the treatment of young people with bipolar disorder. In a study by Robert Findling and colleagues published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2018, participants aged 7–17 who responded well to lithium during a 24-week study were then randomized to receive either lithium continuation (17 participants) or placebo (14 participants) for 28 more weeks. **Those who continued lithium treatment were more likely to stay in the study.** Participants who discontinued the study mostly reported that they did so due to re-emergence of their mood symptoms (mostly in the placebo group). Lithium was well-tolerated and was not associated with any more weight gain than placebo. This study adds to the growing literature on the effectiveness and tolerability of lithium both acutely and in maintenance treatment in childhood bipolar disorder.

Editor's Note: Lithium deserves wider use in both childhood and adult bipolar disorder, both because of its effectiveness and its other assets including. Lithium can reverse gray and white matter deficits in the brain, it has anti-suicidal effects, it protects cognition, and it can increase the length of telomeres, bits of protective material at the end of DNA strands, which deteriorate with age and illness.

7-Year-Olds At Risk for Schizophrenia, But Not Bipolar Disorder, Show Specific Types of Cognitive Dysfunction

A large Danish study investigated whether children at risk for schizophrenia and bipolar disorder would show signs of cognitive problems. The study by researcher Nicoline Hemager and colleagues was published in the journal *JAMA Psychiatry* in 2018.

The researchers identified 7-year-olds,197 who had family members with schizophrenia, 118 who had family members with bipolar disorder, and 199 control 7-year-olds with no family history of these illnesses. Those children at risk for schizophrenia had significantly more cognitive deficits and behavioral disorders than the controls, while those children at risk for bipolar disorder did not differ significantly from the controls. **The deficits among the children at risk for schizophrenia were in the areas of processing speed and working memory, executive and visuospatial functions, and declarative memory and attention.**

The researchers indicated that the neurocognitive profile seen in the children at risk for schizophrenia could help clinicians identify these children for early intervention.

Predicting Onset of Bipolar Disorder in Children at High Risk

At the 2019 meeting of the American Academy of Child and Adolescent Psychiatry, one symposium was devoted to new research on predicting onset of bipolar disorder in children who have a family history of the disorder. Below are some of the findings that were reported.

Symptom Progression

In offspring of parents with bipolar disorder, researcher Anne Cecilia Duffy found that symptoms in the children tended to progress in a typical sequence. Childhood sleep and anxiety disorders were first to appear, then depressive symptoms, then bipolar disorder.

Different Types of Illness May Respond Best to Different Medications

Duffy's research also suggested links between illness features and a good response to specific medications. **Those offspring who developed a psychotic spectrum disorder responded best to atypical antipsychotic medication. Those with classical episodic bipolar I disorder responded well to lithium, especially if there was a family history of lithium responsiveness. Those offspring with bipolar II (and anxiety and substance abuse) responded well to anticonvulsant medications.**

If parents with bipolar disorder had experienced early onset of their illness, their children were more likely to receive a diagnosis of bipolar disorder.

The offspring of lithium-responsive parents tended to be gifted students, while those from lithium non-responders tended to be poorer students.

Comparing Risk Factors for Bipolar Disorder and Unipolar Depression

Researcher Martin Preisig and colleagues also showed that parental early onset of bipolar disorder (before age 21) was a risk factor for the offspring receiving a diagnosis of bipolar disorder. Parental oppositional defiant disorder (ODD) was also a risk factor for bipolar disorder in the offspring. The emergence of depression, conduct disorder, drug use, and sub-syndromal hypomanic symptoms also predicted the onset of mania during childhood.

Conversely, sexual abuse and witnessing violence were strong risk factors associated with a diagnosis of major (unipolar) depressive disorder. Being female and experiencing separation anxiety were also factors that predicted unipolar depression.

Predicting Conversion to Mania

Researcher Danella M. Hafeman reported that mood swings (referred to in the literature as "affective lability"), depression/anxiety, and having a parent who had an early onset of bipolar disorder were linked to later diagnoses of mania. Immediate risk factors that predicted an imminent onset of mania included affective lability, substance abuse, and the presence of sub-threshold manic symptoms.

Early Recognition and Treatment Needed

Researcher Boris Birmaher, the discussant of the symposium, described a sample of 100 children between the ages of 2 and 5; half had a parent with bipolar disorder, and these were compared to community controls. Those children who had a parent with bipolar disorder had a high incidence of attention-deficit hyperactivity disorder (ADHD) and ODD, and their conversion to a diagnosis of bipolar disorder was predicted by early age of onset of bipolar disorder in the parent (again) and by the presence of family conflict.

Birmaher emphasized that a delay before children and adolescents with bipolar disorder received their first treatment for the illness had terrible effects—more suicide attempts, completed suicides, substance abuse, and school failure. Birmaher urged early recognition of bipolar disorder and adequate treatment in order to delay onset of the disorder and to render its course more benign.

Childhood-Onset Bipolar Disorder Incidence

Researcher Anna Van Meter and colleagues showed that the incidence of bipolar disorder in children is about 2% worldwide. Researcher Kathleen Merikangas and colleagues report that 80% of adolescents with a bipolar spectrum disorder are not receiving any kind of treatment. Researcher Ben Goldstein indicated that about 50% of those with a full diagnosis of bipolar disorder receive treatment in Canada (where such treatment is cost-free).

Delayed Treatment Leads to Compounding Challenges

Since longer intervals without treatment predict poorer outcomes in bipolar disorder and schizophrenia, and early onset bipolar disorder has been linked to longer delays before first treatment, a significant number of children, particularly in the US, are at risk for disastrous outcomes. Earlier recognition and treatment is imperative, especially since even bipolar disorder not otherwise specified (BP-NOS) can be severe,

Treating Symptoms of Bipolar Disorder in Children at Risk

impairing, associated with multiple simultaneous comorbid diagnoses, and has a familial (genetic) basis.

Sub-Threshold Bipolar Disorder or BP-NOS is Impairing and Requires Treatment

In Hafeman's research, **children with BP-NOS were almost as ill as those with bipolar I disorder (BP I) and experienced equal incidence of suicide attempts, substance abuse, other simultaneous psychiatric diagnoses, and functional impairment, clearly indicating that they were in need of treatment.** About 50–65% of participants with a family history of bipolar disorder converted from diagnoses of BP-NOS to BP I, while those with BP-NOS and no family history of bipolar disorder converted to BP I at rates of about 30–48%.

Several presenters presented data showing that those with sub-threshold bipolar disorder had severe functional impairment, a high incidence of suicide attempts, and additional diagnoses including ADHD, conduct disorder, anxiety, and substance abuse.

Diagnostic Tool Can Help Identify Children with Bipolar Disorder

Researcher Amy Yule indicated that a tool called the Child Behavior Checklist (CBCL) is effective for making the diagnosis of conduct disorder in children with bipolar disorder, while researcher Joseph Biederman showed that the CBCL can also identify children with bipolar I disorder and is faster and simpler to use in clinical practice than are full structured diagnostic interviews.

Researcher Janet Wozniak found that there was a high incidence of bipolar disorder in first-degree relatives of children with sub-threshold bipolar disorder, suggesting the validity of identifying youth with sub-threshold bipolar symptoms.

As discussed above, there is also a high incidence of children with BP-NOS progressing to a full diagnosis of bipolar I or II disorder (as many as 50% of those with a family history of bipolar disorder). However, the point is not to wait for the negative effects of a full diagnosis before beginning treatment: BP-NOS itself requires treatment.

Discussion and Emerging Consensus on Treatment, Particularly of BP-NOS

Experts in the field agree that **family focused therapy (FFT) or its equivalent is a crucial first step to treatment of depression, cyclothymia (cycling between depressive and hypomanic symptoms that do not meet the threshold for a diagnosis of bipolar disorder), and BP-NOS in children who are at high risk of bipolar disorder because they have a parent with the disorder.**

A second area of agreement is that young people with BP-NOS should have a positive therapeutic coach (which could be a treating physician if no other person is available), who can emphasize important early steps that can improve short- and long-term health. These include maintaining a healthy diet, exercise (such as participation in school sports), the practice of mindfulness and/or meditation, and playing and practicing a musical instrument. Parental support is also critical to decreasing negative expressed emotion.

Early interventions and wellness programs that focus on these factors are part of the successful Vermont Family Based Approach, led by psychiatrist Jim Hudziak, Director of the Vermont Center for Children, Youth, and Families. Since programs like these are not widely available, treating physicians must create their own teams to provide such encouragement, and teach families how to find or establish such a support network.

School teachers should be engaged in support of the treatment of a child with bipolar disorder. Teachers should pay special attention to behavioral symptoms of an ill child. It also may be important for physicians to connect directly with teachers to ensure that children recovering from an episode of bipolar disorder receive extra time for assignments, a decreased academic burden, and other support. Researcher Manon H. Hillegers indicated that intervention by a physician will likely be listened to and believed, while parental requests alone to teachers or to the school may go ignored.

Hillegers, like researcher Lakshmi Yatham and colleagues, have found that it takes a year after a first manic episode for a child's cognition to return to normal, so that special allowances should be made for such students even many months after they have recovered from their mania.

What is BP-NOS?

Bipolar disorder not otherwise specified (BP-NOS) has been used to describe symptoms that do not meet the criteria for a full diagnosis of bipolar I or II disorders. For example, episodes of depression or mania may be shorter or milder than needed for a full diagnosis. Subthreshold symptoms might consist of hypomanic episodes that last two to three days, or fewer than four symptoms of hypomania over four days.

Dr. Post's Recommendations For Treating Youth with Bipolar Symptoms

Our Editor-in-Chief, Dr. Robert M. Post, shares his personal recommendations for the treatment of children and adolescents with symptoms of bipolar disorder. ***Remember: Patients and family members must consult a physician about all information conveyed in the*** **BNN*****. With the exception of lithium, none of the medications or supplements discussed above have been approved by the US Food and Drug Administration for use in children under 10. The findings reported here are in many cases preliminary and cannot be taken as recommendations based on the short summaries provided here. All treatment decisions must be made in conjunction with a patient's treating physician, who is solely responsible for initiating any treatment discussed in the BNN or elsewhere.***

In symptomatic and functionally impaired children, medication is almost always necessary. Many treating psychiatrists would start with an **atypical antipsychotic**, since there is clear evidence of the efficacy of such treatments. The side effects profile should be considered, as there is a considerable difference in the degree of weight gain associated with different atypical antipsychotics. The largest weight gains occur with olanzapine and clozapine, intermediate gains occur with aripiprazole and quetiapine, and the least gains occur with ziprasidone and lurasidone (and the latter has the advantage of being approved by the US Food and Drug Administration for the treatment of bipolar depression in children who are 10–17 years old). The addition of the diabetes drug metformin to decrease weight gain in people taking atypical antipsychotics is increasingly common.

The addition of an **anticonvulsant** medication (such as lamotrigine, carbamazepine/oxcarbazepine, or valproate) or the mood stabilizer lithium may be needed, as multiple studies indicate that combination treatment is typically needed in children (as in adults) to achieve a more complete response or remission.

Interestingly, oxcarbazepine was effective in younger but not older children with mania in a previous placebo-controlled study by Karen D. Wagner and colleagues published in the *American Journal of Psychiatry* in 2006.

Conversely, in a 2015 article in the journal *JAACAP*, researcher Robert Findling reported that in a placebo-controlled study of lamotrigine, 13–17-year-olds responded better than 10–12-year-olds.

Lithium treatment deserves consideration in children with classical presentations of bipolar disorder and those who have family members who have responded well to lithium treatment. Lithium has the benefit of improving the white matter abnormalities seen in the brains of patients with early-onset bipolar disorder. Hafeman and colleagues reported in a 2019 article that children with bipolar disorder who were treated with lithium had better long-term results upon follow up than those treated with atypical antipsychotics or anticonvulsants.

There is much less scientific consensus about other adjunctive treatments for young people with additional bipolar symptoms and comorbidities, but this editor often uses several. **Vitamin D3** is often low in children with psychiatric illness, and may improve mood and cognition.

The antioxidant **N-acetylcysteine (NAC)** helps depression, anxiety, and irritability, and is effective at treating habit-related behaviors such as trichotillomania (compulsive hair-pulling), obsessive-compulsive disorder (OCD), and drug use, including specifically reducing marijuana use in adolescents. A typical dose is 500–600 mg capsules, one capsule twice a day for one week, then two capsules in the morning and two in the evening thereafter.

Folate or folic acid may enhance antidepressant effects and those of lithium. In patients who have a particular low-functioning variant of a gene known as MTHFR, **L-methylfolate** is required instead of folate.

The widely-used supplement **acetyl-L-carnitine (ALC)** is poorly studied in children, but deserves consideration as a supplemental treatment for patients with histories of childhood adversity. In adults with depression, blood levels of ALC may be low, particularly in those with an early onset of bipolar symptoms and a history of childhood adversity (see a 2018 article by Carla Nasca in the journal *PNAS*). There is a modicum of evidence that ALC produces antidepressant effects in adults. ALC may also sensitize insulin receptors and normalize blood pressure.

There is increasing evidence of the role of inflammation in depression, mania, post-traumatic stress disorder (PTSD), and schizophrenia. Checking for abnormalities in inflammatory markers in the blood (especially Il-6 and CRP) may point the way to appropriate therapy with **anti-inflammatory drugs** such as minocycline (100 mg twice a day) or celecoxib (200 mg twice a day) in patients who do not respond fully to first-line medications.

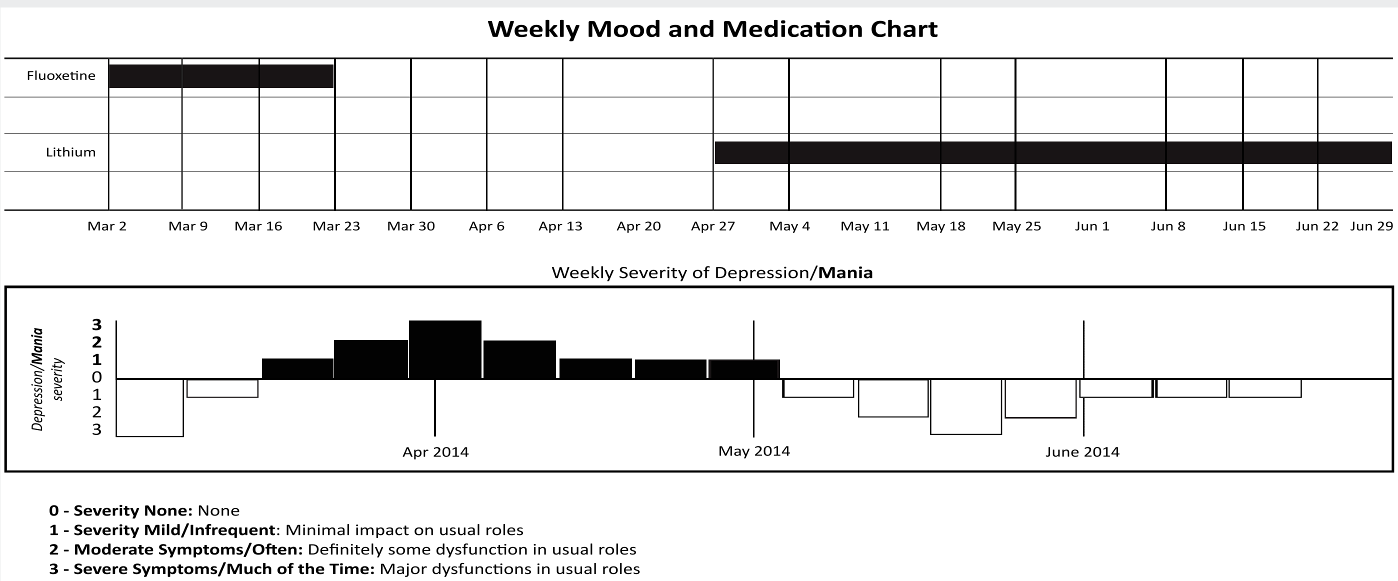
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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 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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