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Bipolar Network News

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Updates from the 2014 Meeting of the International Society for Bipolar Disorders

Vol. 18, Issue 3, 2014

Treatment in Specialized Bipolar Clinic Better Than Treatment as Usual

Danish researcher Lars Kessing recently performed the first randomized controlled study of the efficacy of early intervention in bipolar disorder. He described the findings both in a plenary lecutre at the 2014 meeting of the International Society for Bipolar Disorders and in a 2013 article in the *British Journal of Psychiatry*.

Patients who had been hospitalized for a first episode of mania were randomly assigned to two years of treatment in a specialized clinic versus two years with treatment as usual in the community (the control condition). The researchers predicted that then specialized clinic would decrease subsequent hospitalizations, and increase adherence to medication and patient satisfaction compared to treatment as usual over the subsequent six years.

Treatment at the special clinic began with a phase of post-hospitalization settling in, followed by psychoeducation (15 weeks of 1 session/week). Emphasis was placed on the recognition of breakthrough symptoms—early warning signals of an impending mood episode.

All three outcomes were better in the group who were treated at the specialized clinic than in control group who received treatment as usual. Hospitalizations were reduced 40%, medication compliance was enhanced, and patients were more satisfied. Patients younger than age 36 showed greater improvement and greater differences from the control group than were seen among older patients.

One striking observation was that the difference observed after patients had spent two years in the specialized clinic compared to the control group persisted and grew over the following two to four years, even though these patients had already left the clinic.

The specialized clinic was not only successful, but was also cost-effective. Clinic patient care led to a savings of €3,194 per patient. The costs for clinic patients were 11% of those for control patients.

> The specialized clinic provided 15 weeks of psychoeducation and emphasized recognition of breakthrough symptoms—early warning signs of an impending mood episode.

Editor's Note: We already know that treatment delay is related to poor outcome. (See article by this editor Robert Post et al. in the Journal of Clinical Psychiatry *in 2010.) This study is groundbreaking in demonstrating that the quality of care in a specialized clinic has enormous personal, societal, and financial benefits, and can render the course of illness more benign over a sustained period of at least 6 years.*

This means that a revolution in the care and treatment of patients with bipolar disorder is needed throughout the world, but especially in the US, where the typical treatment paradigm is as bad or worse than the treatment as usual condition in Kessing's Danish study. When patients are discharged from the hospital, they are immediately at increased risk for relapses and, most alarmingly, at 200-fold increased risk of suicide. This post-hospitalization gap in treatment between episodes needs to be better managed. Transitional care is rarely handled well, psychoeducation is rarely given for a sufficient duration, therapy is often unavailable, and medication non-compliance is high. These factors lead to increased illness, re-hospitalizations, and skyrocketing personal and societal costs. Moreover, only 20% of bipolar patients identified in epidemiological studies in the US are in any kind of treatment.

Treatment guidelines must be changed to better address these issues. A first episode of mania should trigger a cascade of sequential treatments: psychoeducation, family

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Also in this issue:

Children of Bipolar Parents Are At Risk for Depression and Bipolar Disorder

The Pittsburgh Bipolar Offspring study, led by Boris Birmaher of the University of Pittsburgh, investigated risk of illness in the offspring of parents with bipolar disorder. The study included 233 parents with bipolar disorder and 143 controls. In addition to bipolar disorder, parents in the study had many other disorders, including anxiety (70%), panic (40%), a disruptive behavior disorder (35%), attention-deficit hyperactivity disorder or ADHD (25%), and substance use disorder (35%).

The offspring averaged age 12 at entry in the study. **Offspring of parents with bipolar disorder had more illness than those of control parents, including bipolar spectrum disorders (10.6% versus 0.8%), depression (10.6% versus 3.6%), anxiety disorder (25.8% versus 10.8%), oppositional defiant disorder or conduct disorder (19.1% versus 8.0%), and ADHD (24.5% versus 6.7%).** Of these differences, only bipolar spectrum disorders and anxiety were statistically significant after correcting for differences in the parents' other diagnoses.

Two factors predicted bipolar spectrum disorders in the offspring: younger age of a parent at birth of child and bipolar disorder in both parents. Older children and those with diagnoses of anxiety or oppositional defiant disorder were more likely to be diagnosed with bipolar disorder.

On long-term follow-up that continued on average until the offspring reached age 20, 23% of those participants who had a parent with bipolar disorder developed any type of bipolar disorder, versus only 1.2% of the children of controls. Of these 23%, about two-thirds had a depressive episode prior to the onset of their bipolar disorder.

Of the offspring of parents with bipolar disorder who developed a bipolar spectrum illness, 12.3% developed bipolar I or II disorders, while 10.7% were diagnosed with bipolar not otherwise specified (NOS). Of those with bipolar NOS, which some consider to be sub-threshold bipolar disorder, about 45% converted to a bipolar I or II diagnosis after several years of prospective follow-up. These data, along with the finding that children with bipolar NOS are highly impaired and take more than a year on average to remit, stress the importance of vigorously treating this subtype, even if it does not meet the full threshold for bipolar I or bipolar II.

Birmaher indicated that although about 50% of the offspring of a bipolar patient had no diagnosis, the high incidence of multiple psychiatric difficulties developing over childhood and adolescence spoke to the importance of attempts at early intervention and prevention. Studies of effective treatment and prevention strategies are desperately needed. So far only family focused therapy (FFT), an intervention developed by researcher David Miklowitz, has shown significant benefits over standard treatment in children with a positive family history of bipolar disorder who already have a diagnosis of anxiety, depression, or bipolar not otherwise specified.

Specialized Clinic

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focused therapy (FFT) developed by David Miklowitz (particularly if the family has high levels of conflict, to enhance communication and coping skills and minimize stress) or its equivalent, substance abuse avoidance education or treatment, emphasis on medication maintenance, development of an early warning system for recognition of breakthrough symptoms and specific ways to deal with them, and the creation of a treatment team for support and monitoring.

Thus the goal would be to construct an equivalent to Kessing's specialized clinic for each patient. Childhood and adolescent onset bipolar disorder is as complex and difficult to manage properly as Type II diabetes, and deserves the same intensive combined efforts of multiple members of the treatment team, including nurses, social workers, psychologists, and physicians. When this is done in an illness like diabetes, the outcome is positive. We now know that the same is true when patients with bipolar disorder receive specialized treatment, and we know that the results are persistent. If such a comprehensive approach to new onset of bipolar disorder is not offered, the patient and his or her family should seek it out and insist that it be delivered.

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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Inflammation Occurs During Both Depression and Mania

There is increasing evidence of a link between mood disorders and inflammation in the body.

At the 2014 meeting of the International Society for Bipolar Disorders, Shang-Ying Tsai discussed increases in measures of inflammation that occur in bipolar disorder as a function of the clinical state of depression, mania, or euthymia (remission). He found that in both mania and depression, there were elevations in various markers of inflammation: STNF-R1, CRP, IL-Ira and SLR-2r.

However, SLR-2r showed some particularly interesting results. **In mania, elevation of SLR-2r, a marker of cell-mediated inflammation, was state-related, meaning it increased during an episode of mania and remained normal during euthymia. In depression, SLR-2r elevation was trait-related, or persistently elevated (even in remission).**

Editor's Note: This study adds to a growing list of studies that confirm the presence of inflammation in patients with bipolar disorder compared to normal controls, including a 2012 article by Tsai in the Journal of Affective Disorders. How elevations in inflammatory markers in a given individual should direct specific types of treatment intervention remains to be further clarified.

Newest Meta-Analysis Shows Lithium Is Better than Placebo at Preventing Both Mania and Depression

A 2004 meta-analysis of previous research showed that lithium was better than placebo at preventing affective episodes and preventing manic episodes. The evidence for the drug's efficacy in preventing depression was less clear. A new meta-analysis by E. Severus et al. (not yet published) confirms the previous findings and provides new evidence that lithium is also better than placebo at preventing depressions.

The study also suggested that lithium is better than anticonvulsant mood stabilizers at preventing relapse and recurrence, but this finding only reached statistical significance in the prevention of new manic and hypomanic episodes.

Editor's Note: These findings highlight the desirability of greater lithium use. The drug is currently prescribed less often in the US than it is in Europe. In addition to lithium's efficacy in the long-term preventative treatment of bipolar disorder, there is evidence that lithium is also the best agent for suicide prevention and for neuroprotective effects.

Differentiating Bipolar Disorder and ADHD in Childhood

At the 2014 meeting of the International Society for Bipolar Disorders, researcher B.N. Kim discussed symptoms that could distinguish between bipolar disorder and attention deficit hyperactivity disorder (ADHD) in childhood. Both disorders are characterized by decreased attention, concentration, and frustration tolerance, and increased activity, impulsiveness, and irritability.

Kim shared several differential symptoms that are more indicative of a bipolar diagnosis and that are inconsistent with a simple ADHD diagnosis (and this editor Robert Post has added several more). Signs and symptoms that suggest bipolar disorder and not ADHD include: decreased need for sleep, brief and extended periods of euphoria, hypersexuality, delusions, hallucinations, suicidal or homicidal impulses and/or actions, extreme aggression, and multiple areas of extreme behavioral dyscontrol. ADHD, on the other hand, is characterized by more difficulty focusing attention, and by less extreme symptoms in general.

International Bipolar Foundation Advocates for Prompt Treatment of Children

Muffy Walker gave an inspirational talk at the 2014 meeting of the International Society for Bipolar Disorders about the International Bipolar Foundation (IBPF, formerly known as the California Bipolar Foundation) she started with three other mothers of children with bipolar disorder.

The organization advocates for better understanding and treatment of the illness in children. Treatment is too often delayed and insufficient, as was the case with Walker's son, who started having trouble at age four and was diagnosed with post-traumatic stress disorder (PTSD), oppositional defiant disorder (ODD), attention-deficit hyperactivity disorder (ADHD), and conduct disorder (CD) before he became severely manic while taking the antidepressant fluoxetine (Prozac).

The foundation has a monthly e-newsletter. Their website is http://ibpf.org.

Methylene Blue Treats BP Depression in Adults

Methylene blue is a chemical compound that has been used to treat a variety of medical conditions. This drug has some actions that resemble lithium's: it inhibits guanylate cyclase, which generates second messenger cyclic GMP, and decreases nitric oxide. New evidence shows it may help depression and anxiety in bipolar disorder when added to lamotrigine.

In patients with bipolar disorder who were all treated with lamotrigine, an active 65mg dose of methylene blue three times per day (for a daily total of 195mg) versus 15mg/day (an inactive dose that produces the same side effect of blue urine) **was more effective at treating depression and anxiety in a 12-week crossover study.** Side effects, in addition to blue urine, included infrequent nausea, diarrhea, headache, and a burning sensation in the urinary tract. Of the 37 randomized study participants, 27 completed both phases of the entire six-month study. Martin Alda, a researcher who presented the double-blind randomized crossover data at the 2014 meeting of the International Society for Bipolar Disorders, indicated that he has also used this preparation clinically with success, although the pharmacy staff who prepared the capsules were not too happy, because everything the drug touches turns blue.

Topiramate Added to Regular Treatment Helps OCD Symptoms in Bipolar Disorder

Until now, there has been little research about treating obsessive compulsive symptoms in people with bipolar disorder.

In a recent four-month double-blind placebo-controlled randomized clinical trial presented by Sharaian et al. at the 2014 meeting of the International Society for Bipolar Disorders, topiramate was more effective than placebo at reducing these symptoms in patients with bipolar disorder when added to their regular treatment. Nine of 17 study participants responded to topiramate (53%), while only two of 16 responded to placebo (12.5%).

Editor's Note: These findings add to the list of comorbidities that topiramate may help with, even though it does not have any efficacy in the treatment of mania itself. Topiramate has helped with avoidance of cocaine and alcohol, bulimia and weight gain, anger attacks, and now obsessive compulsive disorder (OCD). Topiramate is also FDA-approved for migraine prevention in adolescents and adults.

A Possible Explanation for Vitamin D's Antidepressant Effects

Vitamin D plays an important role in the nervous system, regulating the production of neurotrophins, calcium channels, and calcium binding proteins, and it may have antidepressant effects. Researchers are learning more about how the vitamin's effects take place.

At the 2014 meeting of the International Society for Bipolar Disorders, Yilmazer et al. reported that **vitamin D treatment increased the production of glia-derived neurotrophic factor (GDNF).** Neurotrophins like GDNF enhance the survival and growth of neurons. Since other neurotrophins (i.e. brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEG-F)) are low in depression, vitamin D's effect on GDNF could be important to its antidepressant effects.

Erythropoietin Improves Cognitive Function in Bipolar Depression

Bipolar disorder is associated with cognitive dysfunction, and no definitive treatment has yet been found to reverse these problems with memory and attention. A new study by Kamilla W. Miskowiak presented at the 2014 meeting of the International Society of Bipolar Disorders explored the use of erythropoietin, a hormone that induces the production of red blood cells, as a treatment for cognitive dysfunction in bipolar disorder.

Participants in the double-blind study were randomized to receive either eight weekly erythropoietin infusions (40,000 IU) or eight weekly saline infusions. **While there was only a trend toward improvement in verbal memory, there were other statistically significant outcomes: erythropoietin improved sustained attention, recognition of happy faces, and speed of complex information processing across learning, attention, and executive function.** These outcomes were not related to changes in reaction time or mood, and lasted as long as six weeks after the eighth erythropoietin infusion, by which time red blood cell production had normalized.

In a related study published in the journal *Neuropsychopharmacology* in 2014, Miskowiak et al. also found that erythropoietin improved depression, quality of life, and cognitive impairment compared to saline in patients with treatment-resistant major depression. Erythropoietin increased verbal recall and recognition.

As in the study of bipolar depression, these patients received eight weeks of erythropoietin or eight weeks of saline, and erythropoietin's results lasted through six weeks of follow-up.

Vitamin D Important for Brain Function, and Often Deficient

Vitamin D plays an important role in many brain functions, including synapse creation, calcium signaling, reduction of free radicals, neurotransmitter production, immune regulation, and brain development. Deficiencies in vitamin D have been linked to depression and schizophrenia. Some research has suggested that vitamin D supplementation can improve depressive symptoms, but there is still debate about a possible role for vitamin D in treating bipolar disorder.

At the 2014 meeting of the International Society for Bipolar Disorders, researcher Baseok Cha discussed the importance of vitamin D supplementation in bipolar patients, who often have deficient or insufficient levels. **People receive 50 to 90% of their vitamin D from sunlight, and the rest from diet and supplements.** Too much sunscreen can be a problem if it prevents a person from receiving enough vitamin D from sunlight.

The type of vitamin in supplements, D3, is converted to 25 hydroxy vitamin D in the liver, and then to 1,25 hydroxy vitamin D in the kidney. Levels of 25 hydroxy vitamin D below 20 indicate deficiency while levels between 20 and 29 indicate insufficiency. Low levels of 25 hydroxy vitamin D3 in newborns is a risk factor for schizophrenia, and vitamin D supplementation reduces this risk. Fish oils increase vitamin D, and it is possible that some of the therapeutic effects of omega-3 fatty acids in depression relate to vitamin D.

Two out of four recent studies of vitamin D supplementation have been positive, the last by Khoraminya et al. in the *Australia and New Zealand Journal of Psychiatry* in 2013, in which daily doses of 1,500 IU were used. Cha et al. found significantly lower levels of 25 hydroxy vitamin D in a Korean study of 21 patients with schizophrenia, 86 patients with bipolar disorder, and 42 patients with depression (mean levels about 15 µg/ml) compared to 31 controls (mean levels about 20 µg/ml).

The Importance of Folate in Bipolar Disorder

Researchers are exploring the therapeutic potential of nutraceuticals, or nutritional treatments. Folate, also known as folic acid or vitamin B9, is one of the most important nutritional elements for mental health.

The folate found in foods such as dark leafy greens must be broken down further in order to be used in the body. Folate first breaks down into dihydrofolate (DHF), which is turned into tetrahydrofolate (THF). At the 2014 meeting of the International Society for Bipolar Disorders, researcher J.H. Baek described a pathway by which THF is turned into a form called 5,10 MTHF, which is turned into a form called 5 MTHF. **5 MTHF is important for the function of the enzyme tryptophan hydroxylase and for clearing homocysteine, an amino acid that is cardio- and neuro-toxic.**

L-methylfolate, the active ingredient in the medication Deplin, is a form of folate that the brain can use more readily than the folate from food. L-methylfolate is converted directly to 5 MTHF, so it is effective in the 15% to 35% of the normal population who have a deficiency in the enzyme MTHF reductase, which converts THF to 5 MTHF. One genetic variation (a C to T allele variation 677) that results in a type of deficiency in MTHF reductase has a 42% incidence among Asians, 34% among Caucasians, and 8% among Africans, and these individuals would benefit from l-methylfolate.

Folate and Medications for Bipolar Disorder

Certain medications lead to deficits in folate, so patients should consider taking a nutritional supplement.

The anticonvulsant drug lamotrigine inhibits the conversion of folate to DHF and DHF to THF, so folate supplementation is a good idea for those patients taking lamotrigine.

The mood stabilizer valproate inhibits the conversion of toxic homocysteine to methionine and then to s-adenosyl methionine (SAMe), which acts like an internally-produced antidepressant. Thus valproate increases homocysteine, and patients on valproate should be routinely treated with folate and vitamin B12 to help lower homocysteine levels in the blood.

Folate supplements are recommended for depressed patients who are having an inadequate response to antidepressants, since the nutrient helps antidepressants work better even when patients do not have a folate deficiency. Researcher Andrew Stoll recommends folate (1mg for women and 2mg for men). However, those patients who have one of the genetic conditions that leads to a deficiency in MTHF reductase should take l-methylfolate instead of regular folate. Researcher Mauricio Fava and colleagues showed that l-methylfolate at doses of 15mg (but not 7.5mg) was more effective in augmenting the effects of antidepressants than placebo in patients with unipolar depression.

Exercise Helpful for Mood Disorders

While past research on mood disorders has targeted structural and functional abnormalities in the brain, newer research has considered targets such as inflammation, metabolism, and cell resilience. Exercise can have positive effects on systems that regulate metabolism, immune function, and cellular respiration, and therefore improve affective and cognitive difficulties.

At the 2014 meeting of the International Society for Bipolar Disorders, Mohammad Alsuwaidan presented a meta-analysis of the effects of exercise in mood disorders gleaned from English-language studies between 1966 and July 2008. **Exercise increased brain norepinephrine, serotonin, and phenylethanolamine (PEA).**

Alsuwaidan believes runner's high, the feelings of euphoria people often experience after strenuous exercise, may not be linked to opiate (or endorphin) release, as most people believe, but instead to release of PEA or the cannabinoid anandamide, which activates CB 1 cannabinoid receptors, decreases GABA, and increases dopamine in the nucleus accumbens, the reward center of the brain.

Exercise also increases neurogenesis and the production of brain-derived neurotrophic factor (BDNF), which supports the growth of neurons and synapses. Marathon runners also have a post-race elevation in the anti-inflammatory cytokines IL-10 and IL-1Ra.

In people who are out of shape, exercise increases oxidative stress and other toxicities that do not occur with in those who exercise more regularly. Alsuwaidan extolls the benefits of high impact exercise five to seven times per week, and engaging a trainer to encourage exercise. Four minutes of intense exercise (such that you sweat and are not able to talk) is about equal to 45 minutes of mild exercise.

Obesity Worsens Bipolar Disorder, Decreases Gray and White Matter in Brain

According to researcher David J. Bond at the 2014 meeting of the International Society for Bipolar Disorders, "Up to 75% of people with bipolar disorder (BD) are overweight or obese, and these patients suffer more severe psychiatric symptoms than normal-weight patients, including more frequent depressions, more suicide attempts, lower response rates to pharmacotherapy, and greater inter-episode cognitive impairment." Obesity is a chronic inflammatory condition that damages body organs, and it appears as though the brain may be one of these. Adipose (fatty) tissue is an endocrine organ that produces substances that cause inflammation in blood vessels and that damage the heart.

Obesity is associated with decreased total brain volume, and in children, decreased gray matter volume. Obesity increases the risk of cognitive impairment, and decreases memory, attention, and executive functioning. Obesity increases the risk of Alzheimer's disease, as well as multiple sclerosis, Parkinson's, and depression.

In bipolar disorder, obesity decreases response to mood stabilizers and atypical antipsychotics. Bond found that **in patients with a first episode of mania, body mass index (BMI) was inversely related to white matter volume and temporal lobe gray matter volume.** Higher BMIs also led to neurochemical changes including increased hippocampal glutamate and reduced N-acetylaspartate. Bond also noted findings by Roger S. McIntyre that weight loss surgery in patients with bipolar disorder led to more positive treatment outcomes.

Editor's Note: These findings speak to the importance of exercise and good diet, using medications with the least likelihood of weight gain, and treating obesity once it has developed. We have previously noted the weight loss effects of topiramate and zonisamide, and new data support the substantial weight loss with the combination of bupropion (150-300mg) and naltrexone (50mg).

Patients with Bipolar Disorder More Creative; Creativity Associated with Less Functional Connectivity of the Frontal Cortex and Striatum

While bipolar disorder can be a devastating illness, multiple studies indicate it is also associated with high levels of creativity. Researchers T. Su and Y. Kuan compared highly creative and normally creative patients with bipolar disorder to healthy controls with either normal or high creativity in the hopes of clarifying some characteristics of creativity in bipolar disorder. At the 2014 meeting of the International Society for Bipolar Disorders, the researchers reported finding greater creativity in patients with bipolar disorder compared to normal controls, and that **high creativity was associated with altered functional connectivity of two regions of the brain: the medial prefrontal cortex and the striatum**.

The researchers hope to contribute to treatment solutions that can help patients with bipolar disorder reduce their emotional disturbance without losing their more positive cognitive functions like creativity.

Editor's Note: Benson et al. found that compared to normal controls, bipolar patients had more positive hyperconnectivity of many brain regions using positron emission tomography (PET) scans with fludeoxyglucose to measure brain activity. Su and Kuan used functional magnetic resonance imaging (fMRI) and found less connectivity of these two regions. How these differences relate to bipolar disorder and its links to creativity remain to be further studied.

High Impulsivity and Low Resilience Characterize Euthymic Patients with Bipolar Disorder

Resilience is the ability to cope with adversity. While its role in anxiety disorder, post-traumatic stress disorder (PTSD), and unipolar depression has been investigated, there have been few studies of resilience in bipolar disorder.

A recent study presented by B. Cha et al. at the 2014 meeting of the International Society for Bipolar Disorders found that even euthymic patients with bipolar disorder show low levels of resilience (as rated on the Connor-Davidson Resilience Scale). Patients with a history of prior bipolar episodes had greater impulsivity (measured on the Barratt Impulsion Scale) and lower resilience than participants in a control group. Impulsivity in bipolar disorder was associated with lower resilience. Higher Clinical Global Impressions (CGI) scores, greater number of prior depressive episodes, and more impulsiveness were associated with lower resilience scores.

Both high impulsiveness and low resilience may be trait-related phenomena even in patients who have recovered from bipolar disorder. Number of prior depressive episodes is also associated with more cognitive impairment on multiple tests of executive functioning, attention, learning, and memory. Therapy aimed at problem solving and coping skills might help build resilience.

Mood-Stabilizing Drugs Increase Growth in Hippocampal Neurons

Lithium is known for protecting neurons by inducing neurotrophic factors and inhibiting cell death factors. In a new study, other mood-stabilizing drugs had similar neuroprotective and neurotrophic effects on cultured neurons from the hippocampus.

At the 2014 meeting of the International Society for Bipolar Disorders, CH Lee et al. presented evidence that **lithium, carbamazepine, valproic acid, and lamotrigine all increase the outgrowth of dendrites from these cultured neurons**. Therapeutic levels of these drugs increased the production of proteins like brain-derived neurotrophic factor (BDNF), postsynaptic density protein-95 (PSD-95), neurolignin 1 (NLG 1), beta-neurexin, and synaptophysin. However, so far only lithium has been shown to increase the volume of the human hippocampus as measured with MRI.

PANS: Sudden OCD or Eating Disorder Onset Following an Infection

At the 2014 meeting of the International Society for Bipolar Disorder, researcher Kiki Chang discussed Pediatric Acute Onset Neuropsychiatric Syndromes (PANS), a newly identified phenomenon in which children suddenly develop obsessive compulsive disorder (OCD) and/or a restrictive eating disorder following an infection or other process that stimulates an immune/inflammatory reaction in the brain. A similar phenomenon, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), was initially identified by Susan Swedo of the National Institute of Mental Health (NIMH) and refers to children (usually under 6–10 years old) who develop OCD and/or tics following a case of strep throat or scarlet fever.

PANS may have an autoimmune component. In addition to acute onset of OCD and eating restriction, other symptoms include mood episodes (depression, mania), high aggression/irritability, anxiety (particularly separation anxiety), cognitive problems (ADHD, handwriting regression), regressive behaviors, and somatic signs such as sleep difficulties and urinary urgency. Biological abnormalities may include: abnormalities in red blood cell sedimentation rate, elevated C-reactive protein (CRP), high Anti DNase B and/or Antistreptolysin O (ASO) titers (anti-Streptococcus antibodies), mycoplasma IgG or IgM antibodies (signs of some types of pneumonia), ANA (antinuclear antibodies, sign of an autoimmune disease), ferritin (a protein that stores iron), copper, and a panel of tests (the Cunningham Panel) by the company Moleculera Labs that measures antibodies for four neural antibodies (dopamine D1 receptors, dopamine D2 receptors, lysoganglioside (LysoGM-1), and tubulin) and calcium/calmodulin-dependent protein kinase activity (CaMKII).

PANS is three times more likely to affect males than females, and in the Stanford PANS Clinic sample of 50 youth, PANS was associated with strep infections (65%), mycoplasma bacteria (13%), viral or urinary tract infection (58%), and ear and other infections in 16%.

Symptoms included OCD (86%), anxiety (92%), mood disturbance (88%), and aggression (82%).

Treatments include steroids, the immunosuppressant mycophenolate, intravenous immunoglobulin (IVIG), plasma exchange, the tumor necrosis factor blocker infliximab, and sometimes the antibiotic amoxicillin.

Chang also described a case in which a 15-year-old developed minocycline-induced OCD and acute onset of severe mania that included urinary incontinence and was unresponsive to medication. The patient had elevated ANA, anti-thyroid antibodies, and reduced complement C4 proteins, along with elevated antibodies to dopamine D1 and D2 receptors, LysoGM-1, and tubulin. She responded well to treatment that suppressed her immune system.

Maternal Flu Infection Increases Fetus' Risk of Bipolar Disorder with Psychosis

A 2014 study by Sarah E. Canetta et al. in the *American Journal of Psychiatry* suggests that children whose mothers had influenza during pregnancy are at higher risk for bipolar disorder with psychotic features. The same researchers had previously found that maternal influenza during pregnancy increased a child's risk of developing schizophrenia, suggesting that there is a link between maternal influenza and psychotic symptoms in the offspring.

In the current study, influenza infections were identified by measuring levels of flu antibodies in blood.

In a previous study, participants were considered to have influenza if they had been diagnosed clinically. Possibly due to this difference, that study showed a link between maternal flu infections and bipolar disorder in general (not just psychotic cases).

Mania-like State Produced in Rats By Kindling the Lateral Hypothalamus

The lateral hypothalamus is responsible for certain physiological functions (the sleep-wake cycle, appetite, energy expenditure, and sexual functions) that are disrupted during mania. At the 2014 meeting of the International Society for Bipolar Disorders, researcher O. Abulseoud et al. presented evidence that a mania-like state could be produced in rats by "kindling" the lateral hypothalamus with an electrode.

The kindled rats engaged in more motor activity; less rest; more sexual self-stimulation; excessive rearing, feeding, and grooming; and more ethanol consumption. Non-kindled rats (and those kindled in other areas such as the nucleus accumbens shell and the infralimbic cortex) did not engage in this combination of behaviors.

To test the similarity between the mania-like behaviors and human mania, the researchers treated the kindled rats with saline solution, lithium, or valproic acid. **Lithium and valproic acid reduced these behaviors significantly compared to the saline solution.** These treatments also produced long-term increases in mRNA for certain genes (Per1 and CLOCK) that are dysregulated in people with mania.

This animal model may become useful in future research on manic psychopathology in humans.

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Oxytocin for Labor Induction Increases Risk of Bipolar Disorder

Over the past several decades, the practice of giving oxytocin (a hormone that facilitates bonding) to pregnant women to induce labor has become more common, but it may come with several risks to the child. These include increased risk of attention deficit hyperactivity disorder (ADHD), and cognitive impairment. A new study by Freedman et al. presented at the 2014 meeting of the International Society for Bipolar Disorders suggests oxytocin may increase the risk of bipolar disorder as well.

In a sample of 19,000 people, there were 94 cases of bipolar disorder, and birth records revealed that an unexpectedly high number of these cases occurred in people whose mothers had received oxytocin to induce labor, regardless of the duration of the pregnancy. Cognition at ages 3 and 5 was impaired on one measure but not another in those children whose mothers received oxytocin. The researchers concluded that maternal oxytocin to induce labor is a significant risk factor for developing bipolar disorder.

Editor's Note: Oxytocin appears to take its place among other risk factors for bipolar disorder, which include: prematurity, maternal infection, influenza, the bacterial infection toxoplasmosis, higher insolation (a measure of how powerful radiation from the sun is in a given location), childhood adversity, inflammation (as measured by levels of C-reactive protein), heavy marijuana/THC use, and a family history positive for schizophrenia, schizoaffective disorder, or mood disorder, especially bipolar disorder and especially a bilineal history (illness in both parents).

Different Psychotherapies Might Eventually Be Tailored to Different Illness Characteristics

Psychotherapy can play an important role in treating mental illness. At the 2014 meeting of the International Society for Bipolar Disorders, researcher F. Colom gave a plenary talk indicating that just like pharmacotherapy, psychotherapy should differ depending on characteristics of the illness—both its severity and whether the patient has more manic or more depressive symptoms.

For **less severe illness with more depression**, Colom explained that cognitive behavioral therapy (CBT) is ideal.

Psychoeducation and family focused therapy (FFT) is recommended for **intermediate severity**, with a focus on maintaining remission. Family focused therapy also works for **early (prodromal) symptoms**, as reported by researcher David Miklowitz et al. in 2013.

Lars Kessing et al. recently reported that specialty treatment in a clinic (including psychoeducation and vigilance to breakthrough symptoms that may suggest a new episode is imminent) is highly effective following a first episode of mania.

For **more severe illness**, Colom recommends cognitive remediation and rehabilitation to decrease illness burden and increase functioning. Functional remediation focuses on communication, includes homework, and teaches skills such as how to deal with money, time, and organization. It also helps improve social cognition.

For **the most severe illness**, palliative care to relieve symptoms and decrease illness impact is recommended. Colom noted that cognitive behavioral therapy is less effective with patients who have experienced more than 12 episodes (reported by Jan Scott et al. in the *British Journal of Psychiatry* in 2006), as is psychoeducation (Renares et al. 2010, Colom et al. 2014). These data re-emphasize the importance of early intervention, when these psychotherapeutic approaches are more helpful. Colom stresses the importance of behavioral cognitive therapy (BCT) rather than cognitive behavioral therapy (CBT) for those late in the illness whose episodes often arrive spontaneously, unprecipitated by psychosocial stress, and one needs more behavioral approaches to the brain's habit memory system located in the striatum, which may drive highly recurrent illness.

Psychoeducation and Medication Better for Bipolar Disorder than Medication Alone

There is mounting evidence that medication alone is not enough to bring about full remission in bipolar disorder. At the 2014 meeting of the International Society for Bipolar Disorders, researcher T.A. Batista et al. presented evidence that psychoeducation combined with medication may be more helpful than medication alone. In the research team's randomized controlled study of 30 patients with bipolar I or bipolar II disorder, **eight weekly home visits that included both pharmacotherapy and psychoeducation produced more favorable results than eight weekly visits with pharmacotherapy alone**. Those patients who received psychoeducation had reduced depression scores and increased medication adherence compared to the others.

Editor's Note: There are now about a dozen controlled studies indicating the efficacy of psychoeducation. It is time for systematic delivery of psychoeducation, either in a private practice setting, a clinic, or the home environment, to become a mandatory part of the treatment of bipolar disorder.

Researchers Vieta and Colom of Barcelona have some of the best positive longitudinal data on psychoeducation versus treatment as usual and find benefits lasting five years or more. Key components of psychoeducation include learning about disease course and medications, developing a careful monitoring system, and recognition of early signs and symptoms of an impending manic or depressive episode, and key drug treatment maneuvers that could be instituted should such early warning signs develop.

Childhood Onset of Bipolar Illness More Difficult than Adolescent and Adult Onset

Research on early-onset bipolar disorder sometimes lumps childhood-onset in with adolescent onset. Researcher Terence Ketter et al. explored differences in illness among 502 patients at the Stanford Bipolar Disorder Clinic. **The 107 patients with childhood onsets (before age 13) had a more difficult course of illness in almost all domains compared to the 238 patients with adolescent onsets (age 13–18) or the 157 patients with illness onset in adulthood (after age 18).**

Considered separately, both patients with childhood-onset illness and patients with adolescent-onset illness had more comorbid anxiety disorders, alcohol use disorders, eating disorders, prior suicide attempts, rapid cycling in the prior year, and at least five mood episodes over the course of their lifetimes than those patients whose illness began in adulthood. Patients whose illness began in childhood had higher rates of each of these unfavorable illness characteristics and were more likely to have a first-degree relative with a mood disorder.

These data mirror those from the Bipolar Collaborative Network in which this editor (Robert Post) is an investigator, and the larger STEP-BD network led by Perlis et al. All three suggest that in the US, two-thirds of the bipolar disorder seen in adults begins in childhood and adolescence, with about a quarter beginning before age 13.

Ketter suggests that research should not combine childhood and adolescent onset illnesses, which come with different rates of anxiety, alcohol, and eating disorder comorbidity, rapid cycling, and prior episodes. The statistical relevance of some findings can be diluted when the two groups are combined.

Editor's Note: The primary message is that childhood onset bipolar disorder is a more severe version of the illness that deserves greater attention, treatment, and research so that its course can be made more benign. It is troublesome that there are no Federal Drug Administration–approved treatments for children under 10 years of age with bipolar disorder.

Twin Study Helps Clarify Epigenetic Component to Bipolar Disorder

An epigenetic finding from a study of twins may shed light on why some people develop bipolar disorder and others don't.

Epigenetics refers to changes in genes that do not affect the inherited sequence of DNA, but affect how easily the DNA is transcribed to produce proteins. Environmental events such as stress or exposure to chemicals can bring about epigenetic changes by adding or subtracting acetyl or methyl groups from strands of DNA or the histones around which it is wound. In this way twins' DNA can differ—not in its sequence but in its physical structure and the ease with which it produces proteins.

At the 2014 meeting of the International Society for Bipolar Disorders, researcher J. Ayers Ringlera et al. presented their study of pairs of twins in which one twin had bipolar disorder and the other did not. **The ill twins showed more methylation of SLC1A2, the gene for the excitatory amino acid transporter 2 (EAAT2), which clears the excitatory neurotransmitter glutamate from the synapse of neurons.** Methylation of the gene suppresses the amount of transporter expressed, so less glutamate gets cleared.

Editor's Note: Glutamate abnormalities play a role in bipolar disorder. This finding by Ringlera et al. may explain why the drug N-acetylcysteine (NAC) works in bipolar disorder—NAC increases the number of glial glutamate transporters and helps clear excess glutamate from the synapse.

Watch this Space!

The Child Network is Coming

The researchers behind Bipolar Network News are creating a new research network to collect data about children who are at high risk for a mood disorder (because they have a parent with bipolar disorder) or who already have a mood disorder such as anxiety or depression, or preliminary symptoms of one.

The Bipolar Collaborative Network is creating a confidential web-based research site, where parents will be invited to enroll their children aged 2–12. Parents will fill out a brief background form, and each year they will update a checklist of 97 symptoms their child may have experienced. For the duration of the study, parents will rate their children weekly on six symptom clusters, and keep track of any treatments or side effects.

In this way, the Bipolar Collaborative Network will collect and publish data on how the very youngest children with possible mood disorders are being treated in the community, and how well they are doing. Parents will be able to print out the longitudinal weekly ratings in order to assist their child's doctors or clinicians in assessing the effects of treatment.

We look forward to thousands of families participating so we can begin to fill in the gaps in treatment knowledge for these very young children.

This program is still in development but will be available shortly. To be notified when the program launches, go to our website bipolarnews.org, click the link for Child Network, and sign up for email updates.

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