

Bipolar Network News

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In Phase 3 Clinical Trials, Antipsychotic Treatment Lumateperone Is Found Effective in Bipolar Depression

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Lumateperone is an antipsychotic medication that is currently approved by the US Food and Drug Administration for the treatment of schizophrenia (under the trade name Caplyta). New studies suggest that the drug is also effective in bipolar I and bipolar II depression.

Lumateperone modulates the activity of the neurotransmitters dopamine, serotonin, and glutamate. It modulates D1 and D2 dopamine receptors, partially activating presynaptic receptors while partially blocking postsynaptic receptors. Lumateperone acts as an antagonist blocking serotonin 5-HT_{2A} receptors, and it augments activity at both NMDA and AMPA glutamate receptors.

Because of lumateperone's complex pharmacology, it is not clear which of these activities are primarily responsible for its antidepressant and antipsychotic activities.

New research presented at the 2020 meeting of the International Society for Bipolar Disorders showed that lumateperone reduces bipolar depression.

Researcher Susan Kozauer presented research from a six-week study of 377 patients who were randomized to receive treatment with either 42mg of lumateperone (n=188), taken once daily in the evening, or placebo (n=189). The patients had been diagnosed with bipolar I or II disorder and were experiencing an episode of major depression.

Patients taking lumateperone saw significantly greater improvement in depression than those in the placebo group. Among those taking lumateperone, 60% of those who were markedly ill or worse at baseline

improved to mildly ill or better, compared to 43% of those taking placebo.

Researcher Suresh Durgam described improvements in specific symptoms that make up the Montgomery-Åsberg Depression Rating Scale (MADRS) in those patients who received lumateperone. The greatest improvements compared to placebo were in sadness, inner tension, and reduced sleep. By the 29th day of the study, 8 of 10 items on the scale had improved significantly compared to placebo, and all items had improved by day 43.

The side-effects profile of lumateperone was presented by researcher Lakshmi Yatham.

Among those taking lumateperone, 8.5% experienced sleepiness compared to 1.1% of those in the placebo group, while 6.4% of the lumateperone group experienced nausea compared to 2.1% of the placebo group. Most effects were

mild or moderate in severity. Changes in weight, metabolic measures, extrapyramidal motor effects, and prolactin were minimal in both the lumateperone group and the placebo group.

Editor's Note: Lumateperone (Caplyta) joins a list of other atypicals that are efficacious in bipolar depression. These include olanzapine-fluoxetine (Symbyax), quetiapine (Seroquel), lurasidone (Latuda), and cariprazine (Vraylar). Lumateperone is currently only FDA-approved for schizophrenia, but approval for bipolar depression should be rapidly forthcoming based on the data presented at the ISBD meeting.

Bipolar depression used to be an orphan diagnosis, with few efficacious treatments. This is now beginning to change, and treating patients with bipolar disorder using antidepressants designed to treat unipolar depression (for which there is little evidence of efficacy) should begin to recede.

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Cognitive Abnormalities in Patients Newly Diagnosed with Bipolar Disorder

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Kamilla Miskowiak described a study in which she and her colleagues grouped 158 patients in remission from recently diagnosed bipolar disorder into groups based on their neurocognitive functioning and particularly their emotional processing, and also observed cognitive function in 52 first-degree relatives of those with bipolar disorder. These groups were compared to 110 healthy control participants.

Miskowiak and colleagues identified three clusters among the patients with bipolar disorder: 23% were globally impaired, 31% were selectively impaired, and 46% had normal cognition. Those who were globally impaired had problems recognizing facial expressions in social scenarios. Cognitive impairment has previously been documented in patients who have had a longer duration or more episodes of bipolar illness.

First-degree relatives of cognitively impaired patients had impaired recognition of facial expressions, but their cognition in non-emotional areas was normal. Miskowiak and colleagues concluded that the

impaired affective cognition in relatives of patients with neurocognitive impairment was an indication of inherited risk for bipolar disorder.

Editor's Note: Children with bipolar disorder also have this deficit in facial emotion recognition. That 23% of recently diagnosed patients with bipolar disorder were globally impaired indicates that some cognitive impairments can emerge early in the course of bipolar disorder. Researcher Lakshmi Yatham has previously found that cognition improves after a first episode of mania only if no further episodes occur in the one year following, indicating that episode prevention is crucial even after a patient's first episode.

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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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White Matter Disturbances in Bipolar Disorder

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Clare Beasley described the cellular and molecular underpinnings of the white matter abnormalities typically seen in children and adults with bipolar disorder. Researchers consistently see white matter abnormalities in neuroimaging studies of bipolar disorder, but not much is understood about what creates these deficits.

Beasley and colleagues studied autopsy specimens and found that **compared to controls, people with bipolar disorder had a number of abnormalities affecting glial cells, lipid composition, and axons.**

The researchers found increased density of oligodendrocytes (glial cells that produce the myelin that wraps around axons, the long fibers of nerve cells where impulses travel out to other cells) and an associated protein

called CNP in the prefrontal cortex. The myelin is what makes up white matter, while grey matter consists of cell bodies of neurons and glial cells.

People with bipolar disorder also had differently-shaped astrocytes, another type of glial cell that abuts synapses. The researchers found changes in lipid composition, including phospholipid and fatty acid levels, in the white matter of people with bipolar disorder. There were also problems with axons. Beasley and colleagues noted lower density of axon-associated proteins, which are involved in transport of substances along the axons in people with bipolar disorder.

The authors conclude that these data implicate specific disturbances in oligodendrocytes and axonal function associated with the white matter alterations usually seen in neuroimaging of people with bipolar disorder.

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Danish Population-Based Study Identifies New Drug Candidates for the Treatment of Bipolar Disorder

At the 2020 meeting of the International Society for Bipolar Disorders, Lars Kessing of the Psychiatric Center Copenhagen described a study that examined incidence of bipolar disorder among a total of 1,605,365 participants who purchased one of six common medications over a ten-year-period. **The goal of the study was to identify drugs that might be repurposed to prevent or treat bipolar illness.** The drugs that were investigated were non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen), low-dose aspirin, high-dose aspirin, statins, allopurinol, and angiotensin.

Because Denmark has population-based healthcare data, the researchers

were able to identify participants who purchased these medications between 2005 and 2015, and could also assess these participants for two outcome measures: 1) whether they had received a diagnosis of mania or bipolar disorder as an inpatient or outpatient at a psychiatric hospital, and 2) a combined measure of whether they had received a diagnosis for mania or bipolar disorder in any setting or initiated lithium use. The data on these participants were compared to a random sample of 30% of the population of Denmark.

Kessing and colleagues found that **among those with steady use of low-dose aspirin, statins (used to lower blood cholesterol), and angiotensin agents (which can lower blood**

pressure), there was a significant decreased incidence of mania/bipolar disorder on both outcome measures.

In contrast, among those taking non-aspirin NSAIDs and high-dose aspirin, there was an increased incidence of bipolar disorder. (There were no statistically significant findings with regard to allopurinol, which is used to treat gout and kidney stones.)

The researchers concluded that population-based studies such as these can be used to identify drugs that may have secondary benefits, in this case low-dose aspirin, statins, and angiotensin agents, which have already been identified as potentially therapeutic in other research.

Childbirth and Bipolar Disorder

In an abstract for virtual presentation at the 2020 meeting of the International Society for Bipolar Disorders, researcher Ian Jones presented evidence that childbirth may trigger onset of bipolar disorder.

Jones found that 15% of women who experience postpartum mood disorders shortly after childbirth will go on to develop bipolar disorder over time. **A previous diagnosis of bipolar affective disorder is the biggest predictor that a woman will be readmitted for postpartum mental illness.**

In addition, one of the biggest risk factors for postpartum mental disorders is a family history of bipolar disorder in first-degree relatives. The risk of postpartum mental disorders also increases when first-degree relatives have a psychiatric illness of any kind.

Editor's Note: These data are consistent with research on sensitization/kindling, the idea that while early mood episodes may be triggered by psychosocial stress and other endocrine factors, later episodes may emerge more spontaneously. In this case, the stress associated with childbirth can lead to a subsequent bipolar diagnosis (with or without a precipitating stressor) in the future.

The psychosocial stress of childbirth and subsequent sleep deprivation can be severe, and those with a history of a mood disorder should seek additional support during such a time.

Bipolar Disorder in Pregnancy and the Postpartum Period

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Veerle Bergink reported several findings from a recent meta-analysis of articles on pregnancy and bipolar disorder. Bergink and colleagues found that **pregnant women with bipolar disorder have a 37% risk of a postpartum relapse, more than twice the risk of postpartum mental disorders in the general population.**

Using lithium as a treatment in the first trimester of pregnancy increased risk of congenital malformations in the fetus, but the risk was much smaller than previously thought and could be monitored by ultrasound.

Bergink and colleagues also reported that in a sample of 645 women with first-onset postpartum psychosis who received followup over a period of 7 to 25 years, 43% had no subsequent severe episodes outside of the postpartum period.

Another finding was that women with postpartum severe depression or mania had abnormalities in T cells, which are important in immune response.

It's now faster and easier to join the Child Network! See page 7.

Lurasidone Effective Long-Term in Pediatric Bipolar Depression

At the 2020 meeting of the American Society of Clinical Psychopharmacology, researcher Manpreet Singh presented data showing that children aged 10–17 with bipolar depression had an excellent long-term response to the antipsychotic medication lurasidone (trade name Latuda).

Lurasidone has been approved by the US Food and Drug Administration as a monotherapy treatment of bipolar depression in children and adolescents since 2018. Following a six-week double-blind study comparing lurasidone with placebo in 305 children and adolescents, Singh and colleagues carried out an open-label extension study in which all of the young participants, including those in the placebo group, had the option of taking lurasidone for up to two more years.

Of those, 195 children completed one year of treatment, and 93 completed two years of treatment. **Rates of response were 51.0% after the six-week preliminary study; 88.4% at one year; and 91.1% at two years.** Rates of remission were 24.3% after

the six-week study; 61.3% at one year, and 75.6% at two years, while rates of recovery were 17.7% after the preliminary study; 53.8% at one year; and 73.8% at two years.

This improvement in depression had a strong correlation with improvement in functioning, as measured by the Children's Global Assessment score (CGAS). The results show progressive increases in rates of response, remission, and recovery with duration of treatment that are associated with improvement in functioning.

Early Precursors of Mood Disorders in Young Children of Parents with Bipolar or Unipolar Disorder

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Caroline Vandeleur presented findings from a 13-year study of children in Switzerland who have a parent with bipolar disorder or major depressive disorder. In contrast to the findings from the US presented by Danella Hafeman (see article at right), Vandeleur and colleagues found no evidence of psychopathology in 4 year-olds. They did find that in 7-year-olds, children of a parent with major depressive disorder were four times more likely to have a separation anxiety disorder.

In an overall sample of 449 children with a mean age of 10 who were followed up for 13 years, major depression tended to be preceded by anxiety disorders. **Participants who went on to be diagnosed with bipolar disorder had earlier symptoms of depression, subthreshold hypomania, conduct disorders, and drug abuse.** These were especially common in those who had a parent with bipolar disorder.

Editor's Note: These data indirectly confirm other observations in which children at high risk for mood disorders in the US showed earlier signs of psychopathology than those in other countries including the Netherlands and Canada.

Clinical Risk Prediction in Youth at Risk for Bipolar Spectrum Disorder

Researchers from two 15-year studies of bipolar youth, COBY (The Coarse and Outcome of Bipolar Youth Study) and BIOS (Bipolar Offspring Family Study), have used the longitudinal data from their studies in order to create a risk calculator that can predict an individual's likelihood of illness.

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Danella Hafeman presented research on a risk calculator that predicts the 5-year risk for onset of a bipolar disorder spectrum diagnosis (BPSD) in young people at high risk and can reasonably distinguish those who will receive a diagnosis from those who will not.

Some of the factors used in the risk calculator include dimensional measures of mania, depression, anxiety, and mood lability; psychosocial functioning; and the age at which parents were diagnosed with a mood disorder.

Hafeman reported that there was a 25% risk that offspring of a bipolar parent would develop a bipolar disorder spectrum diagnosis. In a population ranging in age from 6 to 18 years, Hafeman and colleagues found that anxiety and depression symptoms were a sign of vulnerability to a bipolar spectrum disorder, while subthreshold manic symptoms indicated that a bipolar spectrum disorder could soon emerge. Sudden or exaggerated changes in mood were also an important predictor of BPSD.

Hafeman and colleagues noted that even in children as young as 2 to 5 years old, there were already signs of anxiety, aggression, attention problems, depression, and sudden mood changes in those who would go on to receive a diagnosis of bipolar spectrum disorder.

The researchers were also able to predict which patients with BPSD would have a relapse. According to Hafeman and

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Characteristics of Youth with Bipolar Spectrum Disorders

In a 2020 article in the *Journal of Child and Adolescent Psychopharmacology*, researcher Gonzalo Salazar de Pablo and colleagues described characteristics of youth with three different bipolar spectrum disorders: bipolar I disorder, bipolar disorder not otherwise specified (NOS) and mood disorder (MD) not otherwise specified. The participants were hospitalized adolescents aged 12–18 years, who were highly impaired with hallucinations, delusions, incoherence, or inability to function.

Mania (especially irritability) and depressive symptoms were common in all three groups.

Many of the youths had comorbid conditions. Approximately 40% of each diagnosis group had an

anxiety disorder. Attention deficit hyperactivity disorder (ADHD) was seen in 29.2% of those with bipolar I disorder, 34.5% of those with bipolar NOS, and 43.5% of those with mood disorder NOS. Oppositional defiant disorder was seen in just over 20% of those with bipolar I or bipolar NOS, and just over 30% of those with mood disorder NOS. Substance use disorders were seen in 8.3% of those with bipolar I and about 21% of those with bipolar NOS or mood disorder NOS. Many of the participants had moderate to severe suicidality.

The median delay before the adolescents received treatment for their moderate to severe symptoms was 21 to 25 weeks. After discharge from the hospital, the adolescents with bipolar I, bipolar NOS, and mood disorder NOS were typically treated with atypical antipsychotics (79.2%, 62.1%, and 56.5%, respectively), mood stabilizers (66.7%, 31.0%, and 34.8%), and lithium (58.3%, 20.7%, 30.4%), with greater use of mood stabilizers and lithium than on admission and less use of antidepressants. Few children were on ADHD medications on admission, and even fewer (4–9%) on discharge.

The authors conclude: **“Youth with BD-I, BD-NOS, and MD-NOS experience considerable symptomatology and are functionally impaired, with few differences observed in psychiatric comorbidity and clinical severity. Moreover, youth with BD-NOS and MD-NOS undergo a [long] period with subthreshold manic symptoms, enabling identification and, possibly, preventive intervention of those at risk for developing [bipolar disorder] or other affective episodes requiring hospitalization.”**

Editor’s Note: These findings replicate many others in the field indicating that children with bipolar spectrum disorders, even those with symptoms short of a full-blown bipolar I diagnosis, are highly impaired

with multiple comorbidities and high levels of suicidality and other dangerous symptoms. These patients deserve systematic pharmacological intervention based on an extensive clinical treatment literature.

The only thing the authors failed to address is that not only does no such clinical treatment literature exist, but there does not seem to be any recognition by the National Institute of Mental Health and other funding bodies that a series of treatment-oriented studies in children and adolescents is urgently needed.

The 2010 epidemiological studies of Kathleen Merikangas and colleagues indicate that 2.2% of adolescents have a bipolar spectrum diagnosis and that 80% of those young people are not in any kind of treatment. This is in part driven by a lack of consensus about appropriate treatment. The magnitude and seriousness of this illness creating lifelong problems, disability, cognitive impairment, and the loss of more than a decade of life expectancy is a public health catastrophe.

In the 1980s, AIDS protesters had to raise awareness, protest, and clamor for treatment studies in a highly confrontational manner before AIDS research was appropriately funded. Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease since 1984, has said he was finally convinced that the AIDS protesters were correct, and he then joined forces with them to foster and accelerate treatment studies. The prognosis for AIDS changed from certain death in the 1980s to a manageable illness today.

We need leaders to demand attention to the lack of studies in bipolar disorder at a threshold that cannot be ignored by leaders of the NIMH. Patient advocacy groups must push the NIMH to fund treatment studies for bipolar disorder. It is clear that without some new form of pressure, the NIMH will fail in its stated mission to help make the lives of those with serious mental illness less grave. The current generation and many in the future generations of patients with bipolar disorder will otherwise face disaster.

Clinical Risk Prediction in Youth

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colleagues, “The most influential recurrence risk factors were shorter recovery lengths, younger age at assessment, earlier mood onset, and more severe prior depression.”

Editor’s Note: Offspring of a parent with bipolar disorder are at high risk for anxiety, depression, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and bipolar disorder. Parents should be alert for the symptoms of these illnesses and seek evaluation and treatment for their children as necessary. Parents should also be aware of the risk factors above that contributed to the risk calculator.

Parents can aid physicians in their evaluation by joining our Child Network and keeping weekly ratings of their children’s symptoms of depression, anxiety, ADHD, oppositional behavior, and mania. Access this resource at our website bipolarnews.org (click on the tab for Child Network).

Increased Dementia Risk in Bipolar Disorder

At the 2020 meeting of the International Society for Bipolar Disorders, researcher Flavio Kapczinski described a recent meta-analysis of 10 studies that found that bipolar disorder is a risk factor for dementia, and that lithium treatment can decrease the incidence of dementia in people with bipolar disorder.

The ten studies included a total of 6,859 participants with bipolar disorder and 487,966 healthy control participants. **People with bipolar disorder were 2.96 times more likely to develop dementia than those without bipolar disorder.** Five of the studies included information about treatment with lithium, which was found to decrease the risk of dementia among those with bipolar disorder by a little more than half (0.54).

Five studies also revealed that the risk of progression to dementia was higher among those with bipolar disorder than among those with major depressive disorder. In addition, one of the ten studies explored predictors of dementia in people with bipolar disorder and found that those who experienced more mood episodes had a higher risk of dementia.

Editor's Note: It appears that the number of mood episodes a person experiences predicts dementia, and it has previously been found to predict the emergence of cognitive impairment. Prevention is the name of the game, and lithium is the best defense. My new mantra: "Prevent Episodes, Protect the Brain, Use More Lithium."

No Association of Benzodiazepines, Z Drugs and Other Anxiolytics with Dementia

Benzodiazepines, so-called Z-drugs (such as zolpidem, zopiclone, and zaleplon), and other anxiolytics are commonly prescribed drugs that have some cognitive side effects. For this reason, **there has been concern that the drugs may increase risk of dementia, and small studies had suggested that this might be the case. However, a new large study found no subsequent dementia risk after taking these drugs.**

In a 2020 article in the *American Journal of Psychiatry*, researchers Merete Osler and Martin Balslev Jørgensen described a cohort and nested case-control study of 235,465 adult patients in Denmark in which they found no association of benzodiazepines, Z-drugs, or other anxiolytics with a subsequent diagnosis of dementia. Participants were patients over the age of 20 who were hospitalized for an affective disorder. Of these, 75.9% had been prescribed one of the drugs in question, and 4.2% went on to be diagnosed with dementia.

While participants in this study who had the lowest use of benzodiazepines or Z drugs showed a minimal increased risk of dementia compared to those who took none of these drugs, those who had the highest use of benzodiazepines and Z drugs actually had the lowest incidence of dementia in the study.

The previous studies may have been "confounded by indication" meaning they did not take the underlying psychiatric condition for which the drugs were prescribed into account.

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Online Consultations with Robert M. Post, MD During the COVID-19 Pandemic

BNN Editor Dr. Robert M. Post worked at the National Institute of Mental Health for 35 years, and has been in private practice for the past 15 years. He offers extensive one-time consultations for children and adults with difficult-to-treat mood disorders from his office in Bethesda, Maryland.

During the current pandemic Dr. Post is offering virtual meetings via Skype, FaceTime, or phone. If you are interested, please call his research assistant, Katrin Kutlucinar at 301-530-8245 to set up an appointment. See robertmpostmd.com for further details.

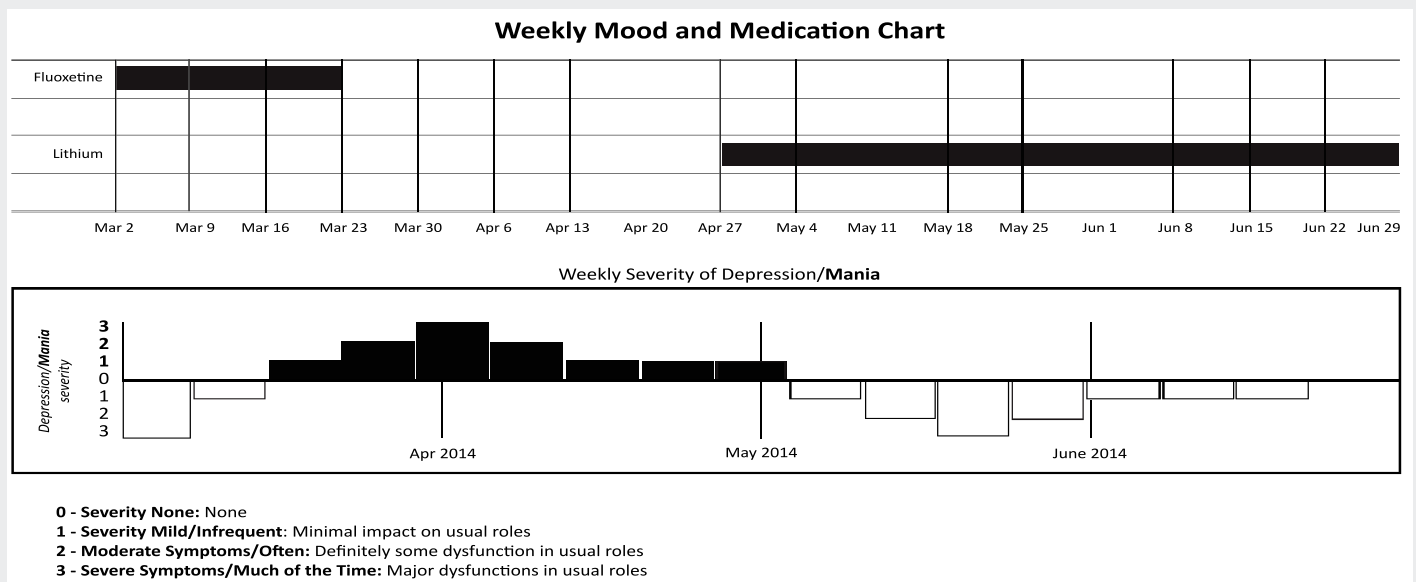
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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

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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