

Bipolar Network News

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Lithium Has Minimal Effects On Renal Function: Results Of Two New Large Controlled Studies

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Earlier this year we described a 2015 study by Harald Aiff and colleagues that suggested that long-term lithium use was associated with a risk of kidney failure. That study, published in the *Journal of Psychopharmacology*, included 630 patients who had taken lithium for at least 10 years. One-third of these patients had evidence of kidney dysfunction, and in 5%, the impairment was severe. Two new studies provide some data that suggest these risks may not be lithium-specific and are comparable to risks that come with taking other medications.

The first, by Stefan Clos et al. in *The Lancet Psychiatry*, included 1,120 patients followed for up to 12 years. On average, these patients had been exposed to lithium for a little over 4.5 years. Clos and colleagues determined patients' estimated glomerular filtration rate (eGFR), a measure of how well the blood is filtered by the kidneys. **The researchers concluded that there was "no effect of stable lithium maintenance therapy on the rate of change of eGFR over time" compared to other drugs such as quetiapine, olanzapine, or valproate.**

The second new study, by Lars Vedel Kessing and colleagues in the journal *JAMA Psychiatry*, included 26,731 patients exposed to lithium and 420,959 exposed to anticonvulsants. Kessing and colleagues concluded that both exposure to lithium and exposure to an anticonvulsant were associated with an increased rate of chronic kidney disease, but lithium was not associated with end-stage kidney disease (the kind that requires dialysis or renal transplantation).

The three studies taken together suggest the following: Taking lithium for an average of 4–5 years does not affect kidney functioning, and longer exposure may not harm kidney function any more than other medications (such as anticonvulsants) would. However, kidney functioning (in terms of eGFR) does decline with age, and is also lower among those with higher baseline eGRF, those with other illnesses, those taking other drugs that affect the kidneys, and those who experience an episode of lithium toxicity.

Long-term use of lithium and anticonvulsants (but not antipsychotics or antidepressants) is associated with chronic kidney impairment. However, Kessing's study shows that long-term lithium use (defined as 60 or more lithium prescriptions) is not associated with end-stage disease.

Editor's Note: Kessing's is the largest controlled study to date to indicate that lithium is not associated with end-stage

Continued on Page 2

A STUDY ASSESSING YOUR CHILD'S MOOD AND BEHAVIOR

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

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



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

Research Study
Principal Investigator: Robert L. Findling, MD, MBA
IRB Study #00026940

Lithium Use for 4–5 Years Has Minimal Effects On Renal Function

Continued from Page 1

kidney disease, and that decreases in kidney function seen with chronic lithium use also occur with exposure to anticonvulsants.

Given lithium's exceptional record of efficacy and safety over the past 40 years, it may be under-prescribed in the US compared to many European countries, and this may have adverse consequences for the long-term course of bipolar disorder. Lithium has many advantages over other medications.

Lithium:

- Reduces mania and depression better than valproate (according to recent comparisons)
- Reduces suicide risk
- Protects neurons in animals
- Increases proteins that protect neurons (like BDNF and BCL2) and decreases cell death factors (like BAX and P53)
- Increases hippocampal and cortical volume in humans
- May slow the progression of mild cognitive impairment

- May reduce the rate of dementia in old age
- Can be used to treat mania in young people (aged 7 to 17; according to new research by Robert Findling et al. in the journal *Pediatrics*)

Given the new data on lithium's long-term effects on kidney function compared to comparable drugs, the case for long-term use of lithium (either alone or in combination with other agents) to prevent both manic and depressive episodes is even stronger.

Bipolar Network News

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Editor-in-Chief: Robert M. Post, MD
Managing Editor: Moira McCauley

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

Although the editors of the *BNN* have made every effort to report accurate information, much of the work detailed here is in abstract or pre-publication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact or omission, or lack of balance. Patients should consult with their physicians, and physicians with the published literature, before making any treatment decisions based on information given in this issue or in any issue of the *BNN*.

As per recent journal disclosure requirements, Dr. Post has consulted with drug companies including Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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Send any comments or suggestions to:
mccauleybcn@gmail.com

BNN
5415 W. Cedar Lane
Suite 201B
Bethesda, MD 20814

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Lithium Safely Reduces Mania in Kids 7–17

The first large, randomized, double-blind study of lithium in children and teens has shown that as in adults, the drug can reduce mania with minimal side effects. The study by researcher Robert Findling was published in the journal *Pediatrics* in October. Lithium is the best available treatment for adults, but until now little research had been done on treatments for children and teens with bipolar disorder.

In the study, 81 participants between the ages of 7 and 17 with a diagnosis of bipolar I disorder and manic or mixed episodes were randomized to receive either lithium or placebo for a period of eight weeks. By the end of the study, those patients taking lithium showed greater reductions in manic symptoms than those taking placebo. **Among those taking lithium,**

47% scored “much improved” or “very much improved” on a scale of symptom severity, compared to 21% of those taking placebo.

Dosing began at 900mg/day for most participants. (Those weighing less than 65 lbs. were started at 600mg/day.) Dosing could be gradually increased. The mean dose for patients aged 7–11 was 1292mg/day, and for patients aged 12–17 it was 1716mg/day.

Side effects were minimal. There were no significant differences in weight gain between the two groups. Those taking lithium had significantly higher levels of thyrotropin, a peptide that regulates thyroid hormones, than those taking placebo. If thyroid function is affected in people taking lithium, the lithium dosage may be decreased, or patients may be prescribed thyroid hormone.

Saphris Reformulated for Kids with Bipolar I

The atypical antipsychotic asenapine has been reformulated for bipolar I disorder in children aged 10–17. The drug (trade name Saphris) was approved by the Food and Drug Administration (FDA) in 2009 for adults with schizophrenia and bipolar disorder. It is sometimes used as a

treatment for mixed episodes (depression with some symptoms of mania).

The new formulation consists of 2.5mg tablets that are taken sublingually (under the tongue), and are available in a black cherry flavor. These can be prescribed as monotherapy for the acute treatment of manic or mixed episodes in children and teens.

Several Types of Psychotherapy Effective in Childhood Bipolar Disorder

Childhood onset bipolar disorder can be highly impairing. Treatment usually includes medication, but several types of psychotherapy have also been found to be superior to treatment as usual. These include family focused therapy, dialectical behavior therapy and multifamily psychoeducation groups, including Rainbow therapy.

Family focused therapy, developed by David Miklowitz, consists of psychoeducation about bipolar disorder and the importance of maintaining a stable medication routine. Families are taught to recognize early symptoms of manic and depressive episodes, and how to cope with them. Families also learn com-

munication and problem solving skills that can prevent stressful interactions.

Dialectical behavior therapy was developed by Marsha Linehan, initially for the treatment of borderline personality disorder. It can be useful in bipolar disorder because participants learn how to manage stressors that might otherwise trigger depression or mania. DBT teaches five skills: mindfulness, distress tolerance, emotion regulation, interpersonal effectiveness, and self management.

Multifamily psychoeducation was developed by Mary Fristad. In groups, children and parents learn about mood disorders, including how to manage symptoms, and also work on communication,

problem solving, emotion regulation, and decreasing family tension.

Rainbow therapy is a type of multifamily approach also known as child and family-focused cognitive-behavioral therapy (CFF CBT). It integrates individual cognitive-behavioral therapy with family psychoeducation and mindfulness skills training. In a recent article in the journal Evidence Based Mental Health, Miklowitz reviewed the current research on Rainbow therapy. While the research to date has many limitations, he highlighted some benefits of Rainbow therapy: its flexibility, and its focus on treating parents' symptoms along with children's illness.

Cognitive Behavioral Therapy Can Prevent Depression in Teens

Adolescents whose parents have a history of depression are at greater risk for depression themselves. A new study suggests that a cognitive-behavioral prevention program aimed at these teens can reduce depression rates compared to the usual care.

The study, by David A. Brent and colleagues in the journal *JAMA Psychiatry*, included 316 participants aged 13–17, each of whom had a parent with a current or prior depression. Half participated in the cognitive-behavioral prevention program in addition to usual care initiated by their families. The program consisted of 8 weeks of 90-minute group sessions focused on developing positive thinking habits and improving problem solving, followed by six monthly sessions. The training was based on the Adolescents Coping with Depression program described in a June 2009 *JAMA* article by Garber et al.

The group who participated in the prevention program had a lower in-

cidence of depression than the group who received only the usual care, and this difference persisted over six years of followup. Most of this effect was due to a reduced incidence of depression in the first nine months following the intervention. (Depression was roughly equal among the two groups following the first nine months.)

Importantly, the benefit of the prevention program was only seen among adolescents whose parents were not depressed at the time of enrollment in the study, underscoring the importance of treating parents' illness in order to keep the whole family healthy.

Benefits of the prevention program included reductions in onsets of depression and days depressed, and improvement in interpersonal and academic competence.

Brent and colleagues say that the study shows that it is possible to prevent depression, and this can have long-term developmental consequenc-

es. They encourage focusing on the entire family's mental health treatment.

While the main benefits came early, Brent suggests that booster sessions for teens who begin to show symptoms of depression might refresh the benefits of the prevention program at a later time.

Editor's Note: This study has enormous health implications as depression in adolescents tends to recur and is associated with a more difficult course than depression beginning in adulthood. Preventing depressions would theoretically have positive consequences for both psychiatric and physical health, as depression is associated with increased risk of suicide and decreased longevity from increases in cardiovascular disease. Researcher Joan Luby recently reported that children with prepubescent onset of depression have decreased hippocampal volume in adolescence, so it is possible that preventing depression may have positive implications for brain volume and function.

Treating Bipolar Disorder in Children and Adolescents

Bipolar disorder in childhood or adolescence can destroy academic, family, and peer relationships and increase vulnerability to drug use, unsafe sexual encounters, disability, and suicide. Treatment is critical to avoid cognitive decline. Given the potential tragic outcomes of undertreating bipolar illness, it is concerning that 40–60% of children and adolescents with bipolar disorder are not in treatment.

In a talk at the 2015 meeting of the International Society for Bipolar Disorder, researcher Cristian Zeni reviewed the existing research on the treatment of bipolar disorder in children and adolescents. **A 2012 study by Geller reported response rates of 68% for the atypical antipsychotic risperidone, 35% for lithium and 24% for valproate.** Risperidone

was linked to weight gain and increases in prolactin, a protein secreted by the pituitary gland, while lithium was linked to more discontinuations and valproate to sedation.

For children or adolescents with aggression, researcher Robert Kowatch recommends quetiapine, aripiprazole, and risperidone. For those with a family history of bipolar disorder, he recommends lithium or alternatively, valproate plus an atypical antipsychotic.

Researcher Robert Findling has found that lamotrigine has positive effects in childhood mania, and Duffy et al. found in a study of 21 children with mania that 13 remained stable on monotherapy with quetiapine for 40 weeks without relapse, while 5 others required combination treatment with more than one drug. In studies by

Karen Wagner, oxcarbazepine was significantly better than placebo at reducing mania in younger children (ages 7–12), but not older children (13–18).

Studies by Duffy and colleagues in 2007 and 2009 recommend lithium for those with a family history of bipolar disorder, atypical antipsychotics for children with no family history of bipolar disorder, and lamotrigine for those with a family history of anxiety disorders.

In children with bipolar disorder and comorbid attention deficit hyperactivity disorder, there is universal agreement that mood should be stabilized first, and then small amounts of stimulants may be added for residual ADHD symptoms. Too often, the opposite occurs, with stimulants given prior

Continued on Page 5

The Adolescent Brain is Reshaping Its Responses to Fear

Adolescence can be a time of vulnerability to illness. Anxiety disorders increase during this period, and three-quarters of adults with anxiety disorders trace the illness back to their childhood or adolescence. The most common treatments for anxiety disorder are based on the idea of fear extinction. A certain stimulus, like a social situation or seeing a spider, provokes a fear reaction in the brain. By gradually increasing exposure to the stimulus and extinction training, the person can become desensitized to the stimulus. New research on rodents presented by Francis S. Lee at the 2015 meeting of the Society of Biological Psychiatry suggests that the extinction process is diminished during adolescence.

At specific stages of maturation, neural circuits related to particular abilities can become flexible. Brain and behavior become sensitive to and are increasingly shaped by experience. Studies of rodents and humans have shown that adolescence is a time when

the neural circuitry for fear extinction is in flux. In mice, this period falls around their 29th day of life. Lee reported that around this time, the mice begin to exhibit resistance to the extinction of fear learning.

In adolescent rodents, there is a surge of contextual fear learning and retrieval that is mediated by hyper-connectivity of the ventral hippocampus and the amygdala to the prelimbic part of the prefrontal cortex. In contrast, the pathway from the amygdala to the infralimbic cortex mediates the extinction of this type of learning. Because the prelimbic pathway for fear learning is overactive, the infralimbic pathway for extinction learning is less effective.

Adolescent mice temporarily lose their ability to retrieve memories related to cue-dependent (as opposed to context-dependent) fear learning. Remarkably, when these animals proceed into adulthood, the fear learning associated with cues returns and becomes accessible again.

This could help explain how teenagers can lose fear conditioning to cues they learned in childhood, such as fearing for their safety when speeding through a red light. The fear is forgotten (or becomes inaccessible) in adolescence, but then what had been learned is again “remembered” (retrieved) in adulthood.

The adolescent brain prunes back 100,000 synapses per second, perhaps accounting for some of the chaos that can characterize adolescence. Adolescents' entire brains are being rewired, in a process that typically replaces excitatory synapses with inhibitory ones. Now it appears that teens may just not be able to recall previously well-learned lessons linking certain cues to fear responses that would tell them to avoid certain situations and behaviors. After a few years, access to the appropriate cue-dependent fear learning returns and more mature choices and responses are likely to re-emerge.

Treating Kids with BP

Continued from Page 4

to mood stabilization with lithium, anticonvulsants (valproate, lamotrigine, carbamazepine/oxcarbazepine) and/or an atypical antipsychotic.

Some options for treatment with little risk of side effects include vitamin D, the antioxidant N-acetylcysteine, and omega-3 fatty acids. Moderately well-tolerated interventions include the anti-inflammatory antibiotic minocycline and the multi-vitamin complex EM Power Plus. The next tier on the tolerability scale includes more traditional drugs with some evidence of efficacy and good tolerability: lamotrigine and oxcarbazepine. Next would be lithium, valproate, carbamazepine extended-release (under the brand name Equetro) and atypical antipsychotics, all of which have some safety concerns. Randomized trials to compare the efficacy and tolerability of the various atypical antipsychotics are needed. Geller's study of risperidone shows these drugs may be effective in children and adolescents, but may also have substantial side effects.

Weight gain and related side effects from atypical antipsychotics are more common in children than in adults. Ziprasidone and lurasidone produce the least weight gain, followed by aripiprazole, quetiapine and risperidone, and then olanzapine and clozapine. Lurasidone has not been studied in adult mania, and some experts have disparaged its potential utility in childhood mania. Aripiprazole, quetiapine, and risperidone are among the most widely prescribed drugs for bipolar disorder in young people. Further exploration of ziprasidone is needed.

More research on atypical antipsychotics is needed, for bipolar disorder in both adults and young people. Childhood-onset bipolar disorder has a more difficult course and outcome than adult-onset illness, and finding effective treatments for young people is essential to preventing difficult outcomes.

Ketamine Improves Sleep, Reduces Suicidal Thoughts For Some

Intravenous ketamine is known for its fast-acting antidepressant effects, which can appear within two hours of an infusion. Researchers are now investigating its use for the reduction of suicidal thoughts. In a study presented in a poster at the 2015 meeting of the Society of Biological Psychiatry, Jennifer L. Vande Voort and colleagues compared the sleep of patients whose suicidal thoughts decreased after a single ketamine infusion (0.5 mg/kg over 40 minutes) to those whose suicidal thoughts remained.

Study participants whose suicidal thoughts diminished after the infusion of ketamine had better sleep quality the following night, with fewer disruptions in sleep than those who did not have an anti-suicidal response to ketamine. The participants who responded well to ketamine had sleep quality similar to that of healthy controls.

Vande Voort and colleagues hope that these new findings about ketamine's effect on sleep may provide clues to the biological mechanism behind ketamine's effect on suicidal ideation.

Ketamine Temporarily Reduces Suicidal Thoughts

Intravenous ketamine can bring about rapid improvement in depression among people with treatment-resistant depression. Because its effects can appear within two hours, ketamine is being studied as a treatment for people with suicidal thoughts.

At the 2015 meeting of the Society of Biological Psychiatry, Laili Soleimani and colleagues presented a poster about their recent double blind, randomized, controlled pilot study of ketamine inpatients and outpatients who scored highly on a measure of suicidal ideation. The 24 participants were randomized to receive either a single intravenous infusion of ketamine (0.5mg/kg) or a single infusion of midazolam (0.045 mg/kg), which shares ketamine's anxiety-reducing effects but does not have antidepressant effects. The participants reported suicidal thoughts afterward, at 24 hours, 48 hours, 72 hours, and 7 days later. **At 48 hours, those who received ketamine reported significantly less suicidal ideation than those who received midazolam,** but this effect was no longer significant at the 72-hour mark.

The findings show that ketamine can briefly reduce suicidal ideation, and the treatment is safe and tolerable for patients. This pilot study paves the way for further study of ketamine in people who are at high risk for suicidal thinking or behavior.

Ketamine: Equal Efficacy When Given With Lithium Or Valproate

Studies of rodents with depression-like behaviors revealed that combining low (sub-therapeutic) doses of lithium and infusions of ketamine produced antidepressant-like effects. Researchers believed this might mean that in humans, lithium could have the unique ability to potentiate the effects of ketamine. On its own, intravenous ketamine is a fast-acting antidepressant whose effects last only a few days.

In a small study by Mark J. Niciu presented at the 2015 meeting of the Society of Biological Psychiatry, patients with bipolar depression taking lithium or valproate mood stabilizers were given ketamine infusions or control infusions. In the 23 patients taking lithium and the 13 taking valproate, **ketamine's antidepressant effects were significantly better than placebo, but there was no difference between lithium and valproate with regard to these antidepressant effects.** These preliminary data in a small number of subjects do not support the proposition that lithium augments the effects of ketamine in depression.

Direct Current Stimulation Improves Negative Symptoms of Schizophrenia

A new double-blind, randomized clinical trial has shown that transcranial direct current stimulation (tDCS) can reduce negative symptoms of schizophrenia, such as thought disorders, poverty of speech, and withdrawal. TDCS, a treatment in which an anode and a cathode electrode placed on the skull are used to apply a steady, low-level current of electricity to the brain, has been shown to improve neuroplasticity, such as neuronal remodeling, by depolarizing or hyperpolarizing neurons. People with schizophrenia have neuroplasticity deficits in parts of the cortex, so a few case reports and one previous randomized clinical trial have explored the use of tDCS in schizophrenia.

The current study, presented by Ulrich Palm at the 2015 meeting of the Society of Biological Psychiatry, included 20 patients with primarily negative symptoms of schizophrenia. The patients, who had been on stable medication regimes for at least three weeks, were randomized to receive either a sham procedure or tDCS with the anode over the left dorsolateral prefrontal cortex and the cathode over the right eye. TDCS stimulation was delivered at a current of 2 mA ten times over two weeks. The patients continued to take their medication and also received functional connectivity magnetic resonance imaging (fcMRI) before and after tDCS treatment. Two weeks following the stimulation, scores on a scale of positive

symptoms (including hallucinations and delusions) and negative symptoms of schizophrenia had decreased significantly in those who received tDCS compared to the sham procedure. A different measure of negative symptoms was significantly lower among the tDCS group throughout the study period and at followup two weeks later. The fcMRI revealed that those who received tDCS had a deactivated cluster in the brain region that includes the nucleus accumbens, the subgenual cortex, and the striatum.

This study suggests that tDCS is a promising treatment for otherwise difficult-to-treat negative symptoms of schizophrenia.

New TMS System Approved for Depression

In August the US Food and Drug Administration (FDA) approved the marketing of the MagVita TMS Therapy system from the company MagVenture. This machine can be used to provide transcranial magnetic stimulation (TMS) to patients with major depression that has not responded to antidepressant drugs. A TMS system uses magnets placed close to the head to stimulate the brain.

There are several existing systems that can provide TMS. The Neuronetics Neurostar TMS machine was the first one to be approved, in 2008. Then came Brainway's Deep TMS machine. Now MagVenture says that the benefits of their new system include a simple design, low operating costs, no disposable components, and safety and efficacy rates comparable to those of other FDA-approved TMS devices.

Treatment with the MagVita system is typically provided five times per week for a duration of six weeks.

As TMS treatment becomes available to more patients, coverage by insurance companies is also increasing, but is still not guaranteed for patients in the US.

RTMS for Depression Increases Volume of Specific Brain Regions

Repeated transcranial magnetic stimulation (rTMS) is a treatment for depression in which magnets placed near the skull stimulate electrical impulses in the brain. In a poster presented at the 2015 meeting of the Society of Biological Psychiatry, Martin Lan and colleagues presented results of the first study of structural changes in the brain following rTMS.

In the study, 27 patients in an episode of major depression underwent magnetic resonance brain scans before and after receiving rTMS treatment over their left prefrontal cortices. **Lan and colleagues reported that several cortical regions related to cognitive appraisal, the subjective experience of emotion, and self-referential processing increased in volume following rTMS treatment: the anterior cingulate, the cingulate body, the precuneus, right insula, and gray matter in the medial frontal gyrus.** The increases ranged from 5.3% to 15.7%, and no regions decreased in volume. More than 92% of the participants showed increased gray matter in all of these regions.

The brain changes were not correlated with antidepressant response to rTMS, but suggest a possible mechanism by which rTMS is effective in some people. Lan and colleagues concluded that rTMS likely had neuroplastic effects in areas of the brain that are important for emotion regulation.

Efficacy of Direct Current Stimulation in Major Depression

A new meta-analysis presented at the 2015 meeting of the Society of Biological Psychiatry has clarified the efficacy of transcranial direct current stimulation (tDCS) in major depression. TDCS is a treatment in which electrodes deliver a steady low level of electrical stimulation to the brain. The meta-analysis presented by Andre Brunoni and colleagues used individual patient data from six recent studies comparing tDCS treatment to a sham treatment, totaling 289 patients. **TDCS treatment was superior to the sham control in terms of antidepressant response (34% to 19%), remission rates (23.1% to 12.7%), and improvement in depression.**

After adjusting for confounding factors, the researchers found that patients who had failed to respond to previous treatments were less likely to respond well to tDCS than other patients. They also found that higher doses of tDCS (in terms of current density, duration, and number of sessions) predicted a better response than lower doses.

Ultrabrief Right Unilateral ECT Similar in Efficacy to Brief ECT with Fewer Side Effects

A new meta-analysis suggests that right unilateral ultrabrief electroconvulsive therapy (ECT) may be a better choice than standard brief pulse ECT for the treatment of severe depression. Researchers at the University of New South Wales in Australia led by Colleen Loo say that while standard ECT (with a pulsewidth of 1.0 ms) is recommended when urgency is paramount, ultrabrief ECT (with a pulsewidth of 0.3 ms) is better for patients at risk for cognitive side effects or those who do not require an urgent response. The researchers' findings were reported in the *Journal of Clinical Psychiatry* in July.

Loo and colleagues analyzed the findings of six different studies that compared right unilateral standard brief pulse ECT with ultrabrief pulse ECT and included a total of 689 patients. **Standard ECT was more effective**, producing more improvement in mood and more remissions, and working faster than ultrabrief ECT. **However, standard ECT also produced greater cognitive side effects**

in every area tested, including thinking, learning and recall, and memory.

(When bilateral ECT is used, the cognitive effects are even worse, and researcher Harold Sackheim and colleagues have reported that the severity of the impairment in autobiographic memory is directly proportional to the number of bilateral ECT treatments a patient received, even when measured one year after the last session of bilateral ECT. This editor (Robert Post) believes bilateral ECT should be avoided if at all possible, as cognitive side effects can occasionally be severe.)

When Loo and colleagues removed nonrandomized trials from the analysis, the differences in efficacy between ultrabrief and standard right unilateral ECT were not statistically significant. Loo told *Medscape Medical News* that while the differences in efficacy between brief and ultrabrief ECT are minimal, the differences in side effects are greater. Right unilateral ultrabrief ECT works about as well as standard right unilateral brief pulse ECT, but preserves patients' cognitive function better.

N-acetylcysteine Reduces Self-Harm, Restores Amygdala Connectivity

N-acetylcysteine (NAC) is an antioxidant nutritional supplement that has been found to reduce a wide range of habitual behaviors, including drug and alcohol use, smoking, trichotillomania (compulsive hair-pulling), and gambling. It also improves depression, anxiety, and obsessive behaviors in adults, as well as irritability and repeated movements in children with autism. **A new study suggests NAC may also be able to reduce non-suicidal self-injury, often thought of as "cutting," in young women aged 13-21.**

The open study, presented in a poster by researcher Kathryn Cullen at the 2015 meeting of the Society of Biological Psychiatry, compared magnetic resonance imaging (MRI) scans of 15 healthy adolescent women to scans of 22 young women who had been engaging in self-injury. The scans were taken before and after the latter group received eight weeks of treatment with NAC. Doses were 1200 mg/day for the first two weeks, 2400mg/day for the next two weeks, and 3600mg/day for the final four

weeks. The young women also reported their self-injury behaviors.

Treatment with NAC reduced self-injury behaviors. The brain scans showed that NAC also increased resting-state functional connectivity between the amygdala and the insula. Connectivity in this region helps people regulate their emotional responses. At baseline, the girls who engaged in self-harm had had deficient connectivity between the amygdala, the prefrontal cortex, insula, and the posterior cingulate cortices compared to the healthy girls, and this deficit improved with NAC treatment.

A PANS Case Study: Immune Treatment Reduced Psychiatric Symptoms

Pediatric acute neuropsychiatric syndrome (PANS) is a little-known syndrome in which a child has an acute onset of psychiatric symptoms following a bacterial or viral infection, when the antibodies generated to fight the infection instead attack neurons in the brain. The behavioral alterations can be severe and resistant to the usual psychotropic drug treatments. PANS often requires antibiotics and immune-targeted therapies.

The following is a case report of a real child who had a sudden onset of depression and violence after getting sick with the flu, pneumonia, and a strep infection at the age of 4. (Names have been changed for privacy.)

Anne contacted this editor (Robert M. Post) seeking a consultation on her 6-year-old son, Jake. Two years earlier, he had suddenly become difficult—depressed, angry, and even violent. This coincided with the emergence of obsessive compulsive symptoms and bedwetting. He went from being able to read short sentences in pre-kindergarten, to being cognitively dull and not even able to recognize letters of the alphabet. He had been diagnosed with a mood disorder, and Anne was told it was probably bipolar disorder. But he didn't respond to any of the typical medications, and suffered side effects including hallucinations, nightmares, bowel accidents, and worsening depression.

The best results came with the atypical antipsychotic risperidone. While it didn't reduce all of Jake's symptoms, Anne described it as "heaven" compared to earlier treatments. But Jake's levels of prolactin started to increase, and he lost bladder control, so he had to stop taking risperidone. Jake's doctor tried 18 different medication regimens with 8 different medications in less than a year without finding one that worked well. Jake had a

horrible time in school, and Anne fretted about the lack of an effective, stable medication, saying, "He's actually worse than I've ever seen him."

Dr. Post recommended that they consider using high doses of quetiapine and valproate for Jake's aggression and behavioral dyscontrol, along with the antioxidant N-acetylcysteine and vitamin D3. However, given that Jake's symptoms were severe, involved cognitive and neurological abnormalities, had begun after a flu-like illness, and were unresponsive to conventional treatment, Dr. Post suggested that Anne get Jake checked out for PANS and start charting Jake's mood on a daily basis.

Jake began taking higher doses of quetiapine and valproate, and improved to the point that Anne reported that they restrained him only once a day, rather than four times per day. But Jake's behavioral dyscontrol continued. In one memorable incident, after feeling picked on by other children at a baseball game, he lashed out at Anne, kicking her in the face with his cleats and punching her glasses off her face.

Anne told Dr. Post that the family had visited a neurologist, who said that she had never heard of PANS and suggested that Anne would have to travel several states away to see Dr. Post if she wanted to pursue the diagnosis.

Dr. Post encouraged Anne to keep looking for a doctor who would take the PANS idea seriously. He sent her a comprehensive review article about PANS by Dr. Kiki Chang and colleagues that was published in the *Journal of Child and Adolescent Psychopharmacology* in 2014.

This past June, Anne found a doctor who understood PANS and

was willing to run the appropriate tests on Jake. The tests revealed that Jake had at one time been infected with the bacteria mycoplasma. His immune system mobilized to fight the infection, but the antibodies it produced (IgG and IgM) also attacked his brain. The doctor recommended anti-inflammatory and antibiotic treatments to target this immune response.

In September, Anne wrote that Jake has made a dramatic improvement. In the beginning of June, Jake was "all over the place," going from severe mania to severe depression. From filling out daily mood charts (available on our website <http://bipolarnews.org> under Mood Charting), Anne could see that

within days of beginning treatment for PANS, Jake's mood stabilized. While he still has some symptoms, Anne says that he has not had more than a mild mood swing since June.

Jake's current medications include 200mg a day of the anti-inflammatory ibuprofen and 250mg a day of the antibiotic azithromycin, plus 20 billion CFUs of a probiotic, 1000 UI of vitamin D3, 50mg of 5HTP, 10mg of Claritin, 300mg twice a day of oxcarbazepine (Trileptal), 0.1mg twice a day of Clonidine ER, 15mg of Zinc, and 15mg twice a day of Armour Thyroid.

Anne says, "My understanding is this is a long and curvy road, but I could not be happier to at least be on the right street." The next step for Jake may be IVIG, or intravenous immunoglobulin, a blood product that contains antibodies from over a thousand blood donors. Anne hopes that eventually Jake can be weaned off the Trileptal and Clonidine.

Atypical antipsychotics are associated with less loss of gray matter in schizophrenia than first-generation antipsychotics.

A PANS Case Study, Immune Treatment Reduced Psychiatric Symptoms

The following are some highlights from Chang's article on the diagnosis, workup, and treatment of PANS.

Diagnosing PANS

The diagnostic criteria for PANS are as follows:

A. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake.

B. Concurrent presence of additional neuropsychiatric symptoms (with similarly severe and acute onset), from at least two of the following seven categories:

- Anxiety
- Emotional instability and/or depression
- Irritability, aggression, and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration in school performance (related to attention deficit hyperactivity disorder (ADHD)-like symptoms, memory deficits, cognitive changes)
- Sensory or motor abnormalities
- Somatic symptoms, including sleep disturbances, bedwetting, or urinary frequency

C. Symptoms that are not better explained by a known neurological or medical disorder

In the article, Chang writes, "Many children with PANS are extremely ill, with extreme compulsions (licking shoes, barking), motor and phonic tics (whooping, wringing hands), behavioral regression, and terrifying episodes of extreme anxiety or aggression...."

"By definition, the individual PANS symptoms overlap with a variety of

psychiatric disorders, such as OCD, Tourette's syndrome, ADHD, depression, and bipolar disorder. However, the acuity of onset and simultaneous presentation of these symptoms differentiate PANS from these psychiatric conditions. The PANS diagnosis is, therefore, limited to cases with acute-onset symptoms in multiple domains."

Testing for PANS

Chang recommends that all patients meeting the criteria for PANS should have the following labwork done:

- Complete blood cell count with manual differential
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Comprehensive metabolic panel
- Urinalysis (to assess hydration) and to rule out inflammation for children with urinary complaints; clean-catch urine culture for those with pyuria
- Throat culture, anti-streptolysin O (ASO) and anti-DNAse B

The following laboratory tests should also be considered:

If there are elevated inflammatory markers, fatigue, rashes, or joint pain, antinuclear antibody (ANA) or fluorescent antinuclear antibody (FANA) should be obtained; if ANA is elevated, proceed with a lupus workup.

Antiphospholipid antibody workup should only be pursued if the patient has chorea, petechiae, migraines, stroke, thrombosis, thrombocytopenia, or levido rash. Workup includes: anticardiolipin antibody, dilute Russell's viper venom time (dRVVT), and b2-glycoprotein I antibodies. If abnormal liver function tests or Kayser-Fleisher rings are present, there is a need to

evaluate for Wilson's disease with ceruloplasmin and 24 urine copper tests.

Infectious disease evaluation: "The most commonly observed antecedent infection seems to be upper respiratory infection, including rhinosinusitis, pharyngitis, or bronchitis." Mycoplasma pneumonia, influenza, Epstein Barr virus, and Borrelia burgdorferi (Lyme disease) are often involved.

Immunodeficiency screening should proceed in multiple steps, complemented with repeated clinical evaluations of the patient. Initial workup should include the following:

- Lymphocyte subsets (T, B, natural killer [NK] cells) with CBC with manual differential
- Quantitative immunoglobulins (IgG, IgA, IgM, IgE) with IgG subclasses
- Vaccine responses (Pneumococcus and tetanus antibody titers)

Treating PANS

Treatment can include: antibiotics, anti-inflammatories, steroids, immune suppressants, IVIG (a mixture of antibodies), or plasmaphoresis.

In a presentation that Dr. Post heard Dr. Chang give, Chang indicated that many children with PANS are severely ill for long periods of time (as Jake was) before the correct diagnosis is made and appropriate treatment begun.

Chang concludes his article by stating that "[r]eferral to a neurologist or rheumatologist can be helpful in some cases, but should be focused on specific signs or symptoms of concern, as the subspecialists may not be experienced with the evaluation of psychiatric symptomatology. Therefore, the responsibility of eval-

Continued on Page 10

Midday Bright Light Therapy Effective in Bipolar Disorder

A recent study of 93 adults with bipolar disorder suggests that midday bright light therapy can be an effective adjunctive treatment for bipolar depression. The study by Dorothy Sit and colleagues was presented at the 2015 meeting of the Society of Biological Psychiatry. Participants had been diagnosed with bipolar I or II disorder, were in a current episode of depression, and were taking stable doses of mood stabilizing medication. They were randomized to receive either **7000-lux broad spectrum light for 45 to 60 minutes each day for six weeks or 50 lux dim red light. The comparison was dramatic: remission rates were 56.5% among those exposed to the 7000-lux light, and 14.3% among those who were exposed to the dim light.** Those who received the bright light also reported better sleep quality and less suicidality.

Editor's Note: These results are striking and raise the issue of whether midday bright light is more effective than early morning bright light, the usual recommendation for seasonal affective disorder (SAD) and other forms of depression. Until comparative studies are available, using midday light may be the way to go.

Low Vitamin D Linked to Cognitive Decline

Low levels of vitamin D levels are common, particularly in older adults and in African Americans and Hispanics. Unfortunately, low vitamin D is associated with decline in two types of cognitive functioning: episodic memory (memories of autobiographical events) and executive function (reasoning, problem-solving, planning, etc.).

A recent study with a particularly diverse group of participants, over half of whom were African American or Hispanic, found that over a period of about 5 years, episodic memory and executive function declined faster in older adults with low levels of vitamin D.

Average vitamin D levels for the entire group of 382 adults were below national standards. Levels of 25-hydroxy vitamin D should be between 20 and 50 nanograms per milliliter of blood. The average fell just below this, at 19.2 ng/mL. Over a quarter of participants had vitamin D deficiency, with levels below 12 ng/mL, and another 35.1% had vitamin D insufficiency, with levels between 12 and 20 ng/mL.

African Americans and Hispanics had lower levels of vitamin D (17.9 ng/mL and 17.2 ng/mL, respectively) than whites (21.7 ng/mL). Average vitamin D levels were lower in participants with dementia compared with those who had mild cognitive impairment or normal cognitive function.

Vitamin D levels can depend on factors such as dairy intake, sun exposure, and exercise. It has not been determined whether taking vitamin D supplements could slow down cognitive decline, but vitamin D supplementation has several benefits. Compared to placebo, supplementation with vitamin D increases response to antidepressants. A high percentage of children with major psychiatric disorders are vitamin D deficient, and it is also estimated that about 40% of adults in the US have a vitamin D deficiency.

The study by researcher Joshua W. Miller and colleagues was published in the journal *JAMA Neurology* in September.

Benefits of a Healthy Lifestyle

In a talk at the 2015 meeting of the International Society for Bipolar Disorder, researcher Michael Berk suggested that a healthy lifestyle may improve mood disorder symptoms.

Diet is important. **A study of more than 20,000 mothers revealed that those with unhealthy diets had children with more externalizing disorders, such as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and mania.** Diets high in fat and sugar were linked to depression. The Nurses' Health Study, a long-term epidemiological study of 50,000 women, showed that people who exercised more were less likely to be depressed, while lower muscle mass was associated with greater depression. Exercise also has anti-inflammatory effects.

Avoiding smoking has benefits, too. A study by Pasco and colleagues showed that people who smoke are at increased risk for a new onset of a mood disorder. Smoking is associated with onset of a more severe mood disorder earlier in life, suicide attempts, alcohol and substance abuse, and decreased response to treatment. Fortunately, quitting smoking can reverse some of these risks.

PANS (continued)

Continued from Page 9

uating PANS falls to primary care clinicians and child psychiatrists."

Dr. Post adds that this case study shows the value of collecting daily mood ratings that can graphically depict symptom variation, progression, or improvement. We offer several types of daily rating forms for free download on our website (bipolarnews.org, click the tab for Mood Charting and look for the Monthly Mood Chart Personal Calendar). **Another option for parents who want to chart their child's mood and behavioral problems is to join our online Child Network, where they can enter weekly ratings of their child's anxiety, depression, attention deficit, oppositional, or manic symptoms on a secure website.** This takes just a few minutes per week and produces a helpful graph that can be printed and sent to the child's doctor. To learn more about joining the Child Network, visit our website at bipolarnews.org and click on the tab for the Child Network.

Lori Altshuler, Leading Figure in American Psychiatry, 1957–2015

We are sad to report the death of Dr. Lori Altshuler, one of the leading figures in American psychiatry. She passed away last month after a 10-year battle with cancer. She was the director of the Mood Disorders Research Program at UCLA and a founding member of the Bipolar Collaborative Network, which included US sites in Los Angeles, Dallas, Cincinnati, and Bethesda and European sites in Utrecht, Freiberg, and Munich, and spawned the *BNN* newsletter.

Dr. Altshuler made important contributions to the understanding of bipolar disorder, particularly with her work on brain imaging. She also conducted countless treatment studies so that patients could be treated based on the best available evidence.

After funding for the Bipolar Collaborative Network ended in 2002, she organized all of the researchers to continue working together, and this resulted in more than 90 publications from the group. **Her tireless and heroic efforts to improve the lives of people with bipolar disorder will be sorely missed.**

Offspring of Parents with Psychiatric Disorders At Increased Risk for Disorders of Their Own

At a symposium at the 2015 meeting of the International Society for Bipolar Disorder, researcher Rudolph Uher discussed FORBOW, his study of families at high risk for mood disorders. Offspring of parents with bipolar disorder and severe depression are at higher risk for a variety of illnesses than offspring of healthy parents.

Uher's data came from a 2014 meta-analysis by Daniel Rasic and colleagues (including Uher) that was published in the journal *Schizophrenia Bulletin*. The article described the risks of developing mental illnesses for 3,863 offspring of parents with schizophrenia, bipolar disorder, or major depression compared to offspring of parents without such disorders.

Previous literature had indicated that offspring of parents with severe mental illness had a 1-in-10 likelihood of developing a severe mental illness of their own by adulthood. Rasic and colleagues suggested that the risk may actually be higher—1-in-3 for the risk of developing a psychotic or major mood disorder,

and 1-in-2 for the risk of developing any mental disorder. An adult child may end up being diagnosed with a different illness than his or her parents.

At the symposium, Uher focused on families in which a parent had bipolar disorder. These families made up 1,492 of the offspring in the Rasic study. The table at right shows the risk of an illness among the offspring of bipolar parents compared to that risk among offspring of healthy parents, otherwise known as relative risk. (For example, offspring of parents with bipolar disorder are 4.24 times more likely to be diagnosed with bipolar disorder themselves than are offspring of non-bipolar parents.) The table also shows the percentage of offspring of parents with bipolar disorder who have each type of disorder.

Editor's Note: These data emphasize the importance of vigilance for problems in children who are at increased risk for mental disorders because they have a family history of mental disorders. One way for parents to better track mood and behavioral symptoms is to join our Child Network. (See page 15.)

Obesity Linked to Illness Severity

In a talk at the 2015 meeting of the International Society for Bipolar Disorder, researcher David Bond reported that 75% of patients in a study of first episode mania had unhealthy body mass indices (BMIs). Forty percent were overweight while thirty-five percent were obese. Higher weight was associated with greater illness severity. Bond said that in other studies obesity has been associated with less time well and a greater risk of relapse into depression.

Obese patients also had lower brain volume, worse memory, and a greater risk of developing early onset dementia compared to other patients. Those who were overweight or obese had a 35% higher risk of developing Alzheimer's disease.

In a different talk at the same meeting, researcher Roger McIntyre reported that among patients with bipolar disorder, those who were obese have greater cognitive problems and more evidence of inflammation than those who were not obese. He has seen indirect antidepressant effects and other health benefits following weight loss from bariatric surgery.

Risk of Mental Illness in Offspring of Parents with Bipolar Disorder

Diagnosis in Offspring	Percent of Offspring	Relative Risk
Bipolar disorder	7%	4.24
Depression	14%	2.29
Schizophrenia	4%	3.14
Any Mood Disorder	21%	2.95
Anxiety Disorder	27%	1.99
Disruptive Behavior	14%	1.84
Substance Abuse	15%	2.04
ADHD	14%	1.65
Any Disorder	62%	1.75

Primates Shed Light on the Neurobiology of Anxiety Disorders in Kids

Studies of primates suggest that the amygdala plays an important role in the development of anxiety disorders. Researcher Ned Kalin suggested at the 2015 meeting of the Society of Biological Psychiatry that the pathology of anxiety begins early in life. When a child with anxiety faces uncertainty, the brain increases activity in the amygdala, the insula, and the prefrontal cortex. Children with an anxious temperament, who are sensitive to new social experiences, are at almost sevenfold risk of developing a social anxiety disorder, depression, or substance abuse.

A study by Patrick H. Roseboom and colleagues presented at the meeting

was based on the finding that corticotropin-releasing hormone (CRH) plays a role in stress and is found in the central nucleus of the amygdala. The researchers used viral vectors to increase CRH in the central nucleus of the amygdala in young rhesus monkeys, hoping to determine what impact increased CRH has on a young brain. Rhesus monkeys and humans share similar genetic and neural structures that allow for complex social and emotional functioning.

Roseboom and colleagues compared the temperaments of five monkeys who received injections increasing the CRH in their amygdala region to

five monkeys who received control injections. As expected, the monkeys with increased CRH showed increases in anxious temperament. Brain scans also revealed increases in metabolism not only in the central nucleus of the amygdala, but also in other parts of the brain that have been linked to anxiety, including the orbitofrontal cortex, the hippocampus, and the brainstem, in the affected monkeys. The degree of increase in amygdala metabolism was directly proportional to the increase in anxious temperament in the monkeys, further linking CRH's effects in the amygdala to anxiety.

Psychiatric Symptoms in Childhood Linked to Struggles in Adulthood

Psychiatric illness is one of the most common health problems among children. A study by William E. Copeland and colleagues in the journal *JAMA Psychiatry* indicates that psychiatric symptoms and diagnoses in childhood can lead to struggles with health, the legal system, personal finances, and social functioning in early adulthood, even if the psychiatric symptoms themselves do not last.

The study included 1420 participants from 11 mostly rural counties in North Carolina, who participated in structured interviews up to six times between the ages of 9 and 16 to determine the existence of psychiatric symptoms and diagnoses. Of these, 1273 were assessed three times during young adulthood, at the ages of 19, 21, and 24–26, for any evidence of social, legal, financial, or health problems.

Participants who had had a childhood psychiatric disorder were six times more likely to have at least one adverse outcome in adulthood compared to participants with no history of psychiatric problems, and nine times more likely to have two or more adverse outcomes in adulthood. Those participants who had psychiatric symptoms that were not sufficient for a particular diagnosis were still three times more likely to have at least one adverse outcome in adulthood, and five times more likely to have at least 2 adverse outcomes. The cumulative number of psychiatric disorders to which a participant was exposed was the best predictor of adverse outcomes in adulthood.

Even moderate psychiatric problems in childhood can disrupt a person's transition to adulthood. However, early treatment and prevention can help reduce the long-term impact of psychiatric illness. Parents of children (aged 2–12) with mood and behavioral symptoms are welcome to join the Child Network, a system for collecting weekly ratings of their children's symptoms and displaying them longitudinally for the child's doctor. See page 15 for details.

Childhood Maltreatment Associated with Suicide Attempts

A history of childhood maltreatment increases the risk that a person will attempt suicide. Different types of maltreatment, such as physical abuse, emotional abuse, sexual abuse, and neglect, often overlap. In a 2015 study in the *Journal of Clinical Psychiatry*, researcher Nicolas Hoertel and colleagues used data from an epidemiological survey of 34,653 Americans to clarify the mechanism by which maltreatment is linked to suicide risk.

Hoertel and colleagues found that childhood maltreatment in general was associated with an increased risk of attempting suicide and an earlier age at first suicide attempt. The analysis controlled for demographic characteristics and psychiatric diagnoses. Most of the risk came from effects that were shared across all the types of maltreatment. However, sexual abuse directly conferred an additional risk of suicide attempt.

In an earlier study of 648 outpatients with bipolar disorder by this editor Robert Post and colleagues (led by Gabriele Leverich), 34% had a history of suicide attempts, and these participants had a higher incidence of traumatic stressors in childhood and more stresses at illness onset than those without a history of suicide attempts. A history of sexual abuse in childhood was also linked to an increased risk of a serious suicide attempt in the earlier study, which appeared in the *Journal of Clinical Psychiatry* in 2003.

Predictors of Bipolar Disorder in At-Risk Youth

A new longitudinal study of 391 youth at risk for bipolar disorder revealed some predictors of the disorder. The study by Danella M. Hafeman and colleagues was presented at the 2015 meeting of the Society of Biological Psychiatry. The participants were aged 6–18 and each had a parent with bipolar disorder. Over the course of the study, 40 developed an illness on the bipolar spectrum, including 21 who developed bipolar I or II. The participants were assessed for various descriptive characteristics and those who developed bipolar disorder were compared to those who developed major depressive disorder.

The most important predictors of bipolar disorder were parental assessment of internalizing symptoms of anxiety or depression, self-assessment of mood changeability, and self-assessment of hostility. A diagnosis of bipolar disorder not otherwise specified (BP-NOS) was the only predictor of a later diagnosis of bipolar I or II.

Editors Note: These data resemble findings from a 2015 study by David Axelson and colleagues in the American Journal of Psychiatry that used the same cohort of participants. The Axelson study indicated that a categorical diagnosis of a major psychiatric disorder occurred in 74% of the offspring of a bipolar parent compared to about 50% of a control group from the community. Depression, anxiety, attention deficit hyperactivity disorder (ADHD), and oppositional disorders were even more common than bipolar disorder in the at-risk population.

The presence of a major psychiatric diagnosis in about three-quarters of the offspring of a parent with bipolar disorder suggests the importance of early vigilance. One way to track symptoms of depression, anxiety, ADHD, oppositional behavior, and bipolar disorder is to join the Child Network, a secure online platform for rating children's moods, medications, and side effects. These weekly ratings can be collected longitudinally and printed out to help parents and clinicians assess mood difficulties in their children. See our last page for details.

Early Experiences Have Lasting Effects on DNA

It is well established that certain early experiences can affect a person's risk of developing a mental illness. Adversity in childhood, including abuse or the loss of a parent, is a risk factor not only for diagnosis of a mood disorder, but also for a more difficult course of illness. This may occur via an epigenetic mechanism. Epigenetics refers to a process by which environmental factors can change the way that DNA is transcribed, for example through the addition of methyl groups to strands of DNA. This tends to inhibit DNA from being transcribed and producing protein growth factors and other neurochemicals that are important for development.

A study by Kieran J. O'Donnell and colleagues presented at the 2015 meeting of the Society of Biological Psychiatry investigated whether epigenetics play a role in the success of a parenting intervention called the Nurse Family Partnership. Participants were 27-year-olds born to women who had received the Nurse Family Partnership intervention or a control intervention. Genome-wide DNA methylation was measured in the 188 participants' blood.

Analysis of the blood revealed that the Nurse Family Partnership intervention was associated with DNA methylation at 1015 sites across 593 genes. Some of these sites were enriched for certain neurodevelopmental processes. Maltreatment in childhood was also associated with methylation at 1552 sites across 878 genes.

Editor's Note: The take-home message of this landmark study is that both positive intervention and maltreatment early in life can have lasting effects on the genome via epigenetic mechanisms.

Link Between Childhood Trauma and Difficult Course of Bipolar Disorder Clarified

A collaboration between Norwegian and French researchers led by Bruno Etain has clarified the pathway by which childhood trauma is linked to worse outcomes among people with bipolar disorder. The researchers, who presented their work in a poster at the 2015 meeting of the Society of Biological Psychiatry, replicated earlier findings by this editor (Robert Post) that patients who experienced trauma as a child had a more adverse course of bipolar disorder. Etain and colleagues found a link between childhood trauma and an earlier age of onset of bipolar disorder, rapid cycling, suicide attempts, and cannabis misuse.

The researchers identified more than 550 patients with bipolar disorder, who answered questionnaires about their history of bipolar disorder and childhood trauma. Their DNA was also analyzed, and the researchers found that the effect of childhood trauma on age of onset was mediated by the presence of common genetic variants in proteins related to stress (the serotonin transporter) and immune function (Toll-like receptors). They also found that the traits of moodiness and impulsivity mediated the effects of trauma on clinical outcomes.

The lasting epigenetic effects of child maltreatment and adversity noted in the above abstract are consistent with a large literature showing more epigenetic effects in these individuals than in controls. While genetics are important, the impact of the environment is also substantial.

Treating Women During Pregnancy and Breastfeeding

A Danish working group has released guidelines for prescribing psychotropic drugs to women who are pregnant or breastfeeding. After a comprehensive review of the literature, researchers from several different Danish medical societies reported that sertraline and citalopram are the first choice among selective serotonin reuptake inhibitors (SSRIs) for depression in women who are pregnant or breastfeeding. The working group suggested that women with bipolar disorder who need a mood stabilizer because of frequent relapses could be prescribed lithium, though lithium use is associated with a small risk of cardiac abnormalities in the child. Lamotrigine may also be used, and has not been associated with any congenital abnormalities.

Valproate and carbamazepine are not recommended for use during pregnancy and breastfeeding. Use of valproate among women of child-bearing age should particularly be avoided due to several risks for the potential child. These include spina bifida and other serious congenital problems, but also severe developmental delay and loss of about 9 IQ points. Other possible treatments for bipolar disorder and schizophrenia in pregnant and breastfeeding women include olanzapine, risperidone, quetiapine, and clozapine. The data about the safety of these medications are not extensive.

The working group included members of the Danish Psychiatric Society, the Danish Society of Obstetrics and Gynecology, the Danish Paediatric Society, and the Danish Society of Clinical Pharmacology. The recommendations may be found in an article by E.R. Larsen and colleagues in a 2015 supplement to the journal *Acta Psychiatrica Scandinavica*.

Maternal Infection During Pregnancy May Increase Risk of Schizophrenia in Offspring

There is mounting evidence from animal studies and epidemiological research that an infection during pregnancy may increase the risk of schizophrenia in the offspring. A recent study by Alan Brown and colleagues presented at the 2015 meeting of the Society of Biological Psychiatry used a large dataset from the Finnish Prenatal Study of Schizophrenia to compare medical data from the mothers of 777 people with schizophrenia (630 with schizophrenia and 147 with schizoaffective disorder) to data from the mothers of 777 healthy people.

The study's biobank contained blood samples taken from the mothers in early to mid-pregnancy, which the researchers used to determine the mothers' levels of C-reactive protein (CRP), an indicator of inflammation. Higher levels of CRP were associated with increased risk of schizophrenia in the offspring. When the researchers analyzed the findings by sex of the offspring, the link between prenatal infection and schizophrenia risk was significant in men, but not women. The effect was also stronger among offspring born after their due date than those born at or before their due date.

Maternal Infection in Mice Leads to Three Generations of Behavioral Changes

Epigenetics is the process by which environmental factors affect the way a person's genes are transcribed. These changes, which may include the addition or subtraction of methyl groups from DNA, change the DNA's structure (how tightly it is wound around the histones that give it shape) but not its sequence. These structural changes, which affect how easily the DNA is transcribed, can then be passed on to future generations. A new study by Ulrike Stadlbauer and colleagues presented at the Society of Biological Psychiatry explored a particular pathway by which an infection in a pregnant mouse can lead to behavioral changes in three following generations of mice.

Pregnant mice were given injections that produced an infection. A first generation of offspring were interbred to create a second generation of offspring, and these were interbred to create a third generation of offspring. The first generation of offspring had epigenetic changes in methylation and hydroxymethy-

lation to promoter regions of two enzymes that regulate synthesis of the neurotransmitter GABA, and these epigenetic changes were associated with reduced mRNA expression of these two genes.

All three generations of offspring had deficits in social interaction, short-term memory, and cued fear conditioning. Interestingly, the second and third offspring generations also exhibited depression-like behavior that had not been present in the original mothers or the first generation of offspring.

Editor's Note: This is another fascinating demonstration of how environmental occurrences, which can include stressors, exposure to drugs, and now immune challenges, can have effects across generations, likely through epigenetic changes that persist in ova or sperm. Amazingly, it turns out that the environment can change traits in future generations, not by inducing changes to gene sequences, but through epigenetic changes to the structure of DNA or histones that persist across generations.

Additional Information about the Child Network:

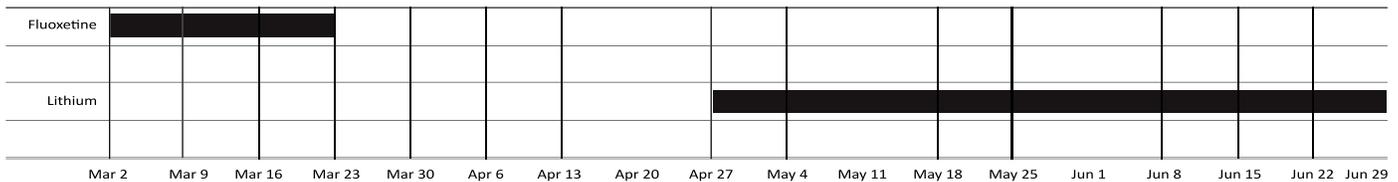
74% of children of a parent with bipolar disorder (Axelson et al. 2015) and 80% of those with unipolar depression (Weissman et al. 2006) will develop a major psychiatric illness follow up. Most of these illnesses including depression, anxiety, oppositional behavior, substance abuse go unrecognized for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

Joining the Child Network can help change that.

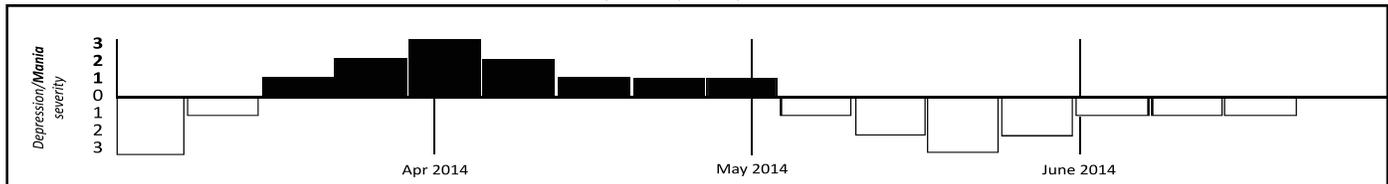
The Child Network is specifically for parents of children ages 2 to 12 who currently have no symptoms or many. In the Child Network parents weekly assess their child on a secure web site. There will also be a short demographics questionnaire and once a year a more detailed symptom checklist. The Network will examine which agents and their combinations that children are already taking are effective, and for which children.

We believe that this network will be very beneficial to its participants. Parents will be able to print out results of the ongoing brief weekly ratings in a graphic form so that the course of the child's symptoms and response to any treatment can easily be visualized. Family members already have access to general information provided in the Bipolar Network News (BNN), participation in this study may help attune parents to the complexities of treatment and engender more careful reading of the BNN and other literature.

Weekly Mood and Medication Chart



Weekly Severity of Depression/Mania



- 0 - Severity None: None
- 1 - Severity Mild/Infrequent: Minimal impact on usual roles
- 2 - Moderate Symptoms/Often: Definitely some dysfunction in usual roles
- 3 - Severe Symptoms/Much of the Time: Major dysfunctions in usual roles

We hope that this brief description of the Child Network study helps to orient you to its purpose and that you will urge parents to use this new tool. We also encourage you and parents to visit www.bipolarnews.org and click on the tab for the Child Network or http://bipolarnews.org/?page_id=2630 to learn more about the Child Network and to access the informed consent documents.

Thank you for your time.

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

Research Study, Principal Investigator: Robert L. Findling, MD, MBA, IRB Study #00026940

BNN
PO Box 18
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED