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Bipolar Network News

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Lithium in Drinking Water May Reduce Dementia

New research suggests that higher trace levels of lithium in drinking water can reduce dementia rates in the general population. In a 2017 article in the *Archives of General Psychiatry*, researcher Lars Kessing and colleagues compared data on 73,731 patients in Denmark with a diagnosis of dementia to 733,653 control participants without this diagnosis between the years 1970 and 2013. They were able to match the data to recorded levels of trace lithium in the drinking water in participants' municipalities of residence.

Lithium levels in the water ranged from 0.6 micrograms per liter to 30.7 micrograms per liter in 151 different locations throughout Denmark. Compared to those exposed to 2.0 to 5.0 micrograms of lithium per liter of water, those exposed to more than 15.0 micrograms per liter had a lower incidence rate of dementia. However, those exposed to 5.1 to 10.0 micrograms per liter had a higher incidence of dementia. The same relationship was also found between lithium exposure levels and both Alzheimer's disease and vascular dementia.

The lithium levels in the water were approximately 10,000 to 300 times lower than typical clinical doses (typically 900–1500mg/day, which produce concentrations ranging from 0.6 to 1.2 meq/L in patients' blood). The minute exposures to lithium in the drinking water occurred over decades in the Danish study, and suggest that there may be long-term positive effects to chronic lifetime exposure to very low lithium levels.

These data follow others regarding exposure to trace lithium. In 2011, researcher Orestes V. Forlenza and colleagues reported in the *British Journal of Psychiatry* that low dose lithium (150–600mg/day) over a period of one year decreased the progression of mild cognitive impairment compared to placebo, while researcher Marielza Andrade Nunes and colleagues reported in the journal *Current Alzheimer's Research* in 2013 that an even smaller dose (0.3mg/day) over a period of 15 months slowed the progression of Alzheimer's dementia. Thus, low or microscopic doses consumed over long periods could slow cognitive deterioration.

Lithium Treatment Lowers Suicide Rate in People with Bipolar Disorder

A large study that made use of a Swedish health database has shown that lithium reduces suicide rates in bipolar disorder. The study by researcher Jie Song and colleagues was published in the *American Journal of Psychiatry* in 2017.

The study included eight years of data from 51,535 people with bipolar disorder. During that time, there were 10,648 suicide-related events recorded, such as suicide attempts or completed suicides. **The researchers compared suicide rates when patients were taking lithium to rates when they were off the drug, and found that lithium reduced attempted or completed suicide by 14%.** Song and colleagues also looked at suicide rates for people taking valproate, and found that these were no better than when patients were off valproate, implying that treatment alone is not enough to reduce the suicide rate and the benefit is specific to lithium use.

Song and colleagues estimate that 12% of the suicide-related events among the patients included in the study might have been avoided if the patients had taken lithium for the entire study period. While there are other clinical considerations to make when selecting an appropriate treatment for a given patient, the researchers suggest that lithium treatment should be considered for patients with bipolar disorder who have expressed suicidal intentions or who are otherwise at risk for suicide.

In This Issue:

In Danish Study, Higher Trace Levels of Lithium in Drinking Water in Certain Regions Do Not Seem to Prevent Bipolar Disorder

Previous studies have found that trace levels of lithium that occur naturally in the drinking water of certain regions are associated with lower rates suicide. Preliminary studies have also shown that lithium in drinking water is associated with lower dementia rates. The trace levels seen in drinking water are many hundreds of times lower than clinical doses of lithium prescribed for bipolar disorder, but they vary greatly according to locality.

A new study by researcher Lars Kessing and colleagues investigated whether chronic exposure to lithium in drinking water might protect against bipolar disorder, but found no evidence that this is the case in Denmark.

In an article published in the journal *Bipolar Disorders* in 2017, Kessing and colleagues describe findings from their analysis of data on 14,820 patients with a diagnosis of mania or bipolar disorder and (for each participant with bipolar disorder) 10 other age- and gender-matched control participants totaling 140,311. The researchers were able to look longitudinally at the participants' exposure to trace levels of lithium in drinking water based on their municipalities of residence.

The investigators hoped to find evidence that greater exposure to lithium was associated with lower rates of bipolar disorder. Kessing and colleagues concluded that trace lithium levels higher than those in Denmark might be needed to find such a result.

Editor's Note: Clinical studies of lithium treatment for children at high risk for bipolar disorder could help clarify whether even conventional therapeutic levels of lithium could reduce or delay the appearance of bipolar disorder.

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The *BNN* is published 4–6 times a year by investigators working with patients with bipolar disorder to better understand the long-term course of illness. The newsletter is available free of charge to all who request it.

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Naturally Occurring Lithium in Texas Drinking Water Reduced Alzheimer's Mortality Rates

Several studies have found that trace levels of lithium that naturally occur in the drinking water of certain regions are associated with reductions in dementia compared to regions with less lithium in the water. The latest such study found that **higher trace levels of lithium in certain Texas counties were associated with less mortality from Alzheimer's disease compared to Texas counties with lower levels of lithium in the water.**

The research by Val Andrew Fajardo and colleagues was published in the *Journal of Alzheimer's Disease* in 2017. Fajardo's team obtained 6,180 water samples from 234 of Texas' 254 counties. They also calculated that there was an increase in the Alzheimer's mortality rate from the period 2000–2006 to the period 2009–2015. However, regions with higher trace levels of lithium were negatively correlated with this increase, suggesting that the lithium in the water had a protective effect on people in those counties.

The researchers controlled for gender, race, education, rural living, and air pollution. Physical inactivity, obesity, and type 2 diabetes seemed to be confounding factors. Obesity and type 2 diabetes were positively correlated with Alzheimer's mortality and negatively correlated with lithium levels in drinking water, meaning that it is possible that lithium also protects against these conditions.

Continuing Lithium Treatment Does Not Increase Kidney Failure

A risk of long-term lithium treatment is that it can cause kidney damage. However, a new study suggests that continuing lithium treatment after a diagnosis of chronic kidney disease does not necessarily increase the risk of irreversible end-stage kidney disease, which is defined as either the need for either chronic dialysis or a kidney transplant.

The 2017 study by researcher Lars Kessing and colleagues in the journal

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TDCS Effective in Bipolar Depression

A 2017 study in the journal *JAMA Psychiatry* reports that transcranial direct current stimulation (tDCS) is an effective add-on treatment for bipolar depression. In the study by researcher Bernardo Sampaio-Junior and colleagues, 59 patients taking medication for bipolar disorder and experiencing a depressive episode were randomized to receive either 10 daily half-hour sessions of tDCS (and then one every two weeks) or an inactive sham stimulation.

TDCS is a painless form of neurostimulation in which electrodes applied to the scalp provide a steady, low current of electricity that modulates neuron activity. Sampaio-Junior describes its low cost, portability and ease of use as some of its benefits. This is the first randomized, sham-controlled study of tDCS in bipolar disorder.

After six weeks of treatment, patients who received real tDCS treatment showed significantly more improvement in their depression than those who received the inactive sham stimulation. In the active group, 67.6% showed sustained response compared to 30.4% in the inactive group. TDCS was well tolerated, with skin redness at the application site the only side effect that was more common in the active group than in the sham group. Mood switching rates were similar across the two groups.

The research was completed as part of the Bipolar Depression Electrical Treatment Trial (BETTER) taking place in Brazil. The group of participants was 68% female with a mean age of 45.9 years. Sixty-one percent of participants had bipolar I disorder while the remainder had been diagnosed with bipolar II.

Continuing Lithium Treatment Does Not Increase Kidney Failure (cont.)

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Acta Psychiatrica Scandinavica used Danish health databases to track data from all individuals who received a diagnosis of chronic kidney disease between 1995 and 2012 and also had a history of lithium treatment (754 patients) or anticonvulsant treatment (5,004 patients). Kessing and colleagues found that **patients who continued taking lithium after an initial diagnosis of chronic kidney disease had decreased rates of end-stage kidney disease.** This also held true for those who continued anticonvulsant treatment after a diagnosis of kidney disease.

One point of uncertainty was introduced by the finding that the subset of participants who were taking lithium specifically to treat bipolar disorder did have a higher rate of end-stage kidney disease. This was not true of the participants who were taking anticonvulsants to treat bipolar disorder.

Kessing and colleagues concluded that after an initial diagnosis of chronic kidney disease, continuing lithium did not necessarily increase end-stage kidney disease. Switching to an anticonvulsant, as is sometimes the practice after a kidney disease diagnosis, may not confer any benefit.

30 Minutes of TDCS Better Than 20 Minutes in Patients with Unipolar Depression

Transcranial direct current stimulation (tDCS) has successfully been used to treat depression. In this treatment, electrodes applied to the scalp provide a constant low level of electricity that can modulate neuron activity. In a 2017 article in the journal *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, researcher Elena L. Pavlova and colleagues report that **both 20- and 30-minute sessions of tDCS improved mild to moderate depression when combined with the selective-serotonin reuptake inhibitor (SSRI) antidepressant sertraline. However, the 30-minute sessions produced more improvement in depression.**

In the study, 69 right-handed patients (average age 37.6) received 50 mg of sertraline (Zoloft) per day and were randomized to one of three tDCS conditions: 10 daily 30-minute sessions, 10 daily 20-minute sessions, or 10 daily sham sessions with no tDCS treatment. The tDCS consisted of 0.5mA anodal current to the left dorsolateral prefrontal cortex.

Both 30-minute and 20-minute tDCS sessions produced greater benefit than the sham sessions. The 30-minute group showed significantly greater percentage improvement in depression scores than the 20-minute group, and included more participants who responded to treatment (89% compared to 68% of the 20-minute group and 50% of the sham group) and more whose depression remitted (70% compared to 27% of the 20-minute group and 35% of the sham group).

Management of Unipolar and Bipolar Depression During Pregnancy

At the Maryland Psychiatric Research Society's continuing medical education conference in November, Lauren Osbourne, Assistant Director of the Women's Mood Disorders Clinic at Johns Hopkins Hospital, gave a presentation on the management of mood and anxiety during pregnancy and lactation. She had a number of important ideas for physicians and patients to consider in their decision-making process.

According to Osbourne, 60%-70% of pregnant women with unipolar depression who discontinue their antidepressants relapse. Of those with bipolar disorder who discontinue their mood stabilizers, 85% relapse, while 37% of those who stay on their medications relapse.

Something to consider when deciding whether to continue medication while pregnant is that **depression in pregnancy carries its own risks for the fetus. These include preterm delivery, low birth weight, poor muscle tone, hypoactivity, increased cortisol, poor reflexes, and increased incidence of attention deficit hyperactivity disorder (ADHD) and other behavioral disorders.**

The placenta makes an enzyme 11-BHSD2 that lowers the stress hormone cortisol in the baby. However, this enzyme is less active in depression, exposing the fetus to higher levels of cortisol.

Thus, the decision about whether to continue medications during pregnancy should consider the risks to the fetus of both the mother's depression and the mother's medications.

Most antidepressants are now considered safe during pregnancy. There have been reports of potential problems, but these data are often confounded by the fact that women with more severe depression are more likely to require antidepressants, along with other risk variables such as smoking or late delivery (after 42 weeks). When these are accounted for by using matched controls, the apparent risks of certain antidepressants are no longer significant. This includes no increased risk of persistent pulmonary hypertension, autism, or cardiac malformations.

There may be a possible increased risk of Neonatal Adaption Syndrome (NAS) in the first weeks of life in babies who were exposed to selective serotonin reuptake inhibitor (SSRI) antidepressants in the third trimester. This syndrome presumably results from antidepressant withdrawal, and can include respiratory distress, temperature changes, decreased feeding, jitteriness/irritability, floppiness or rigidity, hypoglycemia, and jaundice. There is not yet a robust literature on the syndrome, but Osbourne suggested that it disappears within 2 weeks of birth.

In her practice, Osbourne prefers to prescribe sertraline, which has the best safety data, along with fluoxetine. Sertraline is also OK for breastfeeding. There is less data on bupropion, but it also appears to be safe during pregnancy. Endocrine and enzyme changes in pregnancy typically cause a 40% to 50% decrease in concentrations of antidepressants, so doses of antidepressants typically must be increased in order to maintain their effectiveness.

Osbourne ranked mood stabilizers for bipolar disorder, from safest to most worrisome.

Lamotrigine is safest. There is no evidence linking it to birth defects, but higher doses are required because of increased clearance during pregnancy. Lithium is next safest. There are cardiac risks for one in 1,200 patients, but these can be monitored. Carbamazepine is third safest. One percent of babies exposed to carbamazepine will develop spina bifida or craniofacial abnormalities. Valproate is least safe during pregnancy. Seven to ten percent of babies exposed to valproate will develop neural tube defects, other malformations, or developmental delay, with a mean decrease of 9 IQ points. The atypical antipsychotics all appear safe so far.

Alternatives and Adjuncts to Medications in Pregnancy

Non-medication approaches to depression during pregnancy include: psychotherapy (including cognitive behavioral therapy and interpersonal therapy), mindfulness, exercise, yoga, acupuncture, high intensity light, and repeated transcranial magnetic stimulation (rTMS). Nutritional supplements including folic acid, vitamin D3, and omega-3-fatty acids can also be helpful.

The risks of hospitalization for postpartum depression are 23 times higher in women with a history of depression than in women without such a history. Babies born to women experiencing postpartum depression are at risk for: low IQ, developmental lags, ADHD, other behavioral problems, and psychiatric illness. Almost all antidepressants are safe for use during breastfeeding, but sertraline appears to be best, as blood levels in the newborn reach only about 0.5% of maternal levels.

Medications of minor concern during breastfeeding include clozapine and benzodiazepines, because they may cause sedation, and lithium because it requires monitoring of thyroid hormone levels and kidneys.

Editor's Note: The postpartum period is a high-risk period for women in the general population, who have about a 13–20% risk of depression. All women in the general population should be screened for depression after giving birth, and should receive an increase in support even if depression is not present. Women with a history of depression are at even higher risk for depression, and strategies for treatment and increased support should be explored before the baby arrives.

Several Studies Find Lamotrigine is Safe in Pregnancy

Several studies have now suggested that lamotrigine is safe to use during pregnancy. In June 2017, researcher Gali Pariente and colleagues published a systematic review and meta-analysis in the journal *CNS Drugs* in which they reported that **across 21 studies, lamotrigine use during pregnancy was not linked to an increase in birth defects.**

In November 2017, a small study from an Israeli medical center reported data from 83 women who received lamotrigine during their first trimester of pregnancy. The study by Merav Cohen-Israel and colleagues in the *British Journal of Clinical Pharmacology* found that lamotrigine use was not linked to congenital malformations, neurodevelopmental disorders, or withdrawal symptoms in the offspring.

Of the 83 women, 76 received lamotrigine alone, four received it in combination with clonazepam, two with carbamazepine, and one in combination with both levetiracetam and phenytoin.

Folate Supplements Reduce Autism Rates in Offspring of Women Taking Anti-Epileptic Drugs During Pregnancy

A 2017 study form Norway suggests that the offspring of women taking anti-epileptic drugs during pregnancy are less likely to develop autism if the women also take folic acid supplements.

The study by Marte Bjørk and colleagues in the journal *JAMA Neurology* used data from 104,936 children aged 18 to 36 months. **Those whose mothers took anti-epileptic drugs during pregnancy had elevated autism rates, but only if their mothers did not use folic acid supplements.** The mothers' folate levels in weeks 17 to 19 of their pregnancies were inversely related to the degree of autistic traits in their offspring.

Women without epilepsy and women whose epilepsy went untreated during pregnancy had children with similarly low rates of autism to those whose mothers supplemented their anti-epileptic medications with folic acid during pregnancy.

Phthalates in Plastics and Creams Cause Epigenetic Changes to Sperm

A recent study suggests that chemicals called phthalates that are used to make plastic flexible and to improve the texture of lotions, creams, and powders have effects on human sperm. Phthalates have become common in our environment since the invention of plastics, and most people have detectable levels of phthalate metabolites in their bodies.

The study, published by Haotian Wu and colleagues in the journal *Human Reproduction* in 2017, measured DNA methylation in a group of men's sperm and compared this to levels of phthalate metabolites in the men's urine.

DNA methylation changes the structure of a DNA strand. Extra methyl groups are attached to the strand, affecting the way it is transcribed, even though the inherited genetic sequence on the DNA strand remains the same. Changes like these to the structure of DNA and histones, which give DNA its helix shape, are known as epigenetic changes.

Wu and colleagues found 131 regions of DNA methylation in the men's sperm that they could link to at least one of the phthalate metabolites found in the men's urine.

Sperm takes 72 days to mature. Wu and colleagues suggest that exposure to phthalates in plastics or personal care products during this period may cause alterations to sperm, which could potentially affect the ease of conception or the development of potential offspring. The changes the researchers observed affected genes related to growth, development, and cellular function and maintenance.

In addition to chemical exposure, stressors and drug use can also bring about epigenetic changes to sperm. A father's offspring may then have altered risk of drug use or other behaviors as a result of these epigenetic changes.

Phthalates, which can disrupt the endocrine system, have previously been found to alter men's hormone levels and to hurt sperm quality. This is the first study to find that in people, phthalate concentrations measured before conception are associated with DNA methylation in sperm. This was a fairly small study in 48 men, and it remains to be studied whether the changes to sperm affect the offspring's prenatal and early childhood development.

In addition to their presence in flexible plastics, phthalates may also be found in products such as shaving cream, shampoo, soaps, and detergents.

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

Atypical Antipsychotic Drug Aripiprazole Appropriate for Pregnancies

A 2017 systematic review in the *Journal of Affective Disorders* found that the atypical antipsychotic medication apripiprazole (Abilify) was relatively safe for use during pregnancy and lactation. Researcher Alessandro Cuomo and colleagues reviewed 93 articles from the last two decades of research.

Placebo-controlled research on medications used during pregnancy are uncommon, due to ethical reservations about assigning women randomly to each group when their fetus may be affected. However, Cuomo and colleagues were able to find some large prospective studies and large database studies that shed light on aripiprazole's safety during pregnancy. They concluded that the data on aripiprazole during pregnancy and breastfeeding were "relatively reassuring" and that **the benefits of aripiprazole outweigh the potential risks.**

Risks of relapse upon discontinuing a mood stabilizer can be as high as 80%. Illness in the mother conveys risks to the fetus, so the risk-benefit ratio may suggest that staying on effective aripiprazole treatment during pregnancy and lactation makes sense for many patients.

In a comment on the study reported by *Reuters Health*, Dr. Jennifer L. Payne of the Johns Hopkins School of Medicine said, "The main reason to discontinue aripiprazole for pregnancy…would be if it is not working and the mother is actively ill, or if she insisted on doing so. In my mind, the literature supports the use of aripiprazole during pregnancy in mothers with serious mental illness who are responding well to the medication."

Using Antidepressants During Pregnancy Likely Does Not Increase Autism Risk

In the past year or so, several meta-analyses have analyzed data from numerous studies of a possible link between antidepressant use in pregnancy and autism in the offspring. In a 2017 article in the *Journal of Clinical Psychiatry*, researcher Chittaranjan Andrade offers a meta-analysis of these previous meta-analyses, and determines that **while there is a small link between antidepressant use in pregnancy and autism in the offspring, it is most likely the mother's depressive illness rather than the medications that is responsible for this link.**

Andrade found that antidepressant exposure was linked to an increased risk of autism spectrum disorders in the offspring even when the antidepressant use occurred only before conception occurred, when it could not possibly have affected the future fetus' physiology. This implies that it is the mother's illness rather than the antidepressant treatment that is a determinant of autism risk.

In Animals, Exposure to High Fat Diet During Pregnancy Can Affect Offspring's Neurological Development

New research in non-human primates suggests that exposure to a high fat diet during pregnancy and in early development prior to weaning can increase the offspring's propensity for anxiety later in life.

The new research echoes 2010 findings about rats. Researcher Staci D. Bilbo and colleagues reported in the journal of the Federation of American Societies for Experimental Biology that **in rats, a high fat diet during pregnancy and lactation led to offspring with greater body weight, increased inflammation, and problems with anxiety and spatial learning.** Switching to a standard diet after weaning did not eliminate these outcomes.

The recent research by Jacqueline R. Thompson and colleagues, published in the journal *Frontiers in Endocrinology* in July 2017, suggests that maternal nutrition in the primate during pregnancy and lactation can have long-lasting effects on offspring's neurological development, altering the brain and endocrine system. These changes occurred even if the offspring began a normal diet after weaning.

65 female Japanese macaques were divided into two groups, one that received a high-fat diet and one that received a normal diet. In the offspring of mothers who ate a high-fat diet, the researchers found impaired development of neurons containing serotonin. The offspring of the high-fat diet group also showed behavioral alterations such as increased anxiety.

The high rates of obesity in the US and other developed nations make these findings particularly important. The researchers suggest that 64% of women in the US who are of reproductive age are overweight, and 35% are obese. Co-author Elinor Sullivan suggested that the findings from the study could motivate mothers to make healthy nutritional decisions, not only for themselves but for their children as well.

Is Your Child At Risk for a Mood Disorder? See page right.

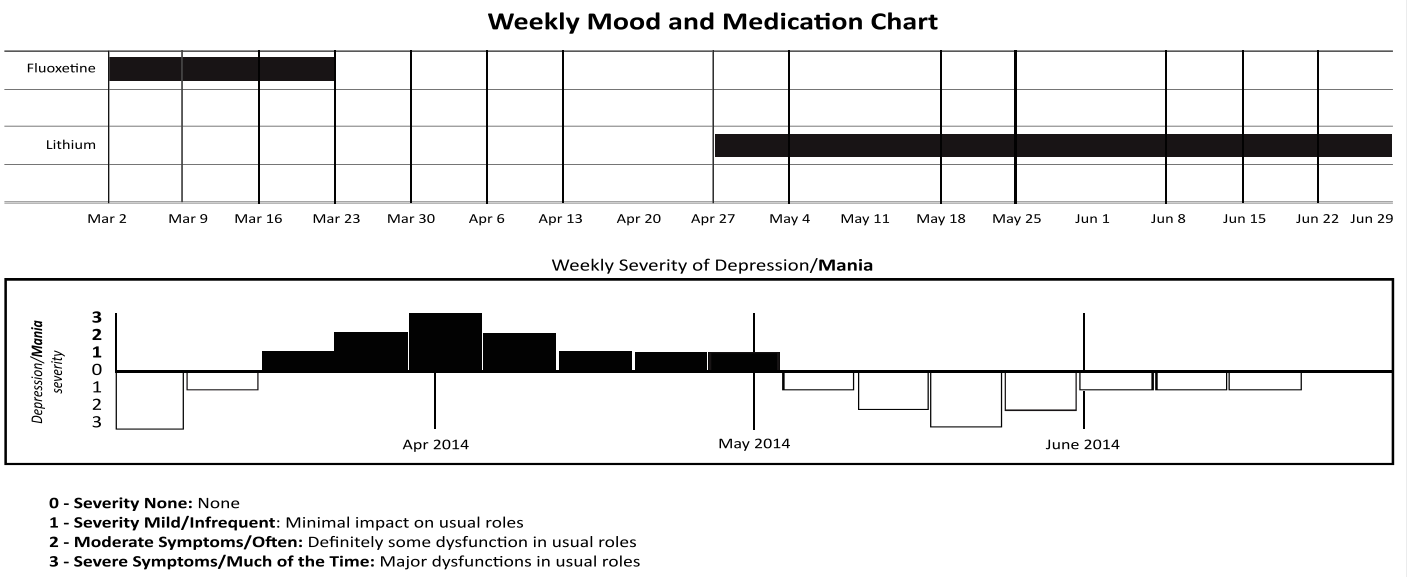
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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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