

# Bipolar Network News

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bipolarnews.org

Vol. 19, Issue 5, 2015

## Omega-3 Fatty Acids Prevent Conversion to Psychosis

A new long-term study of omega-3 polyunsaturated fatty acids for psychosis prevention shows that almost seven years after a 3-month stint of receiving these dietary supplements daily, adolescents and young adults at high risk for psychosis showed fewer symptoms of conversion to full-blown psychosis than those who received placebo during the same period.

The research team, led by Paul Amminger, originally found that among 81 youth (mean age 16.5) at high risk of developing psychosis due to their family histories, the 41 who received 12 weeks of daily supplementa-

tion with 700mg of eicosapentaenoic acid (EPA) omega-3s and 480 mg of docosahexaenoic acid (DHA) omega-3s showed reduced likelihood of conversion to psychosis one year later than the 40 who received placebo.

The team followed up an average of 6.7 years later with 71 of the original 81 participants. **Among those who had received the omega-3 intervention, 9.8% had developed psychosis. Among the placebo group, 40% had developed psychosis, and they had done so earlier.**

In addition, the omega-3 participants were better functioning, they had

required less antipsychotic medication, and they had lower rates of any psychiatric disorder than the placebo group.

Amminger wrote in the journal *Nature Communications*, "Unlike antipsychotics, fish oil tablets have no side effects and aren't stigmatizing to patients."

*Editor's Note: Because of their lack of side effects, a good case can be made for omega-3 fatty acids for patients at high risk for psychosis. The novel thing about this study is that short-term treatment with omega-3 fatty acids seemed to have preventive effects almost 7 years later.*

## Another Expert's Opinion on PTSD Meds: Prazosin, SSRIs, and Mirtazapine

Researcher Albert Sattin has had extensive experience treating veterans with post-traumatic stress disorder (PTSD) in the U.S. Department of Veteran's Affairs medical system. He believes that what is known as "treatment resistance" is really under-treatment, and he described his recommended regimen for thorough treatment of PTSD to this editor (Robert M. Post) at the 2015 meeting of the Society of Biological Psychiatry in May.

**One of the key elements in the regimens he prescribes for patients with PTSD is prazosin, an alpha-1 antagonist drug used to treat hypertension.** Extensive placebo-controlled data by another researcher, Murray Raskind, and colleagues supports the use of prazosin in PTSD. It is typically used to prevent nightmares, but Raskind, Sattin, and others find it has a broad range of positive effects in most domains of PTSD.

Sattin's key insight is that prazosin should be administered three times a

day because of its short half-life. This allows for the treatment of daytime as well as sleep-related PTSD symptoms. Sattin has patients choose from three schedules: 6am, 2pm, 10pm; 7am, 3pm, 11pm; or 8am, 4pm, 12am. Prazosin comes in 1mg, 2mg, and 5mg tablets, but patients must begin by taking the 1mg doses to reduce the risk of orthostatic hypotension (low blood pressure upon standing up), slowly increasing the dose as tolerated and if needed for symptom improvement.

Raskind reported in a poster at the same meeting that in a study of active duty combat soldiers, elevated blood pressure at baseline predicted that a patient would respond well to prazosin,

so for patients with elevated blood pressure, Sattin starts with prazosin.

**For other patients, Sattin begins by prescribing one of the two selective serotonin reuptake inhibitors (SSRIs) approved by the Federal Drug Administration for use in PTSD—sertraline (Zoloft) or paroxetine (Paxil)—and then adds the antidepressant mirtazapine (Remeron) if necessary.** If the patient still remains symptomatic, Sattin then adds prazosin to the regimen with the added warning to take time sitting up or standing up to avoid potential dizziness from low blood pressure.

*Continued on Page 10*

### Rate Children at Risk for Mood Disorders

See our last page for information on the Child Network. Enrolled parents can rate the symptoms of children ages 2-12 on a weekly basis and print out charts of the results to show physicians.

## Blood and Now Brain Inflammation Linked to Depression

There is growing evidence of a link between inflammation of depression. At the 2015 meeting of the Society of Biological Psychiatry, researcher Jeff Meyer summarized past studies on inflammatory markers. These are measurements, for example of certain proteins in the blood, that indicate the presence of inflammation in the body.

**Common inflammatory markers that have been linked to depression include IL-6, TNF-alpha, and c-reactive protein.** At the meeting,

Meyer reviewed the findings on each of these. Twelve studies showed that IL-6 levels are elevated in the blood of patients with depression. Four studies had non-significant results of link between IL-6 and depression, and Meyer found no studies indicating that IL-6 levels were lower in those with depression. Similarly, for TNF-alpha, Meyer found 11 studies linking elevated TNF-alpha with depression, four with non-significant results, and none showing a negative relationship between TNF-alpha and depression. For c-reactive protein, six studies showed that c-reactive protein was elevated in people with depression, six had non-significant results, and none indicated that c-reactive protein was lower in depressed patients.

Most studies that have linked inflammation to depression have done so by measuring inflammatory markers in the blood. It is more

difficult to measure inflammation in the brain of living people, but Meyer has taken advantage of new developments in positron emission tomography (PET) scans to measure translocator protein binding, which illustrates when microglia are activated. Microglial activation is a sign of inflammation. **Translocator protein binding was elevated by about 30% in the prefrontal cortex, anterior cingulate cortex, and insula in study participants who showed symptoms of a major depressive episode compared to healthy control participants.** The implication is that the depressed people with elevated translocator protein binding have more brain inflammation, probably via microglial activation.

*Editor's Note: The antibiotic minocycline reduces microglial activation. It would be interesting to see if minocycline might have better antidepressant effects in people with elevated translocator protein binding.*

### Bipolar Network News

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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.

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As per recent journal disclosure requirements, Dr. Post has consulted to or spoken for Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

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## Preliminary Evidence That Anti-Inflammatory Celecoxib Helps in Bipolar Depression

A study currently in progress indicates that the anti-inflammatory COX-2 inhibitor celecoxib (better known as the arthritis treatment Celebrex) may aid in the treatment of bipolar depression. In a panel session on inflammation at the 2015 meeting of the Society of Biological Psychiatry, researcher Angelos Halaris reported results from the first 26 participants.

Participants were taking mood stabilizers for bipolar disorder and became depressed. They received either 20mg/day of the selective serotonin reuptake inhibitor anti-

depressant escitalopram (Lexapro) plus either 200mg twice a day of celecoxib or placebo for a total of eight weeks. **Those participants who received celecoxib showed greater and more rapid reductions in depression symptoms than those who received placebo.**

The study will continue, and Halaris and colleagues will also observe whether measures of inflammation in patients' blood are correlated with the patients' responsiveness to the combined treatment with escitalopram and celecoxib.

## Brain Inflamed in Bipolar Disorder, Unipolar Depression, Suicide

Depression and bipolar disorder have been linked to high levels of inflammatory proteins in the blood (namely CRP, IL-1, IL-6, and TNF-alpha), but the relationship between these illnesses and inflammation in the brain has not been well-characterized.

At the 2015 meeting of the Society for Biological Psychiatry, researcher Ghanshyam Pandey discussed findings from autopsy studies of people who died with a diagnosis of unipolar depression or bipolar disorder, and teens who died of suicide. The studies compare data from these ill people

with those of controls who are matched for demographic characteristics.

**Pandey found that the brains of those who died of unipolar depression and bipolar disorder showed more signs of inflammation compared to the controls.** This included elevated levels of the inflammatory proteins IL-1B, IL-6, and TNF-alpha, in addition to elevated levels of the mRNA that leads to their production. Pandey also found that those with depression and bipolar disorder had higher levels of mRNA for the receptors to which TNF-alpha and other inflammatory proteins attach themselves.

Pandey performed similar autopsy studies of teens who died of suicide, the second leading cause of death for this age group, compared to teens who died of other causes. There were more signs of inflammation in the prefrontal cortices of teens who died of suicide. These included mRNA and proteins for IL-1B and TNF-alpha, and IL-6 proteins. In contrast to the ill adults, the teens who died of suicide had lower levels of the receptors for inflammatory proteins than controls. Another type of receptor known as toll-like receptors was higher in the ill teens, particularly the mRNA and proteins TLR3 and TLR4.

## Diabetes Common and Worrisome in People with Bipolar Disorder

People with bipolar disorder are three times more likely than the general population to develop type II diabetes. Type II diabetes typically occurs in adulthood and is associated with insulin resistance, as opposed to Type I, which is usually diagnosed in childhood and is associated with insulin deficiency.

In a talk at the 2015 meeting of the Society of Biological Psychiatry, researcher Tomas Hajek reported that in a large group of bipolar patients, 13% reported a history of Type II diabetes, 21% were diagnosed with Type II diabetes upon laboratory evaluation, and 32.2% had pre-diabetes without realizing it. Thus, about half of these patients with bipolar disorder were either affected by diabetes or at risk for it, many without knowing it.

### The Bad News

Diabetes complicates the course of bipolar illness. **Type II diabetes is associated with poorer response to treatment, atrophy of the hippocampus, cognitive**

**impairment, and higher rates of conversion from mild cognitive impairment to full-blown dementia.**

The main effect of Type II diabetes is insulin resistance. The body produces enough insulin, but insulin's effects at its receptors are impaired. Diabetes also causes deficits in growth factors, increases in the enzyme GSK3B, decreases in mitochondria and brain-derived neurotrophic factor (BDNF, which protects neurons), and glucose toxicity.

Recent research by Hajek and colleagues shows that diabetes has several other detrimental effects on the brain in bipolar disorder. On magnetic resonance spectroscopy (MRS) scans, people with Type II diabetes had lower levels of NAA, a marker of neuronal integrity, in the prefrontal cortex. This can indicate impaired functioning. People with Type II diabetes also had lower levels of creatine, indicating impaired energy metabolism. In addition, hippocampal volume decreases with aging, and Type II diabetes accelerated this age-related decline.

Some of diabetes' effects on the brain are mediated by other health factors, including obesity, cerebral blood vessel disease (which affects white matter integrity), and side effects from medications.

### What You Can Do

**Start early with a good diet and exercise, and have regular checkups with a doctor, who can tell you if you have diabetes or are at risk for it.** If so, start long-term preventative treatment with the most effective and easy-to-tolerate medications, and periodically have your fasting blood sugar tested. If these tests are abnormal, have your hemoglobin A1c (HbA1c) checked. This is a measure of good glucose control, and should be under 6. If it creeps upward toward 6 (a sign of pre-diabetes), the drug metformin may be able to prevent the onset of Type II diabetes. If you have Type II diabetes, there are several effective medications that can minimize its effects.



## Atypical Antipsychotics May Slow Loss of Gray Matter in Schizophrenia

Progressive losses in gray matter have been observed in the cortex of people with schizophrenia, and those at high risk for the illness. In the past, studies have shown that the amount of antipsychotics a patient is exposed to is correlated with the extent of their deficits in gray matter, suggesting that antipsychotic treatment could exacerbate gray matter loss.

A new meta-analysis by Antotnio Vita and colleagues in the journal *Biological Psychiatry* shows that first-generation antipsychotics were associated with greater losses in gray matter compared with atypical antipsychotics, which seemed to slow the loss of gray matter.

The meta-analysis analyzed data from 18 longitudinal studies comparing a total of 1155 patients with schizophrenia to 911 healthy control participants. Magnetic resonance imaging (MRI) scans showed that over time, patients with schizophrenia lost more cortical gray matter volume. The patients' cumulative intake of any kind of antipsychotic between MRI scans was associated with gray matter losses. But **when Vita and colleagues drilled down to find differences between patients taking first-generation antipsychotics and those taking second-generation atypical antipsychotics, they found that patients with higher average daily intake of first-generation antipsychotics had greater losses in gray matter, while patients with higher average daily intake of atypical antipsychotics had less progressive losses in gray matter.**

This study is the first to compare the effects of first-generation antipsychotics, which were developed in the 1960s,

with those of atypical antipsychotics, which came into frequent use in the late 1980s, on cortical gray matter loss in schizophrenia. While first-generation antipsychotics are associated with the side effect of tardive dyskinesia, involuntary movements of the face and jaw, atypical antipsychotics are most commonly associated with weight gain.

Three studies have randomly assigned patients with schizophrenia to receive either first-generation or atypical antipsychotics. In these studies as well, second-generation antipsychotics were associated with smaller losses in gray matter.

The authors speculate that either second-generation antipsychotics may have neuroprotective effects, or first-generation antipsychotics may have neurotoxic effects. They also suggest that first-generation antipsychotics may not have the capacity to interfere with the natural progression of schizophrenia in terms of gray matter losses.

Future studies may investigate differences between specific antipsychotic medications' effects on gray matter volume. Vita and colleagues reported that in the analysis, the atypical antipsychotic clozapine was associated with the least loss of gray matter of any medication in the included studies.

*Editor's Note: This study is important because it adds to findings questioning the conclusions of a large National Institute of Mental Health-sponsored study known as CATIE and a meta-analysis by John Geddes published in the journal *BMJ* in 2000, in which he wrote that "There is no clear evidence that atypical antipsychotics are more effective or better tolerated than conventional (first generation) antipsychotics."*

*People taking first-generation antipsychotics exhibit more extrapyramidal side*

*effects (which include muscle spasms, restlessness, or rigidity) and have a higher incidence of tardive dyskinesia. Patients with bipolar disorder are even more prone to tardive dyskinesia than patients with schizophrenia; some 20–30% of people with bipolar disorder exposed to first-generation antipsychotics get this side effect.*

*First-generation antipsychotics can exacerbate bipolar depression, while two atypical antipsychotics, quetiapine and lurasidone, have actually been approved by the Federal Drug Administration (FDA) for the treatment of bipolar depression.*

*Now the meta-analysis by Vita and colleagues suggests that the different classes of antipsychotics have a differential effect on gray matter loss in schizophrenia. This would be consistent with findings that some atypical antipsychotics, such as quetiapine and lurasidone, increase the neuroprotective factor BDNF in the hippocampus and prevent stress from decreasing BDNF, while the first-generation antipsychotic haloperidol exacerbates the effects of stress, further decreasing BDNF in the hippocampus.*

*For all of these reasons, the atypical antipsychotics now appear to be preferable to first-generation antipsychotics for patients with bipolar disorder, and perhaps also for those with schizophrenia.*

*(A note about potential conflict of interest. This editor, Robert M. Post, sometimes serves as a paid speaker for the drug companies AstraZeneca, which makes quetiapine; Sunovion, which produces lurasidone; and Validus, which makes the long-acting carbamazepine drug Equetro. His opinion (expressed in the BNN and elsewhere) that the atypical antipsychotics are preferable to older antipsychotics predated his paid work for these companies.*

*New data suggesting that atypical antipsychotics are better than first-generation antipsychotics in terms of efficacy in bipolar depression, incidence of tardive dyskinesia, effect on BDNF, and now gray matter loss in schizophrenia have emerged since these speaking engagements began.)*

## Animal Studies Shed Light on Molecular Biology of Depression

Dysregulation of the brain in early life can have lasting effects, and the effects of stress and depression can also accumulate. At the 2015 meeting of the Society of Biological Psychiatry, researcher Huda Akil explained that behavioral pathology can “take on a life of its own, leading to deteriorating course of illness and treatment resistance.” She illustrated how preclinical work in animals can help clarify the molecular biology of depression and develop new targets for therapeutics.

### Early Life Experiences Have Long-Term Effects

Akil discuss studies of rodents in which she used new molecular genetic techniques to increase the number of glucocorticoid receptors in the hippocampus early in life (prior to weaning). Glucocorticoid receptors mediate the effects of the stress hormone cortisol in people and corticosterone in rodents. More receptors help shut off cortisol secretion after a stressful event. **People with post-traumatic stress disorder (PTSD) have high levels of glucocorticoid receptors while people with depression have low levels, leading to over-secretion of cortisol in depression.**

The increased glucocorticoid receptors led to a long-term increase in anxiety behaviors and response to stimulants. When Akil carried out the same manipulation on rats that had already been weaned, it had no long-lasting effects, showing that there is a vulnerability window for some long-lasting effects on behavior.

### CLOCK Genes and Circadian Rhythms

Akil also studied CLOCK genes in rodents. These genes, including BMAL-1, Per 1, Per 2, and Per3, play

a role in circadian rhythms, and their transcription induces these 24-hour cycles. In rodents who were induced into a depression-like state, the CLOCK genes were dysregulated and did not correspond to normal circadian rhythms. These data show that depressive states can induce changes in CLOCK genes and circadian rhythms. Others have shown the converse, that abnormal CLOCK genes can induce behavioral abnormalities including mania-like behaviors.

### Fibroblast Growth Factor

Levels of fibroblast growth factor 2 (FGF2) in the hippocampus are low in people with depression. In rodents, FGF2 inhibits anxiety. Decreases in FGF2 are seen in the hippocampus of animals in a depression-like state following repeated defeat by a larger animal. It appears that FGF2 is an endogenous antidepressant (i.e. one that is produced by the brain). When the rodent brain is manipulated to eliminate FGF2, the animals become anxious.

In addition, animals bred to have high stress, low social responsivity, and resistance to new learning also have low FGF2. Treatment with FGF2 reversed these behavioral abnormalities and also increased the production of new neurons. **For the stressed rats, receiving FGF2 on their second day of life increased new neuron production, decreased anxiety, decreased proneness to social defeat stress and increased the bonding hormone oxytocin in the amygdala into adulthood.**

FGF2 had no effect on rats bred for low stress and high social responsivity,

indicating that it only worked for the rats that needed it. Akil compared FGF2 to “personalized medicine for rats.”

Defeat stress affects the way genes are transcribed, and FGF2 was able to reverse one of these specific transcriptional effects, suggesting it could potentially ameliorate some of the long-lasting effects of stress and depression.

“Behavioral pathology can take on a life of its own, leading to deteriorating course of illness and treatment resistance.”

### The Human Brain

Akil also studied the brains of people who had died of depression, bipolar disorder, or schizophrenia. In bipolar disorder, the nucleus accumbens, the

reward center of the brain, was enlarged.

In contrast, Akil described the brains of those people who had died with depression as being “low on fertilizer.” That is, they showed less cell growth, less production of new neurons, more abnormalities in cell shape, and more cell death. Akil said that by the time someone is severely ill, the pathology is all over the brain. The changes Akil saw in the brains of people who were depressed are also consistent with data indicating that several neuroprotective factors, including BDNF and VEG-F, are low in the frontal cortex and the hippocampus of depressed people (while BDNF is high in the nucleus accumbens).

*Editor’s Note: Akil’s studies if humans and animals shed light on how biochemical changes associated with childhood adversity can increase vulnerability to illness. One day these findings may reveal new antidepressant mechanisms that lead to the development of better treatments.*



## Most SSRIs Free of Birth Defect Risk Early in Pregnancy, Exceptions: Fluoxetine and Paroxetine

A large study of women who took selective serotonin reuptake inhibitor (SSRI) antidepressants in the month before pregnancy and throughout the first trimester suggests that there is a smaller risk of birth defects associated with SSRI use than previously thought, though some risks were elevated in women who took paroxetine or fluoxetine.

The 2015 study, by Jennita Reefhuis and colleagues in the journal *BMJ*, investigated the drugs citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, and examined birth defects that had previously been associated with SSRI use in smaller studies. The participants were 17,952 mothers of infants with birth defects and 9,857 mothers of infants without birth defects who had delivered between 1997 and 2009.

Sertraline was the most commonly used SSRI among the women in the

study. **None of the birth defects included in the study were associated with sertraline use early in pregnancy. The study found that some birth defects were 2 to 3.5 times more likely to occur in women who had taken fluoxetine or paroxetine early in their pregnancies.**

Five different birth defects, while uncommon, were statistically linked to paroxetine use: anencephaly (undersized brain), heart problems including atrial septal defects and right ventricular outflow tract obstruction defects, and defects in the abdominal wall including gastroschisis and omphalocele. Two types of birth defects were associated with fluoxetine use: right ventricular outflow tract obstruction defects and craniosynostosis (premature fusion of the skull bones). Absolute incidence of these defects was also low.

## Genetic Inheritance Is Not Everything

*J. Craig Venter, pioneering genetic scientist responsible for sequencing the human genome in 2001, says:*

“Human biology is actually far more complicated than we imagine. Everybody talks about the genes that they received from their mother and father, for this trait or the other. But in reality, those genes have very little impact on life outcomes. Our biology is far too complicated for that and deals with hundreds of thousands of independent factors. **Genes are absolutely not our fate.** They can give us useful information about the increased risk of a disease, but in most cases they will not determine the actual cause of the disease, or the actual incidence of somebody getting it. Most biology will come from the complex interaction of all the proteins and cells working with the environmental factors, not driven directly by the genetic code.”

## RTMS and Other Treatments for Depression in Pregnancy

At the May meeting of the Society of Biological Psychiatry, researcher Deborah Kim gave a talk on the use of repeated transcranial magnetic stimulation (rTMS) for depression in women who are pregnant. In rTMS treatment, an electromagnetic coil is placed against the side of the forehead and magnetic pulses that can penetrate the scalp are converted into small electrical currents that stimulate neurons in the brain. Kim had recently completed an open study of rTMS in pregnant women, in which 70% of the women responded to rTMS. In another controlled randomized study of 30 women (also by Kim), 75% responded to active rTMS and 50% responded to a sham procedure. None of the women included had problems with the fetus or during delivery.

RTMS offers an alternative to women who are reluctant to take antidepressants

during pregnancy. Kim cited data by Lee S. Cohen and colleagues in which **women taking antidepressants show a 68% relapse rate if they stop taking these medications during pregnancy compared to a 26% relapse rate among those who continue taking antidepressants during pregnancy.**

Concerns about antidepressants' potential effects on a fetus may have been overemphasized. Kim summarized the literature on antidepressants in pregnancy, concluding that there is a preponderance of evidence that antidepressants are safe for the mother and fetus, with few serious effects having been observed. Some researchers have been concerned about risks of persistent pulmonary hypertension or autism among offspring of women who took antidepressants during pregnancy, but studies have

shown that the absolute risk of either is small. See above for a new large and comprehensive study in which most SSRIs showed no link to birth defects.

*Editor's Note: For mild depression during pregnancy, exercise and psychotherapy might be optimal, along with folate and vitamin D3. For moderate depression, omega-3 fatty acids might also be helpful, but it now appears that rTMS would be less risky than electroconvulsive therapy (ECT), which in the past has been a typical recommendation for pregnant women, but which exposes the fetus to the effects of anesthesia and seizure. In her summary Kim recommended that women with a pattern of recurrent depression continue antidepressant treatment, especially since a mother's depression itself poses non-trivial risks to the fetus.*

## RTMS Study Identifies Glutamate as a Biomarker for Depression Treatment

At the 3rd Annual Meeting of the Transcranial Magnetic Stimulation Society, Canadian researcher Frank MacMaster discussed his study of repeated transcranial magnetic stimulation (rTMS) in 50 children with depression. RTMS is a non-invasive procedure in which an electromagnetic coil is placed against the side of the forehead and magnetic pulses that can penetrate the scalp are converted into small electrical currents that stimulate neurons in the brain. The study was designed to identify biomarkers, or characteristics that might indicate which patients were likely to respond to the treatment. All of the patients received rTMS at a frequency of 10 Hz. Using magnetic resonance spectroscopy (MRS) technology, MacMaster found that **children who responded well to rTMS treatment had low levels of the neurotransmitter glutamate at the beginning of the study, but their**

**glutamate levels increased as their depression improved. Children who didn't improve had higher glutamate levels at the beginning of the study, and these fell during the rTMS treatment.**

MacMaster hopes that glutamate levels and other biological indicators such as inflammation will eventually pinpoint which treatments are likely to work best for children with depression. At the meeting, MacMaster said that in Canada, only a quarter of the 1,200,000 children with depression receive appropriate treatment for it. Very little funding is devoted to research on children's mental health, a serious deficit when one considers that most depression, anxiety, attention deficit hyperactivity disorder (ADHD), bipolar disorder, oppositional behavior, conduct disorder, and substance abuse begins in childhood and adolescence, and early onset of these illnesses has been repeatedly linked to poorer outcomes.

*Editor's Note: The strategy of identifying biomarkers is an important one. MacMaster noted that this type of research is possible due to the phenomenal improvements in brain imaging techniques that have occurred over the past several decades. These techniques include magnetic resonance imaging (MRI) to a resolution of 1 mm; functional MRI; diffusion tensor imaging (DTI), which can depict the connectivity of white matter tracts; and spectroscopy, which can be used to identify chemical markers of neuronal health and inhibitory and excitatory neurotransmitters, and analyze membrane integrity and metabolic changes. These methods provide exquisite views of the living brain, the most complicated structure in the universe. The biomarkers these techniques may identify will allow clinicians to predict how a patient will respond to a given treatment, to choose treatments more rapidly, and to treat patients more effectively.*

## Low Oxytocin Linked to Depression in Moms

At a panel at the 2015 meeting of the Society of Biological Psychiatry, researcher Andrea Gonzales described her team's study of mechanisms related to postpartum depression and the bonding hormone oxytocin. In the study of 26 women at eight months postpartum, the team examined whether there were connections between a mother's levels of oxytocin at baseline and after interacting with her child, her mood symptoms, and whether she was mistreated in childhood.

Those women who scored low on a history of maltreatment in childhood had bigger increases in oxytocin in their blood and saliva after interacting with their children. Those with high trauma scores but low levels of depression also saw big boosts in oxytocin after seeing their children. Those women who had both a history of trauma in childhood and current depressive symptoms

did not get as big a boost of oxytocin after interacting with their children.

Gonzales and colleagues concluded that postpartum depression is linked to dysregulation of oxytocin levels, and that a history of trauma in the mother's childhood can make this worse.

The researchers hope that these findings may make it easier to identify which women are at risk for postpartum depression, and that they may point to possible treatments in the future.

**Postpartum depression is a problem for about 13% of mothers in the year after they give birth, and mother-child bonding may be disturbed if a mother is depressed.**

One way to foster better bonding between a depressed mother and her newborn is to use video feedback. A mother views video of herself interacting with her child while a trained professional helps her identify opportunities for greater physical contact.

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## Personalizing Transcranial Magnetic Stimulation for Better Results

At the 3rd Annual Meeting of the Clinical TMS Society this past May, this editor (Robert M. Post) discussed remission rates for repeated transcranial magnetic stimulation (rTMS), which at 30% leave room for improvement. It may be possible to personalize treatment parameters to achieve better success in individual patients.

**RTMS is a non-invasive procedure in which a magnetic coil placed near a patient's head delivers electrical currents to their brain.** High frequency stimulation (10Hz to 20Hz) increases brain activity as measured on PET scans, and low frequency stimulation (1Hz) decreases it, so it might be possible to choose the best frequency for an individual patient based on their baseline level of brain activity. If this is not possible, patients who fail to respond to one frequency might be switched over to the other frequency.

RTMS can be given during active positive cognitive behavioral therapy.

Patients primed with positive thoughts and feelings may find that rTMS enhances these. (Some practitioners in the audience indicated that they already combine therapy and rTMS and have seen good results).

RTMS might enhance extinction learning, or the breaking of a habitual way of thinking, as it stimulates the media prefrontal cortex, a critical area for new learning. D-cycloserine, a partial glutamate agonist, has been shown to enhance extinction, and since rTMS releases glutamate and BDNF, it might also do the same.

It may also be possible to use rTMS in conjunction with medications (such as valproate) that affect epigenetic changes on the histones around which DNA is wrapped (because valproate is a histone de-acetylase inhibitor, preventing the removal of acetyl groups from the histones and allowing them to be transcribed more easily). Valproate enhances extinction

learning in animals, so the stimulation of the medial prefrontal cortex and the increase in BDNF and glutamate that occur with rTMS may interact to potentiate this extinction learning.

One could also envision using rTMS to enhance learning during the memory re-consolidation window that opens 5 minutes to an hour after a person actively recalls old memories, and which can lead to more permanent memory alterations in anxiety disorders, post-traumatic stress disorder (PTSD), and substance abuse.

**Since patients are awake and able to talk during rTMS, making use of evoked thoughts and memories specifically for a given patient may lead to enhanced clinical effects,** because these neural pathways are more selective activated and potentiated, leading to what is called experience-dependent neuroplasticity.

## Deep RTMS May Reduce OCD Symptoms

Obsessive compulsive disorder (OCD) occurs in about 2% of the population worldwide. Selective serotonin reuptake inhibitor (SSRI) antidepressants are the most commonly used treatment for OCD, but not all patients respond adequately to them.

At the 2015 meeting of the Transcranial Magnetic Stimulation Society, researcher Joseph Zohar presented evidence that deep repeated transcranial magnetic stimulation (rTMS) targeted over the medial prefrontal cortex may reduce OCD symptoms. In rTMS treatment, an electromagnetic coil is placed against the patient's head and magnetic pulses that can penetrate the scalp are converted into small electrical currents that stimulate neurons in the brain. In Zohar's study, patients with OCD were randomized to receive deep rTMS at frequencies of either 20 Hz or 1 Hz, or a sham procedure. **The 20 Hz rTMS resulted in a 28% reduction in OCD symptoms** compared to the

other two groups, indicating that the 20 Hz treatment had a large effect size.

In addition to the rTMS procedures, all patients also received cognitive behavioral therapy, high doses of SSRIs, and relapse prevention training.

*Editor's Note: It is interesting that 20 Hz rTMS, which activates the prefrontal cortex, was more effective than 1 Hz, which decreases activity there. Other attempts to treat OCD have focused on suppressing frontal-striatal-thalamic circuits, which are overactive in the disorder. Since the medial prefrontal cortex is an important area for the new learning required for the extinction of anxiety symptoms in a variety of disorders, increasing activity in this medial prefrontal target area with 20 Hz may activate that extinction process allowing new learning rather than nonspecifically suppressing hyperactive frontal-striatal-thalamic circuits as 1 Hz rTMS would do.*

## RTMS in the Elderly and After ECT

At the 2015 meeting of the Society of Biological Psychiatry in May, researcher Daniel Blumberger reported to this editor (Robert M. Post) that he has found repeated transcranial magnetic stimulation (rTMS) to be effective for depression in late life. Blumberger noted that **it may be necessary to use higher intensity stimulation (i.e. at 120% of motor threshold instead of the usual 110% of motor threshold) in the elderly in order to overcome the gap between the skull and the brain, which can grow with age due to brain atrophy.**

Blumberger has also successfully used rTMS as a followup treatment to a successful course of electroconvulsive therapy (ECT), administering rTMS twice a week for up to 66 treatments in a given patient in order to maintain remission of their depression.



## US More Restrictive Than Canada in Access to RTMS

At the 2015 meeting of the Transcranial Magnetic Stimulation Society, Linda Carpenter, an American researcher who specializes in repeated transcranial magnetic stimulation (rTMS), a method of treating depression by using a magnetic coil placed near the scalp to stimulate neurons, compared notes with Jeff Daskalakis, a Canadian researcher who also studies rTMS.

Carpenter described the limited approval rTMS enjoys in the US. **RTMS has been approved by the Federal Drug Administration for the treatment of unipolar depression under very limited parameters (only at a frequency of 10Hz). RTMS has limited availability in the US, and many healthcare companies do not cover it.** Providers face scrutiny of study recruitment practices and recordkeeping by insurers and the Joint Commission (formerly the Joint Commission of Accreditation of Healthcare Organizations), which assesses healthcare quality.

In contrast, Daskalakis and his Canadian colleagues can and do use rTMS to treat a broader range of illnesses including bipolar disorder. In Canada rTMS is used to treat unipolar depression, schizophrenia, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), and clinicians can adjust the parameters to treat adolescents and the elderly.

The situation in the US is unfair. Because rTMS has not been approved for the treatment of bipolar disorder, Carpenter and other clinicians in the US are unable to treat bipolar depression even though a wide range of experts and published studies report that rTMS is as effective (or possibly even more so) for patients with bipolar depression than for those with unipolar depression.

Few treatments are available for bipolar depression. The discrepancy is even sadder when one considers

that there are already more than 20 FDA-approved antidepressants that can be used to treat unipolar depression, but only three approved medications for bipolar depression. Bipolar depression is an orphan illness, which lacks a powerful voice advocating for more treatment research about optimal therapeutic strategies.

In 2013, the National Institute for Mental Health (NIMH) launched a new initiative known as Research Domain Criteria (RDoC), in the hopes of adjusting the framework for research on mental disorders to incorporate genetics, imaging, and other data into the diagnosis and description of illnesses, as opposed to an earlier system that relied mainly on behavioral reports.

One concern about this change at the NIMH, which funds much of the research that leads to Federal Drug Administration-approved treatments, is that clinical treatment studies to collect data on particular illnesses or

in particular populations (e.g. bipolar illness in children) could lose out to studies focused on the collection of data on a broad range of symptoms involved in a spectrum of illnesses, particularly studies of biomarkers, or biological measurements that indicate the presence of an illness.

This change may make it difficult for researchers to find funding for collection of data about therapeutics for specific illnesses like bipolar disorder, limiting the already sparse funding for the study of bipolar disorder in children and adults. Bipolar disorder is a complicated illness that can differ from one person to the next, and may include depression, hypomania, mania, mixed states, rapid cycling, comorbid anxiety or substance abuse disorders, and cognitive impairment. This diversity of presentation may make new drug exploration under the new framework even more tenuous for patients with bipolar disorder.

## Studies of Medications and RTMS Lacking in Children and Adolescents

At the 2015 meeting of the Transcranial Magnetic Stimulation Society in May, researcher Stephanie Ameis discussed the dearth of medication studies in children, particularly for depression but also for schizophrenia and autism spectrum disorders, which share the symptom of impaired executive functioning, which can include skills such as planning and problem solving.

Ameis noted that in a literature review, **there were a total of 1046 controlled pharmacological treatment studies in adults compared to only 106 in children**, which reflects a relative absence of treatment knowledge, especially for depression (where there were 303 studies in adults versus only 17 in children) and

bipolar disorder (where there were 174 studies of adults and 24 of children).

Ameis then reviewed the few studies of rTMS for depression in young people. She identified several series with only a total of 33 children and adolescents who had been treated with rTMS. She is beginning to study rTMS in patients with high-functioning autism (40 patients aged 16 to 25 have been randomized in her study). Ameis also described a 2013 study of rTMS in which patients with schizophrenia showed improved performance on a test of working memory published by Mera S. Barr and colleagues in the journal *Biological Psychiatry*. Ameis cited this as a rationale for studying rTMS's effect on cognitive performance in people with autism.

## Chronic Drug Use and Recovery

George Koob, Director of the National Institute on Alcohol Abuse and Alcoholism, discussed the neuroscience of chronic drug use at the 2015 meeting of the Society of Biological Psychiatry. His basic message was that **chronic drug use is associated with A) loss of the reward value of the drug and B) a progressive increase in dysphoria and stress when off the drug. Both factors drive craving and drug seeking.**

Access to high as opposed to moderate doses of a drug lead to an escalation in drug intake, and associated persistent increases in withdrawal dysphoria, which Koob called “the dark side.”

Koob explained that a month of detoxification is not sufficient, and that people quitting a drug need more time to let dopamine increase

and to let levels of corticotropin releasing factor (CRF), which drives the anxiety and dysphoria of withdrawal, normalize. He stressed that for people addicted to opiates, it is important to taper levels of the drug to minimize withdrawal symptoms.

In addition to CRF, dynorphin also plays a role in chronic drug abuse. This opiate peptide acts at kappa opiate receptors and is associated with anxiety, dysphoria, and psychosis as opposed to morphine, which acts at mu opiate receptors and is associated with euphoria and decreased pain. Koob found that administration of the kappa opiate antagonist norbinaltorphimine (nor-BNI) blocks dose escalation of methamphetamine and brings abstinence-related compulsive drug seeking back to baseline.

## Chronic Stress “Makes You Stupid”

At the 2015 meeting of the Society of Biological Psychiatry, Bruce McEwen, professor of neuroscience at Rockefeller University, gave an overview of stress’s effect on the brain. He explained that “chronic stress makes you stupid,” and said that while one can compensate for the effects of chronic stress, one cannot reverse them.

**Short-term stress can be helpful, increasing cortisol, with generally positive effects. When stress lasts longer, the chronic increase in cortisol starts to cause problems: impaired memory, endangered neurons, decreased bone and muscle, and metabolic abnormalities.**

McEwen said that chronic stress shrinks the dendrites in the medial pre-

frontal cortex and the hippocampus. A healthy prefrontal cortex is necessary for new learning and memory.

Chronic stress also enlarges the orbital frontal cortex and the amygdala. An oversized orbital frontal cortex can induce habits, making a person susceptible to repetitive thinking and obsessions, addictions, or other compulsive behavior. An oversized amygdala can provoke fear and anxiety.

*Editor’s Note: Stress can make people more susceptible to substance abuse, which in turn leads to losses in cortical control. As noted in previous BNNs, resilience to stress can be taught and practiced.*

## Another Expert’s Opinion on PTSD

*Continued from Page 1*

The SSRIs shut down the firing of noradrenergic (NE) and serotonergic (5HT) neurons. Sattin sees the mirtazapine as important in reversing this shut-down. Mirtazapine blocks the inhibitory alpha-2 autoreceptors on these neurons and thus increases their firing. Because mirtazapine also blocks 5HT-2 receptors and H-1 receptors (with antihistamine effects), it can be quite sedating. The sedation can help patients with the profound sleep disturbance that typically accompanies PTSD.

*Editor’s Note: It is important to remember that Sattin’s opinions reported to this editor at the meeting are just that, i.e. the personal treatment preferences of one individual clinician.*

*Most information provided in the BNN is preliminary and based on abstracts, presentations at scientific meetings, and anecdotal reports, which cannot fully reflect the risk to benefit ratio of pursuing any particular treatment.*

*A patient’s treating physician, who is medically responsible for their care, must research and confirm the appropriateness of any treatment. What one doctor might recommend, another might condemn.*

*In this regard it is interesting to note the dramatic differences in the PTSD treatment strategies of Sattin versus researcher David Bakish, whose recommendations we described in 2014. Bakish offered an extensive, complicated treatment sequence using multiple drugs to target different symptoms of PTSD, and none of the drugs he typically uses overlap with those used by Sattin.*

**See page right for an opportunity to rate children’s mood or behavioral symptoms.**

## Join the Child Network!

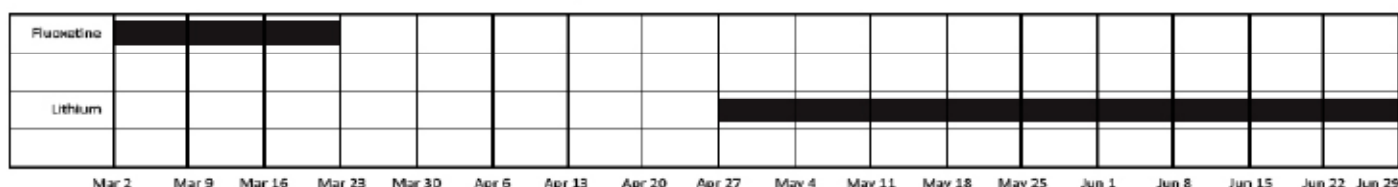
### For Children with Mood and Behavioral Disorders

We are reaching out to you to let you know about a new study that the Bipolar Collaborative Network is implementing called the Child Network. Our goal is to **foster collective knowledge about childhood mood and behavioral disorders by acquiring data about children who have or may be vulnerable to childhood-onset depression and bipolar disorders and associated conditions**. Depressive, oppositional, and bipolar disorders as well as anxiety in very young children have not been well studied for their course and for treatment effectiveness and tolerability. Our goal is to compile and analyze the varied treatments for children with these disorders. How well a child responds to a specific treatment may provide new preliminary information of use to others, and assist parents and physicians in assessing treatment options.

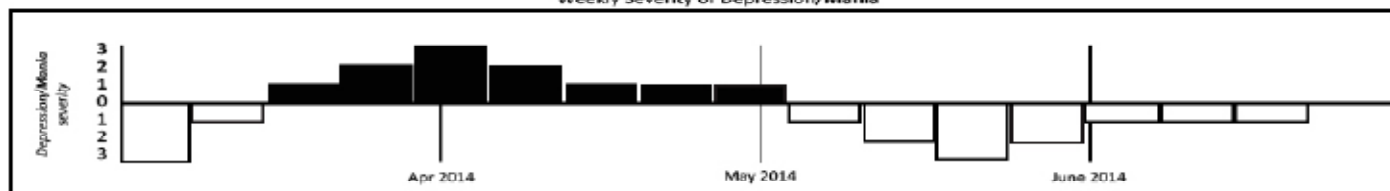
The Child Network is specifically for parents of children ages 2 to 12 who have few symptoms, minor (prodromal) symptoms, or the full onset of a psychiatric illness prior to age 13. Participating in the Child Network will primarily involve a confidential, few-minute parental assessment of their child every Sunday evening, the listing of medications, other treatments, and any side effects that occurred in the prior week. There will also be a short demographic questionnaire and a once-a-year more detailed symptom checklist. This study does not involve new treatments. The network is only meant to document what is currently being done in the community.

We believe that this network will also benefit its participants. **Parents will be able to print out results of the ongoing brief weekly ratings in graphic form so that the course of the child's symptoms and response to treatment can easily be visualized, as illustrated below.**

**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 encourage you to visit [www.bipolarnews.org](http://www.bipolarnews.org) and click on the tab for Child Network to learn more about the study and to access the informed consent documents.

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