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Bipolar Network News

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Updates from the 2019 Meeting of the International Society for Bipolar Disorders

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Lithium Now FDA-Approved for Bipolar Disorder in Children 7–17

In April 2019, the US Food and Drug Administration approved lithium for both the acute treatment of mania and for ongoing maintenance treatment of bipolar disorder in children and adolescents aged 7 to 17. Combined analysis of several studies indicates that **lithium is effective and well-tolerated in both children and adolescents with bipolar disorder, both for acute treatment and to prevent bipolar episodes**.

Lithium Reverses Some White Matter Abnormalities in Young People with Bipolar Disorder

Multiple groups of researchers have reported the presence of white matter tract abnormalities in patients with bipolar disorder. Some of these abnormalities correlate with the degree of cognitive dysfunction in these patients. These white matter tract abnormalities, which are measured with diffusion tensor imaging (DTI), are widespread and can appear as early as childhood in people with bipolar disorder. Researcher Vivian Kafantaris mentioned at the 2019 meeting of the International Society for Bipolar Disorders that lithium treatment in children and adolescents normalizes these alterations, as described in an article she and her colleagues published in the journal *Bipolar Disorders* in 2017.

Editor's Note: This is another reason to consider the use of lithium in children with bipolar disorder. Lithium treatment may help normalize some of the earliest signs of neuropathology in the illness.

In This Issue:

Finding Optimum Lithium Levels

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Willem Nolen discussed optimal lithium levels to prevent episodes of bipolar disorder. Based on the limited number of controlled trials that have examined this issue and a survey of experts in the field, Nolen concluded that **the standard dosing target to prevent bipolar episodes would be a blood concentration of 0.6 to 0.8 mEq/liter.** This concentration could be dropped to 0.4 to 0.6 mEq/liter for patients who responded well to a higher dosage but needed to reduce side effects, and the concentration could be increased to 0.8 to 1.0 mEq/liter for patients who tolerated lithium treatment but showed an inadequate response.

There was no consensus as to optimal blood concentrations of lithium to prevent bipolar episodes in children and adolescents, but some researchers endorsed the same standard recommended for adults. For elderly patients, the majority of researchers recommended a slightly lower concentration of 0.4 to 0.6 mEq/liter, with the option to increase to a maximum of 0.8 mEq/liter in those under age 80 and 0.7 mEq/liter in those over age 80.

Small Percentage of Patients Do Not Re-Respond After Stopping Lithium

Researcher Ralph Kupka reviewed the literature on the small subgroup of patients who do well on long-term lithium treatment, stop taking the drug, suffer a relapse, and then fail to re-respond as well as they had (or, in some cases, at all) once they begin taking lithium again. These observations are supported by small case series, and appear to occur in approximately 10 to 15% of patients who stop taking lithium. **Slowly tapering off lithium treatment did not seem to influence whether or not patients would re-respond to lithium later, while there was some indication that more time off lithium could lower the likelihood of a good re-response.**

Earlier data from researcher Trisha Suppes suggested that slowly tapering off lithium treatment (over about two weeks) is superior to tapering rapidly (over a few days), and a slow taper reduced the rate of relapse. Kupka added that he would taper lithium even more slowly (over a period of one to two months) so that early signs of relapse could more readily be observed.

Lithium Reverses Thinning of the Cortex That Occurs in Bipolar Disorder

In a 2018 article in the journal *Molecular Psychiatry*, researcher Derrek P. Hibar reported findings from the largest study to date of cortical gray matter thickness. Researchers in the ENIGMA Bipolar Disorder Working Group, which comprises 28 international research groups, contributed brain magnetic resonance imaging (MRI) from 1837 adults with bipolar disorder and 2582 healthy control participants.

Hibar and colleagues in the working group found that in adults with bipolar disorder, cortical gray matter was thinner in the frontal, temporal, and parietal regions of both brain hemispheres. They also found that bipolar disorder had the strongest effect on three regions in the left hemisphere: the pars opercularis, the fusiform gyrus, and the rostral middle frontal cortex.

Those who had had bipolar disorder longer (after accounting for age at the time of the MRI) had less cortical thickness in the frontal, medial parietal, and occipital regions.

A history of psychosis was associated with reduced surface area.

The researchers reported the effects of various drug treatment types on cortical thickness and surface area. **In adults and adolescents, lithium was associated with improvements in cortical thickness, and the researchers hypothesized that lithium's protective effect on gray matter was responsible for this finding.** Antipsychotics were associated with decreased cortical thickness.

In people taking anticonvulsant treatments, the thinnest parts of the cortex were the areas responsibly for visual processing. Visual deficits are sometimes reported in people taking anticonvulsive treatments.

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Early Predictors of Suicide, and Lithium for Prevention

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Gin S. Malhi discussed early predictors of suicide in people with bipolar disorder, such as younger age of illness onset, early life stressors, and family history of suicide. **Impulsivity, hopelessness, cognitive deficits and substance use are risk factors, both for suicide in general and for an imminent suicide attempt.** Proximal risk factors that indicate someone may make a suicide attempt soon include: mood swings, rapid cycling, increased depression, hospitalization, and severe anxiety.

Editor's Note: Among all psychotropic drugs, lithium has the best data supporting its anti-suicide effects, both at therapeutic doses in patients with bipolar disorder and at trace levels in the water supply in the general population. People who live in locations where more lithium is naturally present in the water supply have lower rates of suicide than those who live in places with less lithium in the water. Malhi also noted that the antioxidant N-acetylcysteine (NAC), which has positive effects on mood and habitual behaviors, can reduce the incidence of lithium-induced dysfunction of the kidneys.

Infliximab Helps the Subgroup of Bipolar Depressed Patients Who Faced Adversity in Childhood

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Mike Cosgrove and colleagues described a study of infliximab in adults with bipolar disorder and found persistent significant improvements on the drug only in those with a history of childhood adversity. **Childhood adversity is consistently associated with elevated levels of inflammatory cytokines, and baseline inflammation may be a prerequisite for a positive effect from infliximab, which works by blocking the inflammatory cytokine TNF alpha.**

In 2013, researcher Charles L. Raison and colleagues reported in the journal *JAMA Psychiatry* that infliximab, an antibody used to treat chronic inflammatory conditions that works by targeting the inflammatory marker TNF alpha, had antidepressant effects only among individuals with elevated levels of the inflammatory marker C-reactive protein (CRP). Those with low CRP at baseline actually worsened on infliximab.

Links Between Mixed Depression, Insulin Resistance, Inflammation, and Cognition

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Roger McIntyre discussed links between obesity, diabetes, and cardiovascular problems; increased inflammation; and decreased functioning of the neural networks involved in cognition.

McIntyre and colleagues analyzed 121 studies that included empirical research and meta-analyses. McIntyre and colleagues found that patients with higher levels of inflammatory markers have more insulin resistance and cognitive dysfunction. A meta-analysis revealed that the inflammatory markers IL-6, TNF alpha, and CRP were significantly elevated in people with bipolar disorder compared to normal controls, while IL-1B was not.

People with depression who had a few manic traits (mixed depression) were particularly likely to have insulin resistance and elevated levels of pro-inflammatory markers.

People with mixed depression have increases in inflammation and increased incidence of cardiovascular disorder. People experiencing a first episode of mixed depression who are overweight show increased signs of brain aging.

In studies McIntyre and colleagues analyzed, **diabetes or pre-diabetes occurred in 50% of depressed patients, and these patients had the greatest amount of cognitive dysfunction.**

Treatment

McIntyre noted that taking the antipsychotic drug **lurasidone** for bipolar depression worked best in both adults and children who had elevated levels of CRP at baseline. The fast-acting antidepressant **ketamine** also works well in those who show baseline inflammation .

The anti-diabetes drug **liraglutide** (Victoza, Saxenda) improves mixed depression symptoms and cognition in obesity, diabetes, and mixed depression. Liraglutide belongs to a class of drugs called glucagon-like peptide-1 (GLP-1) receptor agonists or incretin mimetics. They work by increasing insulin release from the pancreas and decreasing excessive glucagon release.

McIntyre now routinely uses liraglutide for cognitive deficits in patients with obesity or diabetes, including patients with mixed depression. It is injected under the skin at 0.6 mg daily, then the dosage is increased to 1.2 mg and then 1.8 mg. Victoza reduces major cardiovascular events in those with type 2 diabetes. The higher-dose Saxenda (3mg) can be used for weight control.

Another anti-diabetes drug, **pioglitazine**, has also been reported to be helpful in bipolar depression.

McIntyre found that the antibody infliximab, which can be used as an intravenous treatment for chronic inflammation and works by blocking the effects of TNF-alpha, did not improve depression, but did improve cognition.

McIntyre also supports the use of **acetyl-L-carnitine**, a potential adjunctive treatment that can reverse the insulin resistance that often occurs with obesity and thus could theoretically improve cognition.

McIntyre described preliminary literature suggesting the effectiveness of drugs such as **statins, calcium channel blockers, and biguanides such as the diabetes treatment metformin** in reducing inflammation.

Bariatric surgery to reduce the size of the stomach was another option discussed by McIntyre. He said the intervention is safe for patients with bipolar disorder and can help them recover cognitive function.

McIntyre noted that offspring of a mother with obesity have decreased response to sensory cues, reward preference, cognitive control, and motor control. Obesity and the inflammation that goes along with it apparently affect offspring via epigenetic mechanisms, meaning obesity may change the structure of inherited DNA (without changing its sequence).

Inflammation Associated with Cognitive Deficits

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Katherine E. Burdick and colleagues at Brigham and Women's Hospital and Harvard Medical School reported that in 240 patients with bipolar disorder who were not currently having a manic or depressive episode, markers of inflammation were associated with cognitive deficits.

Inflammation was associated with cognitive deficits in general, and there were also some relationships between specific inflammatory markers and types of cognitive processing. They found that the inflammatory markers TNF-alpha, TNFR1, and TNFR2 influenced cognitive flexibility. The inflammatory marker VEGF influenced reward processing, while IL-6/IL-6r influenced spatial processing. IL-1beta and Il-1RA influenced social cognition.

Burdick and colleagues found it was important to include both primary and secondary mediators of inflammation in their research "as the effects of the primary pro-inflammatory cytokines can be blocked by a number of decoy receptors and soluble antagonists." Elevations in these can provide additional information about the function of the immune system.

Editor's Note: Targeting inflammation with the anti-inflammatory treatments minocycline and celecoxib has been shown to improve depression. Now the role of anti-inflammatory drugs in improving cognition deserves further attention.

Obesity Associated with Inflammation and Brain Abnormalities

At the 2019 meeting of the International Society for Bipolar Disorders, researcher David J. Bond reviewed the data on the **multiple adverse effects of obesity in patients with bipolar disorder. These include increased cardiovascular risk, poorer response to treatment, brain abnormalities, and decreased cognitive function, which is correlated with the degree of overweight.**

Editor's Note: These data emphasize the importance of starting a nutritious diet early in life and sustaining it through adulthood, avoiding the drugs most associated with weight gain such as clozapine and olanzapine, and facilitating weight loss with drugs. There are several treatments that can aid in weight loss. One is the diabetes treatment metformin, starting at a high dose of 500mg twice daily, and increasing to 1000mg twice daily if tolerated. The anticonvulsants topiramate or zonisamide also promote weight loss. The most effective option is a combination of the antidepressant bupropion sustained release (at a dose of 150–300mg) plus the anti–substance abuse drug naltrexone (50mg). This combination was associated with a loss of 10% of body weight over 12 weeks in women with diabetes.

Inflammation Predicts Lower Frontal and Temporal White Matter Volumes in Early-Stage Bipolar Disorder

At the 2019 meeting of the International Society for Bipolar Disorders, researcher David Bond found that **seven inflammatory cytokines predicted lower white matter volumes in the left frontal and bilateral temporal lobes, as well as in the cingulate and inferior frontal gyri.** Bond noted that greater inflammation did not predict lower parietal or occipital white matter volumes, suggesting that inflammation had a greater effect on white matter volume in those parts of the brain most closely linked to mood disorders.

More Than 70% of People with Bipolar Disorder Have Additional Psychiatric Illness

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Kathleen R. Merikangas reviewed large scale community studies of people with bipolar disorder in multiple countries. She reported that **more than 70% have three or more lifetime disorders,** not just bipolar disorder.

Preliminary findings suggested that adolescents with bipolar disorder did not tend to have other disorders in addition to their bipolar disorder, but as they approached young adulthood these became more common. She concluded, "These findings suggest that early intervention may prevent the secondary comorbidity that is related to greater impairment, worse course and poorer treatment response in bipolar disorder."

Editor's Note: It is a major deficit that not only is there limited data on early intervention in general, but virtually none about early intervention in the face of multiple comorbidities. This lack of treatment knowledge means that the majority of people with bipolar disorder are facing challenges that could be mitigated if only the needed clinical treatment research were done.

Comorbid Psychiatric Disorders Impair Response to Psychosocial Treatment in Adolescents with Bipolar Disorder

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Marc J. Weintraub and colleagues followed 145 adolescents with bipolar disorder over a period of two years. **Those with comorbid disorders (compared to those with bipolar disorder alone) fared more poorly in response to psychosocial treatment.**

Weintraub and colleagues found that the adolescents who had anxiety disorders in addition to their bipolar disorder spent more weeks depressed, had more severe symptoms of (hypo) mania, and had more family conflict over the course of the study than those adolescents who had bipolar disorder alone.

Participants who had attention deficit hyperactivity disorder (ADHD) in addition to their bipolar disorder had more weeks with (hypo)manic symptoms, had more severe (hypo)manic symptoms, and greater family conflict than those with bipolar disorder alone.

Those participants with comorbid oppositional defiant disorder (ODD) or conflict disorder in addition to their bipolar disorder had more depressive symptoms and family conflict throughout the study.

Editor's Note: How to better approach treatment in these diagnostically complex young people is an urgent unmet need, as most research excludes participants with more than one psychiatric disorder. Clinicians treating young people with bipolar disorder and comorbidities such as anxiety disorder, ADHD, and ODD must generally rely on inferences from children with these illnesses, using their own intuition about best treatment approaches rather than having evidence from systematic studies about how best to treat these children. It appears that both psychosocial and pharmacological treatments must be tailored to these more complicated presentations.

Treating Bipolar Depression in Teens

At the 2019 meeting of the International Society for Bipolar Disorders, **researcher Ben Goldstein discussed a case of a 15-year-old with bipolar depression and his recommended treatments for the adolescent.** Goldstein endorsed the use of an atypical antipsychotic such as lurasidone, and perhaps also quetiapine. Goldstein noted 2015 findings from researcher Robert Findling that lamotrigine was significantly more effective than placebo in adolescents 13–18 years old, but was not effective in those aged 10–12.

(In adults, researcher John Geddes and colleagues found that in patients with an inadequate antidepressant response to quetiapine, the addition of lamotrigine was more effective than adding a placebo, both acutely and in long-term follow-up. The only caveat was that lamotrigine was less effective in those who were also being treated with folate.)

Editor's Note: Some other treatments could augment the effects of the regimen proposed by Goldstein, including lithium and the antioxidant N-acetylcysteine, which, it should be noted, takes more than eight weeks to become effective. Vitamin D3 could also be considered, as it is often low in children with psychiatric disorders. One treatment that went unmentioned at the meeting was repeated transcranial magnetic stimulation, or rTMS, which is effective and well-tolerated in adolescents with depression.

For patients with more rapidly cycling bipolar disorder and only partial response to medications, the combination of the three Ls (lurasidone, lamotrigine, and lithium) could have considerable appeal, given that each drug is from a different class of medications, has a different mechanism of action, targets a different mood phase, and is relatively well-tolerated both alone and in combination with other drugs.

Psychiatric Risks in Offspring of Parents with Bipolar/Unipolar Disorders

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Martin Preisig and colleagues from Lausanne, Switzerland reported on a longitudinal study of mood disorders in offspring of parents with bipolar disorder, unipolar depression, or no history of psychiatric illness. The study included 446 children (with an average age of 10.1 years at the beginning of the study), who participated for an average of 11.9 years.

Preisig and colleagues found that **bipolar disorder in the offspring was preceded by sub-threshold hypomania, major depression, and conduct disorder. Bipolar disorder in the offspring was also predicted by parental early-onset bipolar disorder.**

Major depression was preceded by separation anxiety disorder, and witnessing violence or being a victim of sexual abuse.

Preisig and colleagues concluded that not only did bipolar disorder and major depressive disorder have different familial origins, they also had different antecedents and risk factors.

Cannabis May Produce More Brain Changes in Teens with Bipolar Disorder than in Healthy Teens

At the 2019 meeting of the International Society for Bipolar Disorders, researcher Benjamin Goldstein of Sunnybrook Research Institute in Toronto reported that adolescents with bipolar disorder who smoked marijuana had greater deficits in certain brain areas than did adolescents who did not have bipolar disorder. **The areas affected included the dorsal lateral and rostral middle frontal cortex, and middle cortex. Goldstein concluded, "Adolescents with [bipolar disorder] may be particularly sensitive to the neurostructural effects of cannabis."**

Marijuana in general causes adverse changes in brain structure and cognition and vulnerability to paranoia and psychosis. Heavy use in adolescence is associated with an increased incidence of the onset of bipolar disorder and schizophrenia. The Goldstein data suggest several possible causal mechanisms. Those with bipolar disorder may already have brain abnormalities that are exacerbated by marijuana use. Alternatively, marijuana and bipolar disorder together may impact brain structure more than either factor alone would.

Alcohol Use Disorders That Begin Before Age 21 May Cause Lasting Changes to Amygdala

In a 2019 article in the journal *Translational Psychiatry*, researcher John Peyton Bohnsack and colleagues report that people with alcohol use disorders that began before they were 21 years of age show amygdala changes that people with alcohol use disorders that began after the age of 21 do not appear to have.

The amygdalas of those who began abusing alcohol in adolescence showed greater expression of the long non-coding RNA known as BDNF-AS. The increased BDNF-AS was associated with decreased levels of brain-derived neurotrophic factor (BDNF) in the amygdala. BDNF protects neurons and is important for learning and memory.

According to Bohnsack and colleagues, "Adolescence is a critical period in brain development and adolescent drinking decreases orbitofrontal cortex activity and increases amygdala activity leading to less executive control, more emotional impulsivity, alterations in decision-making, and [a higher risk of engaging] in risky behaviors and develop[ing] mental health problems later in life."

Newly Identified Effects of Antioxidant N-Acetylcysteine

In a talk at the 2019 meeting of the International Society for Bipolar Disorders, researcher Michael Berk, who was responsible for some of the initial findings on the effects of the antioxidant N-acetylcysteine (NAC), summarized some of the newer findings about the treatment.

NAC has been found to be effective in bipolar depression and in the treatment of both positive and negative symptoms of schizophrenia. It also helps in the avoidance of cocaine, alcohol, tobacco, and marijuana. It can reduce habitual behaviors such as gambling, obsessive compulsive disorder (OCD), and trichotillomania (compulsive hair-pulling) and irritability and motor stereotypy (repeated movements) in autism.

A 2016 study by researcher Sudie E. Back and colleagues in the *Journal of Clinical Psychiatry* found that **NAC improved symptoms of post-traumatic stress disorder (PTSD) in veterans who also had depression and substance use disorders at a dosage of 2.4 grams/day.**

According to Berk, NAC also reduces the incidence of lithium-related renal failure and reduces mitochrondrial toxicity. One study reported that it improved working memory in patients with schizophrenia.

In his talk, Berk also noted that statins offer an interesting new avenue for treatment. Several studies have suggested statins can improve mood or reduce the likelihood of a depressive recurrence. Angiotension-active drugs (inhibitors) have also been reported to decrease the incidence of depression and to improve cognition.

In Mice, Knockout of Circadian CLOCK Genes Resembles Mania

Colleen McClung reviewed and extended previous findings of hers that knocking out a gene known as CLOCK in mice could reproduce most aspects of bipolar mania, including symptoms such as hyperactivity; decreased sleep; less depression; more impulsivity, risk taking, and novelty seeking; and increased reward-seeking including substances such as cocaine, alcohol, and sucrose. This syndrome in mice can be reversed by giving the mice lithium and valproate.

Knocking out the CLOCK gene produced an increased firing rate and burst firing of dopamine neurons in the ventral tegmental area (VTA). Localized knockout of the CLOCK gene in the VTA alone also reproduced the increase in dopamine cell firing.

When McClung and colleagues knocked out CLOCK in the medial prefrontal cortex, the normal development of a type of neurons called GABAergic parvalbumin interneurons did not occur in adolescent mice, and in adulthood, certain neural nets did not mature, leading to increases in oxidative stress, mitochondrial and cellular dysfunction, and the behavioral abnormalities that resembled mania. This animal model thus gives insight into how a genetic deficit in circadian rhythm genes in humans could influence the timing of behavioral abnormalities starting in adolescence and lasting through adulthood.

Mitochondrial Dysfunction May Plays a Key Role in Bipolar Disorder

At the 2019 meeting of the International Society for Bipolar Disorders, researchers Ana Andreazza, Olivia Dean and colleagues reviewed substantial data that implicate mitochondrial dysfunction in the mood and energy fluctuations that make up bipolar disorder. **Most of the neurobiological alterations known to occur in bipolar disorder have a relationship to mitochondria, which produce energy within cells.** These alterations include abnormalities in glutamate, gene expression, apoptosis (cell death), oxidative stress, low ATP (a molecule that stores energy), altered ion pumps, increased intracellular calcium, and insufficient glutathionine (an antioxidant made up of three amino acids).

Coenzyme Q10 is a mitochrondrial enhancer of Complex I, an enzyme that is key to the first step in mitochondrial energy production. A 2018 controlled study by Maryam Mehrpooya and colleagues published in the *Journal of Clinical Psychopharmacology* found that 200mg/day of CoQ10 was more effective than placebo at reducing symptoms of bipolar depression when added to patients' stable treatment regimens that included mood stabilizers and antidepressants. The effect size was large (0.87), and it took eight weeks for the benefit over placebo to appear. Response rate to CoQ10 was 72% compared to 12% to placebo.

Editor's Note: Some formulations of CoQ10 do not cross the blood-brain barrier easily, so only a very small percentage of the CoQ10 gets into the brain. Thus, consumers should be careful about the type of product they purchase. The one made by Takeda Pharmaceutical Company is likely to be effective.

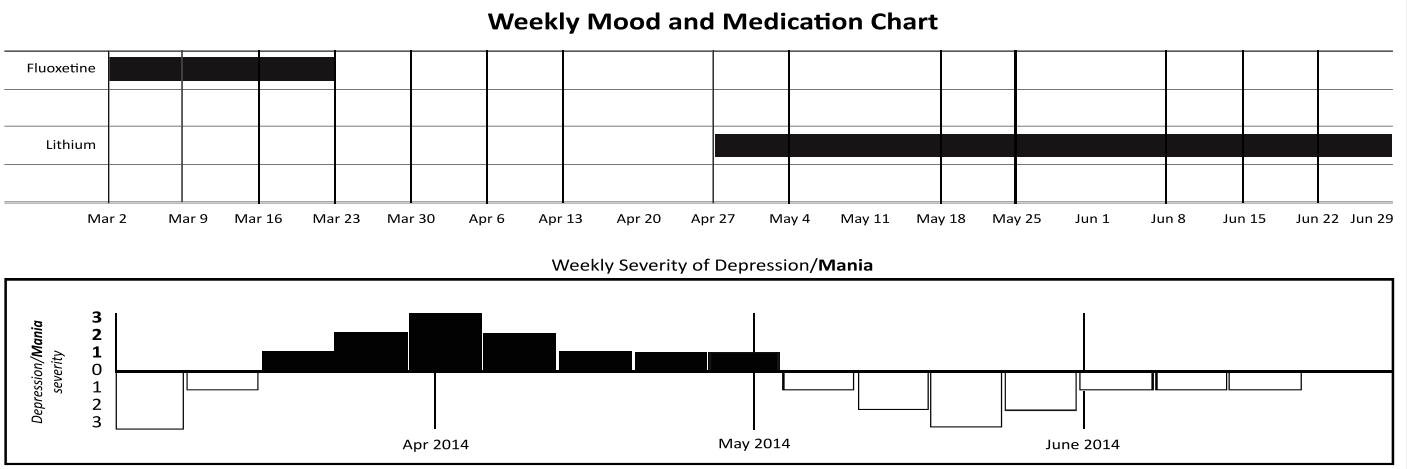
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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.

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