

Bipolar Network News

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Omega-3 Fatty Acids Improve Mood In Youth with Bipolar Depression

Children who have a parent with bipolar disorder are at risk for bipolar illness, but it may first present as depression. Treating these children with antidepressants has the risk of bringing on manic episodes. Researchers are looking for treatment options for youth at risk for bipolar disorder.

Robert McNamara and colleagues found that **12 weeks of omega-3 fatty acids (2,100 mg/day) significantly improved response rates in medication-free youth ages 9–20 years compared to placebo (64% versus 36%)**. Omega-3 fatty acids but not placebo also reduced the activa-

tion of limbic structures in the brain (the left parahippocampal gyrus) in response to emotional stimuli.

Editor's Note: These data add to the literature on the positive effects of 1–2 grams of omega-3 fatty acids in depression. Given the safety of omega-3 fatty acids and the ambiguous effects of antidepressants in bipolar depression, omega-3 fatty acids would appear to a good alternative, especially since the FDA-approved atypical antipsychotics (quetiapine and lurasidone) are not approved for bipolar depression in people under age 18.

People with High Inflammation Respond Best to EPA Omega-3 Fatty Acids in Depression

There is some evidence that omega-3 fatty acid supplements can reduce depression, but researchers are trying to clarify which omega-3s are most helpful, and for whom. A new study suggests that depressed people with higher inflammation may respond best to EPA omega-3 fatty acids compared to DHA omega-3 fatty acids or placebo.

Researchers led by M.H. Rapaport divided people with major depressive disorder into “high” and “low” inflammation groups based on their levels of the inflammatory markers IL-1ra, IL-6, high-sensitivity C-reactive protein, leptin, and adiponectin. Participants were randomized to receive eight weeks of treatment

with EPA omega-3 supplements (1060mg/day), DHA omega-3 supplements (900mg/day), or placebo.

While overall treatment differences among the three groups as a whole were negligible, the high inflammation group improved more on EPA than on placebo or DHA, and more on placebo than on DHA.

Editor's Note: These data add to a study by Rudolph Uher et al. in which people with high levels of C-reactive protein responded better to the tricyclic antidepressant nortriptylene, while those with low levels of the inflammatory marker responded better to the selective serotonin reuptake inhibitor antidepressant escitalopram.

Omega-3 Fatty Acids Improve Attention in Boys

A new study finds that omega-3 fatty acid supplementation improves attention in boys both with and without attention deficit hyperactivity disorder (ADHD). The study by Dienke J. Bos and colleagues in the journal *Neuropsychopharmacology* included 40 boys (aged 8–14) with ADHD and 39 demographically matched controls. Participants were given 10 g per day of margarine supplemented with either omega-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) or placebo.

The children who received EPA/DHA supplementation showed improvements in attention (as rated by parents) compared to those who received placebo. Improvement was greater in the children with ADHD. Supplementation did not affect cognitive control or brain activity on functional magnetic resonance imaging (fMRI). Those boys who received omega-3s showed higher DHA levels on followup.

Also in this issue:

Effective Treatments Go Beyond Medication	p. 2–3
Mother's Mood and Behavior Affect Kids' Mental Health	p. 3
Treatments Updates	p. 4–7
Bipolar Disorder in Primary Care	p. 6
Risk Factors for Illness	p. 7–10
Predictors of Bipolar Disorder in Children	p. 10

Collaborative Care and Education Reduces Bipolar Depression

There is increasing evidence that patients with bipolar disorder benefit from special programs or clinics designed to teach them skills to cope with their illness. A 2015 article by Trijntje Y.G. van der Voort and colleagues in the *British Journal of Psychiatry* evaluated the effectiveness of a Dutch program that provided collaborative care to people with bipolar disorder. One hundred thirty-eight patients in an outpatient clinic were randomized to receive either treatment as usual or a program of nurse-provided

collaborative care that included psychoeducation, problem-solving treatment, systematic relapse prevention contracts, and monitoring of outcomes. These services were managed by mental health nurses.

Those patients who received collaborative care had significantly less time with depressive symptoms at the 6-month and 12-month marks, and less severe depressive symptoms at 12 months (all findings with p values less than .01). There was no significant difference in manic symptoms

or treatment adherence. The authors suggest that collaborative care improves treatment for people with bipolar disorder, especially depression, which is most closely linked to impaired quality of life and disability.

Editor's Note: Given this study and about a dozen others like it, it is time to conclude that psychoeducation and other components of collaborative care noted here are critical to the long-term management of bipolar disorder. Patients and their family members should insist that this be a part of routine care.

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.

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 to or spoken for Abbott, Astra Zeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Jansen, and Pfizer.

The opinions expressed in the *BNN* are solely those of the editors, and do not represent the views of any scientific entity or foundation.

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Specialty Treatment Effective for First Episodes of Psychosis

A study published online in the journal *Psychiatric Services* comparing **a specialty clinic that provides medication, family education, cognitive-behavioral therapy (CBT), and case management to improve employment and educational outcomes** with treatment as usual for people in a first episode of psychosis found that the specialty treatment was associated with fewer and shorter hospital stays and better vocational engagement during one year of follow-up.

Most participants were referred to the study from inpatient psychiatric units. Those randomly assigned to receive treatment as usual typically did so in outpatient treatment settings. Those randomly assigned to the specialty treatment group joined the Specialized Treatment Early in Psychosis (STEP) program at the Connecticut Mental Health Center, where they could choose from any of the available interventions.

Other studies have found that comprehensive intervention encompassing psychoeducation, family therapy and other services can reduce psychotic symptoms. The authors of this study, Vinod H. Srihari and colleagues, concluded that a US public-sector model of early intervention in psychotic illness could be both feasible and effective.

Editor's Note: In the British Journal of Psychiatry in 2013, Kessing et al. demonstrated even more dramatic and persistent benefits (for at least 6 years) of 2 years of specialty clinic care versus treatment as usual for patients with a first hospitalization for mania (many of whom were also psychotic). Together these two articles indicate the extreme importance of getting off to a good start in the management of major psychiatric illness. Such specialty programs are desperately needed for better management of childhood-onset mania.

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Intervention in Early Childhood Can Help Children Cope with Stress

Enduring stressful life events in childhood can affect children long-term. Children who experience neglect can show increased levels of cortisol, a stress hormone. Family interventions can reduce these levels, and a new study shows that the impact of these interventions can be lasting.

The study, by Kristin Bernard and colleagues in the journal *JAMA Pediatrics*, included 115 children whose families had been referred to Child Protective Services after allegations of neglect. After an incident of neglect in early childhood, **the families received either an experimental intervention called ABC (focused on increasing parental nurturance to child distress, increasing synchronous interactions, and decreasing frightening parental behavior) or a control intervention (which provided educational information about child development).**

When the children reached pre-school age about three years later, the researchers collected the children's cortisol levels at waking and bedtime on three different days. **The children whose families received the ABC intervention had more typical cortisol levels than those whose families had received the control intervention.**

The ABC children had higher morning cortisol, with a steeper decline throughout the day, compared to a more blunted cortisol rhythm in the control group children. These patterns resembled differences in the two groups observed three months after the initial intervention. The authors concluded that the ABC intervention has long-term effects on children's physiological stress system, helping them maintain health and adjustment.

Mother's Treatment for Depression Can Affect Children's Symptoms

Studies have found that when a depressed mother's symptoms remit, her children are less likely to show psychiatric symptoms. A new study by Myrna M. Weissman and colleagues in the *American Journal of Psychiatry* randomized 76 mothers to treatment with escitalopram, bupropion, or a combination of the two, and assessed the impact of the mothers' treatment on their 135 children (aged 7–17).

There were no significant differences in the mothers' symptoms or remission, but **children's depressive symptoms and functioning improved more if their mothers received (only) escitalopram.** Only in that group was a mother's improvement associated with her children's improvement.

Mothers in the escitalopram group reported greater improvement in their ability to listen and talk to their children compared to the mothers in other groups, and the children of the mothers in the escitalopram group reported that their mothers were more caring.

Children of mothers with low negative affect improved significantly, while children of mothers with high negative affect only improved if their mothers were in the escitalopram group.

The authors suggest that for a mother's improvement to help her children's symptoms, her anxious distress and irritability must be reduced, and these may be better targeted with escitalopram than bupropion.

Maternal Warmth Does Not Negate the Effects of Corporal Punishment on Their Children

New research shows that expressions of maternal warmth following corporal punishment do not reduce children's anxiety, and may even increase it.

The study by Jennifer E. Lansford and colleagues was published in the *Journal of Clinical Child & Adolescent Psychiatry*. The researchers interviewed over a thousand children aged 7–10 and their mothers about what type of physical punishment occurs in their family, and about anxiety and aggression in the children. They followed up again after one and two years.

The study took place in eight countries: China, Colombia, Italy, Jordan, Kenya, the Philippines, Thailand, and the United States.

In general, corporal punishment increased anxiety in the children, while maternal warmth decreased it. How warmth and physical punishment interacted depended on the country.

Anxiety increased over time in families where the mothers were high on both corporal punishment and warmth.

Lansford and colleagues wrote that it might be "simply too confusing and unnerving for a child to be hit hard and loved warmly all in the same home."

The researchers suggest that parents use nonphysical ways to promote desirable behavior in their children, including putting younger children in time-out and requiring teenagers to participate in activities that help others.

See page 11 for information about a new study of children at risk for bipolar disorder.

Antipsychotics That Worked for A First Episode May Not Work As Well for a Second Episode

In new research by Ofer Agid and colleagues, patients in their first schizophrenic episode who reached remission in response to one of two antipsychotic medications (risperidone or olanzapine) and relapsed due to medication non-adherence were re-treated with the same medication regimen that had brought about remission. **Reinitiating the same treatment was not as successful in bringing about remission of the patients' second psychotic episodes.**

Patients showed different types of trajectories in their first remission, from immediate to gradual improvement, and these predicted parallel trajectories of their treatment response during the second episode, though the muted response to antipsychotics existed across the board. Dopamine is the main target of antipsychotic treatments, but its role in schizophrenia is not straightforward, and Agid and

colleagues stress that response and relapse are multidimensional processes.

Editor's Note: These data are consistent with the research of J.A. Lieberman and colleagues fifteen years ago, which showed that response to antipsychotic treatment is poorer in successive episodes of psychosis. The findings are also consistent with the idea of episode sensitization in mood disorders, developed by this author (Robert Post). Episode sensitization refers to the case in which greater numbers of prior depressions or manias are associated with faster relapse and a greater degree of treatment resistance.

The data raise major doubts about the common practice of quitting medications to see if remission can be maintained without them. There are dozens of studies in patients with schizophrenia showing that continuous treatment is more effective than intermittent treatment.

Meta-Analysis Shows Effectiveness of Ketamine for Bipolar and Unipolar Depression

Ketamine, an anesthetic sometimes used intravenously in the treatment of depression, can bring about rapid onset of antidepressant effects. A new meta-analysis by researcher Michael Bloch and colleagues presented at a recent conference showed that **ketamine's maximum antidepressant effects occur within one day of administration, and its effects remain significant (compared to control conditions) one week following infusion.** Ketamine's effects were diminished in patients taking other medications. There was a trend for better response in patients with bipolar disorder than with unipolar disorder.

Bloch and colleagues analyzed eight earlier studies including a total of 180 participants. In each study, ketamine had been compared to a

control condition, either an infusion of saline solution or of midazolam, which mimics ketamine's sensory effects but does not have antidepressant effects. The researchers are calling for more meta-analyses of ketamine studies to determine which patients respond best to ketamine and how to sustain ketamine's effects.

Editor's Note: In another poster presented at the same conference, James Murrough reported that patients with slower processing speed responded best to ketamine. Other findings have shown that those with a history of alcohol abuse and a common genetic variant of brain-derived neurotrophic factor (BDNF), the val-66-val allele of proBDNF, are more likely to respond to ketamine.

Transcranial Direct Current Stimulation May Improve Cognition in Schizophrenia

A recent study by Robert Smith and colleagues studied the use of transcranial direct current stimulation (tDCS) in patients with schizophrenia. TDCS is very low level current that has a positive (anode) or negative (cathode) electrode. Anodal stimulation of the cortex is usually associated with positive effects on mood and cognition. Patients received either five sessions of active tDCS for 20 minutes (at 2 milli Amps) or a sham stimulation for the same period. Then, one day after the final session, the patients were measured on a variety of scales for cognition and illness. **Patients who received the active tDCS showed more improvements in working memory and attention than patients who received the sham treatment.**

There was no difference in the two groups' schizophrenic symptoms, including hallucinations. Smith and colleagues suggest that the improvements in cognition may result from changes to brain connectivity networks, since abnormalities in these networks have been identified in patients with schizophrenia and bipolar disorder.

Replications of this type of study are needed to clarify the effect of tDCS on cognition in schizophrenia, but given the safety and convenience of the procedure, the findings are promising.

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Cariprazine More Potent Than Aripiprazole At Dopamine D3 Receptors

Cariprazine is a new atypical antipsychotic that has positive results in the treatment of schizophrenia, bipolar mania and depression, and as an add-on treatment to antidepressants in unipolar depression. In a recent study by Frank Tarazi and colleagues, cariprazine shared some actions with aripiprazole (trade name Abilify), which is approved by the Federal Drug Administration as an adjunctive treatment for unipolar depression in addition to treating mania in bipolar disorder and schizophrenia.

The researchers concluded that cariprazine was more potent than aripiprazole at dopamine receptors, especially D3 receptors.

Both cariprazine and aripiprazole partially block dopamine receptors. They allow a little stimulation of the receptors (activating or agonist effects) while preventing dopamine from binding there. With ongoing treatment, this blocking action prompts an

increase in the number of dopamine receptors to compensate for the blocking.

In rats, both drugs led to increases in several types of dopamine receptors, but cariprazine did so at lower doses. Following 28 days of treatment with aripiprazole at doses of 5–15 mg/kg, rats had higher levels of D2 and D4 receptors in several brain regions than other rats that received no drug. Higher doses of aripiprazole also increased D3 receptors in some regions, indicating that the drug works less well at those receptors. Lower doses of cariprazine (0.06–0.6 mg/kg) increased D2 and D4 receptors significantly, and increased D3 receptors more than aripiprazole did, and in a greater number of forebrain regions.

Among antipsychotic drugs, both aripiprazole and cariprazine are unique in providing a little stimulation (partial agonist effects) at dopamine receptors, while all others drugs in the class are pure blockers (antagonists) of dopamine receptors.

Ziprasidone Added to Escitalopram Improved Unipolar Depression

In a new study of patients with major depressive disorder who did not improve after eight weeks of the selective serotonin reuptake inhibitor (SSRI) antidepressant escitalopram, the addition of the atypical antipsychotic ziprasidone improved their depression more than did placebo. Patients took the combination of escitalopram (20mg/day on average) and ziprasidone twice a day at doses of 20–80 mg.

This was the first randomized, double-blind placebo controlled trial of ziprasidone as an adjunct treatment for unipolar depression. While ziprasidone was more efficacious than placebo, discontinuation of the study

due to intolerance was higher among the patients who received ziprasidone.

Editor's Note: Two atypical antipsychotics (quetiapine and aripiprazole) have been approved by the Federal Drug Administration for augmentation of antidepressants in unipolar depression. Now there have also been placebo-controlled positive trials of two others (ziprasidone and cariprazine).

These findings are of particular interest as the studies of ziprasidone monotherapy in bipolar depression not only failed, but response to ziprasidone and placebo was virtually identical (and negligible).

Evidence for Cariprazine's Efficacy in Bipolar Depression

In an eight-week study of the drug cariprazine for bipolar depression by Joe Calabrese and colleagues, **patients who received 1.5mg/day doses of the drug showed more improvement in their illness and higher remission rates after six weeks than patients who received placebo.** Side effects were rare, with mild or moderate akathisia (restless legs) being most common. Cariprazine is a dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors.

High Blood Pressure is a Marker of Good Response to Prazosin in PTSD

Prazosin, an alpha-1 adrenoceptor antagonist, has been found to be effective at reducing symptoms of post-traumatic stress disorder (PTSD), including nightmares. Researchers led by Murray Raskind hypothesized that there may be a link between blood pressure and response to prazosin, since resting blood pressure can be used to measure alpha-1 adrenoceptor responsiveness. In a study of active duty combat soldiers with PTSD, **higher resting blood pressure and smaller drop in blood pressure when going from lying down to standing up predicted a better response to prazosin.**

The researchers believe that blood pressure can be used to estimate the central nervous system's responsiveness to norepinephrine, which prazosin blocks. In patients with PTSD who received placebo instead of prazosin, blood pressure did not predict improvement. Raskind and colleagues hope to be better able to predict response to prazosin in PTSD by measuring patients' baseline blood pressure.

Bipolar Disorder Is Often Overlooked in Primary Care

A 2014 study by Joseph M. Cerimele and colleagues in the journal *Psychiatric Services* found that primary care patients with bipolar disorder had severe depression and anxiety, symptoms of other psychiatric illnesses, and psychosocial problems such as housing difficulties, homelessness, or lack of support. Only 26% were referred to specialty mental health care despite the severity of these problems. These findings suggest the primary care setting, where many patients obtain their care, provides insufficient support for people with bipolar disorder.

Editor's Note: There are several ways to overcome the deficient recognition and treatment of bipolar disorder in primary care.

Record mood fluctuations

It is critical that patients keep a detailed longitudinal record of mood fluctuations in order to enhance the likelihood that their doctor can perform a well-informed evaluation and assessment of the effects of treatment. Several ways of doing this are available. We offer a variety of printable daily mood charts available on our website (<http://bipolarnews.org>). Another option is What's My M3, a free app that can be downloaded from the iTunes Store or Google Play. In a three-minute survey, it screens for depression, anxiety, OCD, PTSD, and mania. The ratings can be done longitudinally and printed out to assist a physician in the evaluation, assessment of course of symptoms, and response to treatment.

Parents of children aged 2-12 with mood or behavioral problems (or at risk for them because they have a parent with a diagnosis of depression or bipolar disorder) can rate their children each week as part of a new study. These ratings, which will help determine how children with symptoms of mental illness are being treated in the community, are done via a secure website and can be printed out to help a treating physician or other clinician

to evaluate the children's course of illness and responses to treatments. Access to informed consent documents and more information about participation in the study, known as the Child Network, is available via our website (click on the tab for Child Network).

Learn about mood disorders

Patients should educate themselves about the signs and symptoms of mood disorders. Many books on this topic are available, and the BNN newsletter tries to update patients and clinicians about the latest findings about the treatment of depression and bipolar disorder.

Get extra help

Patients can seek out consultations with experts in bipolar disorder, who may be able to provide extra guidance to help primary care physicians arrive at the appropriate diagnosis or find an optimal treatment plan and back up approaches if the initial options do not bring about remission.

Finding a psychotherapist who can provide psychoeducation

about bipolar disorder and cognitive behavioral or other specialized therapies may also be of great use, as more than a dozen randomized studies document the effectiveness of psychoeducation and/or psychotherapy compared to treatment as usual.

Talk about mood at every medical evaluation

Many medical problems such as heart disease and diabetes require careful monitoring, with patients as active participants. Likewise, careful monitoring of mood is a critical component of good treatment and should yield positive short-term and long-term results in recurrent depression and bipolar disorder.

Since depression can complicate many medical illnesses, patients should get in the habit of asking physicians not only about their blood sugar, blood pressure, or cholesterol, but also, "What about my low mood, anxiety, or insomnia?" It may be just the spark a physician needs to better attend to these equally important health issues.

Recovery and Relapse After a First Mania

The timeframe during which recovery and recurrence occur in people with a first episode of mania are somewhat variable. A meta-analysis by Andréanne Gignac and colleagues published in the *Journal of Clinical Psychiatry* in 2015 offers some new information. The meta-analysis included eight studies with a total of 734 participants in a first episode of mania. **Syndromal recovery rates (when patients no longer met diagnostic criteria for bipolar disorder) were 77.4% at six months after first episode of mania and 84.2% at one year after. However, some symptoms lingered, and only 62.1% of patients reached a period of symptomatic recovery within one year.**

Recurrence rates were 25.7% within six months, 41.0% within one year, and 59.7% by four years. Those who were younger at the time of the first episode were at higher risk for relapse within one year.

Editor's Note: On the positive side, most recovered, but on the negative side, at one year, 60% remained symptomatic and 40% had a recurrence. What is not clear is how intensively patients were treated and monitored. The main message of this study is that a first episode of mania is not trivial and deserves concerted acute and long-term treatment. When expert multimodal treatment is given results are vastly more superior than treatment as usual (Kessing et al. British Journal of Psychiatry 2013).

Exercise May Help Reduce Cocaine Use

In studies of rodents, running on a wheel reduces cocaine self-administration. A recent study by Richard de la Garza and colleagues investigated whether running or walking on a treadmill can reduce cocaine cravings and use in humans. In the study of 24 participants who had been using cocaine an average of 19.7 years, participants were randomized to run, walk, or sit for 30 minutes three times per week for four consecutive weeks. **After exercising, the participants reported having less craving for cocaine.** Fitness measures such as body weight and resting

heart rate improved in both walkers and runners. While not statistically significant, by the end of the study there was a trend indicating that exercise improved abstinence from cocaine and decreased daily craving for cocaine.

Editor's Note: Exercise Increases brain-derived neurotrophic factor (BDNF) and neurogenesis. In rodents, cocaine is associated with decreases in BDNF in the frontal cortex, and injecting BDNF there decreases cocaine seeking. Whether this BDNF effect or the general effects of exercise on mood and conditioning account for these positive cocaine effects remains to be ascertained.

Low Dose Quetiapine Promising In Borderline Personality Disorder

Borderline personality disorder is characterized by mood instability, cognitive symptoms, impulsive or risky behavior, and disturbed interpersonal relationships. There are no Federal Drug Administration-approved treatments, but several small open studies of the atypical antipsychotic quetiapine (trade name Seroquel) have been promising. Rapid mood shifts in borderline personality disorder resemble to some extent those in bipolar disorder, for which quetiapine is an approved treatment. The drug may also curb impulsivity and self-harm.

A blind, placebo-controlled study by Donald W. Black and colleagues published in the *American Journal of Psychiatry* in 2014 compared a low dose of quetiapine (150mg/day) with a moderate dose (300mg/day) and with placebo for the treatment of borderline personality disorder. **The low dose of quetiapine led to significant improvement over the other doses, particularly reducing verbal and physical aggression.**

The study included 95 participants randomized to each of the three treatment groups. All met DSM-IV criteria for borderline personality disorder, and each participant received eight

weeks of active treatment. (One week of 50mg/day followed by seven weeks of 150mg/day for the low dose group, and one week of 50mg/day followed by 3 weeks of 150mg/day and 4 weeks of 300mg/day for the moderate dose group.)

Eighty-eight percent of the participants experienced an adverse event during the study, including sedation, dry mouth, increased heart rate, or decrease in blood pressure. None were serious. Sedation was most common in the group receiving moderate doses of quetiapine.

All groups improved over the 8-week study, particularly during weeks 2-6. Response rates of participants who completed the study were 82% for the low dose group, 74% for the moderate dose group, and 48% for placebo. (Large benefits from placebo are common in studies of borderline personality.) Improvement in symptoms was greatest in the low dose quetiapine group, significantly higher than the moderate dose quetiapine group. Time to improvement was shorter on quetiapine than on placebo.

The researchers concluded that low doses of quetiapine are both effective and well-tolerated in the treatment of borderline personality disorder.

Short Telomeres in a Rat Model of Depression, Lithium Reverses Abnormality

Telomeres are repeated DNA sequences that sit at the end of chromosomes and protect them during cell replication. Telomeres get shorter with aging and with stressors or psychiatric illnesses. Researcher Alexandre Mathe and colleagues recently found that **in a line of rats bred to be more susceptible to stress and depression-like behavior, hippocampal telomeres were shorter than in normal rats or rats bred to be less susceptible.** The susceptible rats also had lower levels of enzymes that maintain telomere length. Both telomerase activity and Tert (telomerase reverse transcriptase) expression were reduced in the susceptible rat compared to the other rats. However, lithium reversed the low levels of telomerase activity and Tert expression.

Editor's Note: Lithium increases hippocampal volume in people, and also increases human telomerase. Researcher Lina Martinsson reported in 2013 that lithium increases telomere length in white cells. Now lithium has increased hippocampal telomerase in a rat model of depression. Short telomeres are associated with aging and increased vulnerability to a wide range of medical and psychiatric disorders. Since people with bipolar disorder are prone to memory problems, medical problems, and short telomeres, they might want to talk to their physician about including lithium in their treatment regimen, if they are not already taking it.

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Lithium in Drinking Water Associated with Lower Suicide Rates in Men

Studies in Japan, Austria, and Texas have reported that trace amounts of lithium in drinking water are associated with lower suicide rates. A new study seeks to clarify these findings by removing any statistical factors other than lithium levels that could produce these results.

The study, published in the *Journal of Clinical Psychiatry*, collected 434 lithium samples in drinking water over three years, and compared these with suicide

rates in the population of 274 municipalities of Kyushi Island in Japan.

The researchers, led by Nobuyoshi Ishii, then controlled for size of population, proportion of elderly people, proportion of one-person households, proportion of people with a college education or more, proportion of people engaging in primary industry, overall unemployment rates, annual marriage rates, annual mean temperature, and annual savings in per person in Japan's

popular postal bank. **In places with slightly higher trace levels of lithium in drinking water, there was a lower rate of suicides in men.** Suicide rates for women and overall were not significantly associated with lithium levels.

Editor's Note: This is the fourth positive study indicating that higher trace levels of lithium in drinking water decrease suicide rates in the general population.

Abnormal Levels of Cytokines Found in Brains of Suicide Victims

Cytokines are chemical messengers that send signals between immune cells and between the immune system and the central nervous system. Their levels in blood are considered a measure of inflammation, which has been implicated in depression and stress. A new study by Ghanshyam Pandey and colleagues reported increased levels of cytokines in the brains of people who committed suicide. **In the prefrontal cortices of people who died by suicide, there were significantly elevated levels of the inflammatory cytokines IL-1 beta, IL-6 and TNF-alpha compared to the brains of normal controls.** There were also lower levels of protein expression of the cytokine receptors IL-1R1, IL-1R2 and IL-1R antagonist (IL1RA) in the suicide brains compared to controls.

The researchers concluded that abnormalities in proinflammatory cytokines and their receptors are associated with the pathophysiology of depression and suicide. This research provides direct confirmation of the indirect measures of inflammation observed in the blood of depressed patients compared to controls.

Exposure to Stress Hormone Leads to Poor Decision-Making

Adolescence may be a period of particular vulnerability to the effects of stress. New research by Shannon Gourley indicates a possible mechanism for this vulnerability. **When Gourley exposed adolescent mice to low levels of the stress hormone corticosterone (the equivalent to human cortisol), they developed habit-based rather than goal-oriented decision-making, leading to behaviors that resembled human depression, which lasted into adulthood.** Adult mice that were exposed to the low levels of corticosterone were not affected by it.

Gourley also used an alternative method of producing these stress responses a second time by silencing the trkB receptor for brain-derived neurotrophic factor (BDNF) in the amygdala and hippocampus of the mice. The depression-like behaviors that resulted, such as lack of motivation, were able to be reversed by treating the mice with 7,8-dihydroxyflavone, a drug that activated the trkB receptor. In the adolescent mice, this treatment had antidepressant effects that lasted into adulthood, even though the treatment stopped earlier.

Brain Activity Differentiates Bipolar Disorder from Unipolar

Both bipolar disorder and unipolar depression often begin in childhood or adolescence, but it can be difficult to distinguish the two using symptoms only. People with bipolar illness may go a decade without receiving a correct diagnosis. Researcher Jorge Almeida and colleagues recently performed a meta-analysis of previous studies to determine what neural activity is typical of children with bipolar disorder versus children with unipolar depression while processing images of facial emotion. They found that **youth with bipolar disorder were more likely to show limbic hyperactivity and cortical hypoactivity during emotional face processing than youth with unipolar depression.** Almeida and colleagues hope that this type of data may eventually be used to diagnose these disorders or to measure whether treatment has been successful.

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Gene CACNA1C is Associated with Early-Onset Bipolar Disorder

Several genes have previously been implicated in bipolar illness. In a recent study, researchers at the Mayo Clinic, led by Paul Croarkin, compared variations in three genes (CACNA1C, ANK3, and ODZN) across 69 children aged 6–15 with mania, a 776-person control group from the Mayo Biobank database, and 732 adults with bipolar disorder (some with onset in childhood and adolescence and some with onset in adulthood, also from the Biobank). All participants were Caucasian, to minimize confounding by population stratification. The researchers found

that **the minor allele of rs10848632 in CACNA1C was associated with childhood onset of bipolar disorder. The haplotype (or sequence of nucleotides) T-G-G-T was associated with risk. Genetic risk scores were also associated with early onset of illness.**

Editor's Note: In research by Michael McCarthy and colleagues (see below), CACNA1C has been linked to abnormal circadian rhythms in bipolar disorder and to responsiveness to lithium treatment. Together, these data suggest the importance of studying the calcium channel blocker

nimodipine (which blocks calcium influx through CACNA1C) in childhood-onset bipolar disorder. A 1999 case report by Pablo A. Davanzo and colleagues described a teenager with ultra rapid cycling bipolar disorder (multiple mood switches/day) that did not respond to a host of conventional medications, who improved dramatically on nimodipine, reaching remission. This author (Robert M. Post) has also seen confirmed responsiveness in adults with rapid cycling bipolar disorder (reported in the 2008 book Treatment of Bipolar Illness: A Casebook for Clinicians and Patients, by Post and Gabriele S. Leverich).

Low Vitamin D in Childhood Can Predict Hardening of the Arteries in Adulthood

A new study from Finland suggests that low vitamin D levels in childhood and adolescence can predict atherosclerosis, or hardening of the arteries, in adulthood. The study, by Markus Juonala and colleagues in the *Journal of Clinical Endocrinology & Metabolism*, included 2,148 people whose vitamin D levels were measured at ages 3–18. They were checked for atherosclerosis at ages 30–45. **Those participants with the lowest levels of vitamin D in their youth were at much higher risk for thickened arteries as adults.** The finding was independent of other cardiovascular risk factors such as smoking, high blood pressure, poor eating, lack of exercise, and obesity.

Editor's Note: While it is not yet clear if low vitamin D levels directly cause the development of atherosclerosis, it is important to maintain sufficient vitamin D in childhood for a host of reasons, including strong bones. Children with sufficient vitamin D levels are more likely to have normal moods and behavior than those deficient in vitamin D.

Calcium Channel May Be Responsible for Circadian Rhythm Abnormalities in Bipolar Disorder

Genetic variation in L-type calcium channel genes have been linked to bipolar disorder. Since calcium plays an important role in circadian rhythms, abnormalities in the calcium channel in bipolar disorder could explain some of the circadian rhythm disturbances patients with bipolar disorder exhibit. New research by Michael McCarthy and colleagues shows that **calcium channels in general, and the gene CACNA1C in particular, affect signaling pathways that regulate circadian rhythms in both human and animal cells. The researchers also found that calcium channels affected how lithium changes circadian rhythms, suggesting a mechanism by which the treatment may work.** They suggest that drugs that affect the L-type calcium channel may be promising treatments for bipolar disorder.

Editor's Note: The L-type calcium channel blocker nimodipine has had an-

tidepressant, antimanic, and anticycling effects in some patients with bipolar disorder in small studies both by Peggy Pazzaglia and colleagues (including this author Robert Post) and a larger randomized study by Haroon R. Chaudhry.

The clinical effects of nimodipine results thus align with studies linking the CACNA1C gene to bipolar illness and its early onset, increased expression of the gene in the brain of bipolar patients in autopsy studies, increased levels of calcium in white cells of bipolar patients, and a variety of other neurobiological phenomena observed in normal controls carrying the risk gene.

The new link found between CACNA1C and circadian rhythms further links the L-type calcium channel abnormality and bipolar disorder, as well as the therapeutic effects of the L-type calcium channel blocker nimodipine. This drug deserves further study, especially in those with the genetic variation in CACNA1C that has been linked to bipolar disorder.

Learn about the Child Network study: See page 11

Subthreshold Episodes of Mania Best Predictor of Bipolar Disorder in Kids

Relatively little attention has been paid to the children of a parent with bipolar disorder, who are at risk not only for the onset of bipolar disorder, but also anxiety, depression, and multiple other disorders. These children deserve a special focus, as on average 74.2% will receive a major (Axis 1) psychiatric diagnosis within seven years.

New research published by David Axelson and colleagues in the *American Journal of Psychiatry* describes a longitudinal study comparing children who have a parent with bipolar disorder to demographically matched children in the general public. Offspring at high risk for bipolar disorder because they have a parent with the disorder had significantly higher rates of subthreshold

mania or hypomania (13.3% versus 1.2%) or what is known as bipolar disorder not otherwise specified (BP-NOS); manic, mixed, or hypomanic episodes (9.2% versus 0.8%); major depressive episodes (32.0% versus 14.9%); and anxiety disorders (39.9% versus 21.8%) than offspring of parents without bipolar disorder. Subthreshold episodes of mania or hypomania (those that resemble but do not meet the full requirements for bipolar disorder in terms of duration) were the best predictor of later manic episodes. This finding was observed prospectively, meaning that patients who were diagnosed with manic episodes during a follow-up assessment

were likely to have been diagnosed with a subthreshold manic or hypomanic episode during a previous assessment.

The study included 391 children (aged 6–18) of at least one bipolar parent, and compared these to 248 children of parents without bipolar disorder in the community. The participants took part in follow-up assessments every 2.5 years on average, for a total of about 6.8 years. Each follow-up assessment included retrospective analysis of symptoms that had occurred since the previous assessment.

In addition to having more subthreshold manic or hypomanic episodes; manic, mixed, or hypomanic episodes; and major depressive episodes, the high-risk children also showed more non-mood-related axis 1 disorders, including attention deficit hyperactivity disorder (ADHD), disruptive behavior disorders, and anxiety disorders than the children of parents without bipolar disorder. Axelson suggested that monitoring for these symptoms may help with early identification and treatment.

Children with a bipolar parent were diagnosed with bipolar spectrum disorders at rates of 23% compared to 3.2% in the comparison offspring. Mean age of onset of mania or hypomania in the high-risk offspring was 13.4 years. Of those offspring who had a manic episode, more than half had the episode before age 12, with the earliest occurring at age 8.1.

Compared to previous studies of children of parents with bipolar disorder, this study found that the mean age

of onset of manic or hypomanic episodes was younger, possibly because other studies did not include young children. Another new finding was that major depressive episodes and disruptive behavioral disorders were risk factors for mania and hypomania.

Parents of children who are at high risk for developing bipolar spectrum disorders should be aware of the common precursors to mania – subthreshold manic or hypomanic symptoms and non-mood disorders – and make sure that clinicians assess for these symptoms and differentiate them from the symptoms of depression or other disorders.

Editor's Note: In Axelson's study, 74.2% of the offspring of a bipolar parent suffered a major (Axis I) psychiatric disorder. However, 48.4% of the offspring from the comparison group of community controls also had an Axis 1 psychiatric disorder. These high rates of illness and dysfunction indicate the importance of monitoring a variety of symptom areas and getting appropriate evaluation and treatment in the face of symptoms that are associated with impairment in both high risk children and in the general population.

One way of doing this is for parents to join our new Child Network, a study collecting information about how children at risk for bipolar disorder or with symptoms of bipolar disorder are being treated in the community and how well they are doing. Parents rate their children on a weekly basis for depression, anxiety, ADHD, oppositionality, and mania-like symptoms. Parents will be able to produce a longitudinal chart of their children's symptoms and response to treatment, which may assist their child's physician with early detection of illness and with treatment. See our website (<http://bipolarnews.org>) for more information and to access informed consent documents. (Click on the tab for Child Network.)

BP-NOS, depressive episodes, and disruptive behavioral disorders are predictors of subsequent conversion to full-blown bipolar disorder.

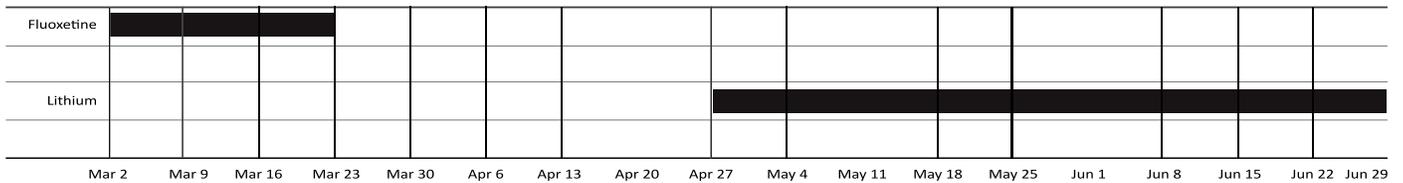
Parents with Mood Disorders and Their Clinicians,

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.

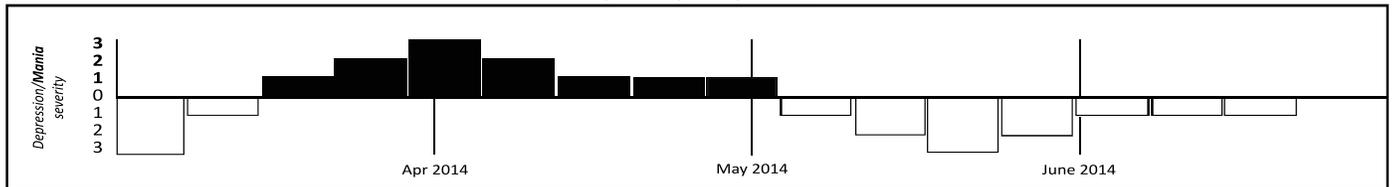
The Child Network is specifically for parents of children ages 2 to 12 who have few symptoms, minor (prodromal) symptoms, or the full onset of a psychiatric illness prior to age 13. Participating in the Child Network will primarily involve a confidential, few-minute parental assessment of their child 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 treatment. 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 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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