Free

Bipolar Network News

Published since 1995 | *The latest news on bipolar disorder research from around the world* | bipolarnews.org

Vol. 21, Issue 4, 2017

Untreated Episodes of Bipolar Disorder Worsen Over Time, But Prevention is Possible

A 2017 literature review by researcher Lars V. Kessing and Per K. Andersen in the journal *Acta Psychiatrica Scandinavica* reports that the greater a patient's number of previous episodes of bipolar disorder, the more likely that patient is to have a more difficult course of illness and poorer outcomes. **The number of episodes was associated with more rapid recurrences, duration and severity of episodes, more automatic episodes (i.e. not triggered by stress), risk of dementia, treatment resistance, lack of recovery between episodes, and brain volume losses.**

In an article in the journal *Bipolar Disorders* in 2016, BNN Editor-in-Chief Robert M. Post described the value of preventive treatment in reducing episodes and protecting the brain from the damage that accompanies them.

Given that episodes, stressors, and bouts of substance abuse can affect the way genes are transcribed via a phenomenon known as epigenetics, preventing these occurrences could lead to an easier course of illness and improved outcomes. Patients should provide their physicians with feedback about their response to prior medications and any side effects they experience over time so that their medication regime can be adjusted until it is maximally effective.

Patients with severe illness and multiple previous episodes may need a complex medication regimen that includes multiple types of medications that target different systems of neurotransmitters.

This philosophy of treatment is presented in several publications, including the 2008 book *Treatment of Bipolar Illness: A Casebook for Clinicians and Patients* by Post and Gabrielle Leverich, and more recently in the article "Treatment of Bipolar Depression: Evolving Recommendations" in the journal *Psychiatric Clinics of North America*. An open access article by Post, "New Perspectives on the Course and Treatment of Bipolar Disorders," published in the journal *Edizioni Minerva Medica S.p.A.* in 2017, describes the need for early and sometimes complex combination therapy, including the non-intuitive idea that more medications (carefully prescribed) can actually produce fewer side effects than large doses of a single medication.

Another good resource for patients is a daily personal calendar that can be used to track ongoing symptoms, side effects, and response to medications. We offer several types of these calendars free on our website, bipolarnews.org. Click on the 'Mood Charting' tab.

My Mood Monitor, or What's My M3, is a validated screening instrument that can detect depression, anxiety disorders, and mania in response to weekly self-reports. It is available online and as an app, and can be used to track illness course and response to treatment.

In This Issue:

Generic Seroquel XR Approved

Earlier this year, **the US Food and Drug Administration approved a generic version of Seroquel XR tablets,** which are used to treat both depression and mania in bipolar disorder, schizophrenia, and to augment the effects of antidepressants in unipolar depression. Also known as quetiapine, the generic tablets will be available in 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg doses.

Seroquel XR is taken once per day several hours before bedtime in the acute treatment for bipolar depression (300 mg/day), mania or mixed episodes (300–600 mg/day) or their prevention (400 mg/day); or paired with antidepressants to treat unipolar depression (150–300 mg/day).

The generic tablets, which are expected to be more affordable than Seroquel XR, are produced by Pharmadax Inc.

Offspring of Bipolar Parents Have More Psychiatric Illness

A 2017 study from the Czech Republic found that children and adolescents with at least one parent with bipolar disorder had much higher lifetime rates of mood and anxiety disorders than their peers who did not have a parent with bipolar disorder. The offspring of bipolar parents also had lower quality of life, less social support, poorer self-perception, poorer relationships with their peers and parents, and more difficult home lives than those whose parents did not have bipolar disorder.

Bipolar Network News
bipolarnews.org

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

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

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

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

To subscribe or unsubscribe, see our website or email us at:

info@bipolarnews.org.

Note that we do not accept requests to subscribe friends or family members. Please have them contact us directly.

The study by Michal Goetz and colleagues in the *Journal of Child and Adolescent Psychopharmacology* reported that 86% of the children of bipolar parents would be diagnosed with a psychiatric disorder in their lifetime. Similarly, David Axelson and colleagues from the Pittsburgh Bipolar Offspring Study reported in the *American Journal of Psychiatry* in 2015 that 74.2% of children with a parent with bipolar disorder would receive a lifetime psychiatric diagnosis, and a 2006 study by Myrna M. Weissman in the *American Journal of Psychiatry* found that the offspring of a unipolar depressed parent were three times more likely to have a psychiatric illness than offspring of nondepressed parents over 20 years of follow-up. Another study by this editor (Robert M. Post) and colleagues in the Bipolar Collaborative Network published in the *Journal of Affective Disorders* in 2016 found that a third of children at high risk due to a parent's bipolar diagnosis would go on to have a psychiatric illness.

The Goetz study included a total of 86 participants between the ages of 7 and 18. Half had a parent with bipolar disorder and half did not. One limitation of the study was its recruitment procedure. Parents with bipolar disorder who enrolled their children in the study may have done so out of concern for their offspring's mental health, increasing illness rates in the group with bipolar parents. Researchers were also aware of parents' diagnoses, which may have affected their ratings of the young people's symptoms. Despite these limitations, the study and its predecessors still suggest that psychiatric illness in a parent puts children at very high risk for a psychiatric illness themselves and can affect their wellbeing in a variety of ways.

Goetz and colleagues suggest that there is a need for proactive and complex care of families with psychiatric illness. They suggest that good communication is needed between adult and youth psychiatric services, with physicians who treat adults with bipolar disorder inquiring about those patients' children and referring them to specialized psychiatric services for youth.

Editor's Note: I not only endorse the conclusions of Goetz and colleagues, but would further recommend that parents with a diagnosis of bipolar disorder or unipolar depression discuss their children's mood and behavior with their own psychiatrists and the children's primary care physicians.

Parents of children aged 2 to 12 may enroll in our own Child Network, a secure online portal where they can record weekly ratings of their children's symptoms and share these with their physicians. (For more information, see page 11 or visit our website bipolarnews.org and click on the Child Network tab.)

There are many effective psychotherapeutic interventions for children with anxiety and mood disorders that should be sought for a child with symptoms that impair his or her functioning. Two evidence-based treatments are Family Focused Therapy, which incorporates family members into treatment so that they better understand the illness and can be supportive of the affected child, and cognitive behavioral therapy, in which negative patterns of thoughts and behaviors are challenged and patients are taught more effective problem-solving skills. When childhood psychiatric illness is recognized and treated appropriately, the results are often excellent, and it is possible that heading off the illness early may even prevent the development of more severe illness later in the child's life.

bipolarnews.org

Evidence-Based Psychotherapies for Young Children

As many as 7–10% of children under the age of 5 have mood or behavioral problems, and this risk is even higher when a parent has a mood disorder. However, many families are not able to access treatment for these children due to their location, a lack of providers, or insurance problems.

A 2016 article by Mary Margaret Gleason and colleagues in the journal *Technical Report in Pediatrics* summarizes psychotherapeutic treatments for children that are supported with rigorous evidence. Some of these include infant-parent psychotherapy, video feedback for positive parenting, attachment biobehavioral catch-up (or ABC, in which caregivers are taught to re-interpret the signals of children who previously experienced maltreatment, providing nurturing in response), parent-child interaction therapy, and programs that combine parenting support with illness prevention, such as the Incredible Years series (for behavioral difficulties), the New Forest Programme (for attention-deficit hyperactivity disorder or ADHD), and Helping the Noncompliant Child (for oppositional behavior).

Gleason and colleagues suggest that pediatricians should take the lead in assessing young children and recommending appropriate psychotherapeutic approaches.

One resource available to parents is our own Child Network. It consists of an online portal where parents can provide weekly ratings of their children's symptoms. These can be provided to the child's physician to facilitate diagnosis and to clinicians to more effectively evaluate the results of treatment. The data provided to the Child Network will in turn help us understand how children are being treated in the community. To learn more or join the network, visit our website bipolarnews.org and click on the tab for Child Network. There a few initial forms to fill out, but the weekly rating process is quick and can provide a great picture of a child's wellbeing over time, including evaluating the effectiveness of any treatments.

Brain Scans Differentiate Suicidal from Non-Suicidal Patients with Bipolar Disorder

People with bipolar disorder are at high risk for suicidal behavior beginning in adolescence and young adulthood. A 2017 study by Jennifer A. Y. Johnston and colleagues in the *American Journal of Psychiatry* uses several brain-scanning techniques to identify neurobiological features associated with suicidal behavior in people with bipolar disorder compared to people with bipolar disorder who have never attempted suicide. Clarifying which neural systems are involved in suicidal behavior may allow for better prevention efforts.

The study included 26 participants who had attempted suicide and 42 who had not. Johnston and colleagues used structural, diffusion tensor, and functional magnetic resonance imaging (MRI) techniques to identify differences in the brains of attempters and non-attempters.

Compared to those who had never attempted suicide, those who had exhibited reductions in gray matter volume in the orbitofrontal cortex, hippocampus, and cerebellum. They also had reduced white matter integrity in the uncinate fasciculus, ventral frontal, and right cerebellum regions. In addition, attempters had reduced functional connectivity between the amygdala and the left ventral and right rostral prefrontal cortex. Better right rostral prefrontal connectivity was associated with less suicidal ideation, while better connectivity of the left ventral prefrontal area was linked to less lethal suicide attempts.

Deep TMS May Improve Treatment-Resistant Bipolar Depression

Deep transcranial magnetic stimulation (dTMS) is a non-invasive treatment that has been shown to be effective in unipolar depression. It consists of a helmet fitted to the head, which uses magnetic coils to create an electric field in a desired brain region.

A 2017 double-blind randomized study by Diego F. Taveres and colleagues in the journal *Neuropsychopharmacology* found that **20 sessions of dTMS targeting the left dorsolateral prefrontal cortex produced greater improvement in bipolar depression over 4 weeks of treatment than the same number of sham sessions in which participants wore a helmet that delivered similar sounds and scalp sensations without the electrical effects to the brain.** The participants had treatment-resistant bipolar depression that was being treated with medication.

However, dTMS' effects were not significantly different from those of the sham over four additional weeks of follow-up, nor were remission rates significantly different across the two groups. Out of 50 participants, seven dropped out of the study—two from the sham group, and five from the active dTMS group. But there were no occasions on which a participant switched into mania following treatment.

This study suggests that dTMS has the potential to more rapidly improve treatment-resistant bipolar depression as well as unipolar depression.

Three Experts' Different Approaches to Treating PTSD in Veterans

In the *BNN* we have previously described some experts' preferred treatment algorithms for patients with treatment-resistant post-traumatic stress disorder (PTSD), which is often complicated by traumatic brain injury (TBI). In this article, we update and expand upon these expert views.

David Bakish has worked as Medical Director at the Ottawa Psychopharmacology Clinic and is a former professor of psychiatry at the University of Ottawa in Ottawa, Ontario. In addition, he works with the Canadian military seeing patients with PTSD, substance abuse, and traumatic brain injuries. He uses a symptom-driven approach to PTSD, including 6 to 7 targeted medications added in sequence.

Albert Sattin is a professor of psychiatry and biobehavioral sciences at UCLA, belongs to their Brain Research Institute, and is affiliated with both the Ronald Reagan UCLA Medical Center and the Veterans Affairs Greater Los Angeles Healthcare System. He prefers to treat PTSD with a three-part combination of the blood pressure–lowering drug prazosin, a selective serotonin reuptake inhibitor (SSRI) antidepressant, and the atypical antidepressant mirtazapine.

Murray Raskind pioneered placebo-controlled studies of prazosin for PTSD and served as director of the Veterans Affairs Puget Sound Health Care System Mental Health Service, in addition to serving in the Department of Psychiatry and Behavioral Sciences at the University of Washington School of Medicine. Raskind's approach to PTSD includes prazosin, the tricyclic antidepressant amitriptyline, and if needed for sleep, the sedative zolpidem.

Only SSRIs are approved by the US Food and Drug Administration (FDA) for the treatment of PTSD, but these on their own are rarely sufficient to handle the insomnia and other symptoms that accompany PTSD. Exposure therapy, in which patients are gradually led to approach trauma-related memories, feelings, and situations they previously avoided, is the most recommended type of therapy, but it too is often insufficient to treat all the complexities of the illness.

Bakish's Approach

As of early 2014, Bakish's preferred regimen for patients with severe PTSD and traumatic brain injury began with **levetiracetam** (Keppra) to improve sleep and cognition. If needed, he also added trazodone for better sleep. Second, for mood, Bakish would add **desvenlafaxine** (Pristique) because it causes fewer interactions with other drugs than venlafaxine. Third, for mood, energy, cognition, and smoking cessation, Bakish recommends **bupropion** (Wellbutrin). Fourth, for alcohol and drug abuse and anger attacks, he would add **topiramate** (Topamax) to the regimen. Fifth, for depression, anxiety, and irritability, and particularly if topiramate caused cognitive dysfunction, Bakish would add **lamotrigine** (Lamictall). Sixth, patients with paranoia would be prescribed an atypical antipsychotic such as **aripiprazole** (Abilify). Lastly, patients with mood instability would be prescribed **lithium** (which can also provide neuroprotection, anti-suicide effects, and overall health benefits).

By carefully and sequentially adding each of these medications at low doses and titrating the doses slowly upward while remaining below each patient's threshold for side effects, Bakish found that this complex combination treatment was well tolerated by patients and regularly brought about excellent response, often including symptom remission and good cognitive function after 3 to 4 months in highly impaired Canadian special forces soldiers. (See more details of his dosing strategy in the original article in the BNN at bipolarnews.org.)

Sattin's Approach

Sattin's key insight (discussed with this editor in late 2015) is that **prazosin should be administered three times a day because of its short half-life.** This allows for the treatment of daytime as well as sleep-related PTSD symptoms. Sattin has patients choose one of three different schedules: 6am/2pm/10pm, 7am/3pm/11pm, or 8am/4pm/12am. Prazosin comes in 1 mg, 2 mg, and 5 mg tablets, but patients must begin by taking the 1 mg doses to reduce the risk of orthostatic hypotension (low blood pressure upon standing up). The dose is slowly increased as tolerated and as needed for symptom improvement. For patients with elevated blood pressure at baseline, which Raskind has shown is a predictor of good response to prazosin, **Sattin starts his sequence with prazosin, and then follows with an SSRI and mirtazapine (Remeron).**

For patients without elevated blood pressure at baseline, Sattin begins by prescribing one of the two selective serotonin reuptake inhibitors (SSRIs) approved by the FDA for use in PTSD—sertraline (Zoloft) or paroxetine (Paxil)—and then adds mirtazapine if necessary, which additionally targets the insomnia typically associated with PTSD. If these patients still remain symptomatic, Sattin then adds prazosin to their regimen.

Raskind's Approach

Raskind's approach, which he shared with this editor in late 2016, resembles Sattin's more closely than Bakish's. Raskind recommends beginning with **prazosin** with the triple goal of improving PTSD symptoms and nightmares, preventing migraines, and helping patients avoid alcohol. Raskind then suggests adding **amitriptyline** (Elavil) for its ability to treat depression and sleep disturbance, its anti-pain effects, and its prevention of migraines. Lastly, Raskind adds **zolpidem** (Ambien) if needed for continued insomnia.

More Approaches to PTSD in Veterans, Continued

Additional Options

To add to this diversity of opinion, this editor would also suggest consideration of a few other treatments. **N-acetylcysteine** (NAC) can improve depression and obsessive ruminations as well as decreasing cravings for substances such as alcohol, tobacco, cocaine, and marijuana. Dosage can begin at 500/600 mg twice daily and be increased to 1000/1200 mg twice daily. A recent study by Susie E. Back and colleagues (see page 7) reported success using NAC to treat combined PTSD and substance abuse.

Neuropsychological approaches such as those that make use of the memory reconsolidation window also deserve further consideration. See page 6 for more details on these approaches. This therapy has some similarities to processes used in Eye Movement Desensitization and Reprocessing (EMDR) therapy, also used for trauma.

Vagal nerve stimulation, consisting of a pacemaker-like device implanted under the skin in the chest that delivers regular, mild electrical pulses to the brain via the left vagus nerve, can enhance extinction learning such as eliminating a fear response that is no longer appropriate to a patient's current environment.

The histone deacetylase inhibitor **valproate** has also been shown to enhance extinction learning in animals, by increasing an allele of brain-derived neurotrophic factor (BDNF) that is important for extinction learning.

There is some literature that suggests that anticonvulsants such as **carbamazepine and valproate** could be used to improve sleep and reduce flashbacks in PTSD. This requires further study.

Intravenous **ketamine** has also been found to improve treatment-resistant PTSD.

A wealth of data now supports the finding that patients with PTSD have increased inflammatory markers (such as CRP, Il-1, Il-6, and TNF alpha). How best to approach these abnormalities from a treatment perspective remains to be studied.

Editor's Note: There is a vast array of treatment options (almost none of which are FDA-approved) for patients with difficult-to-treat PTSD, which is often complicated by traumatic brain injury. How best to choose among them and in what order to introduce them in a given patient is a bit of a mystery. Traditional placebo-controlled studies of single medications are not likely to be clinically helpful in determining the appropriate sequence of available treatments.

Making patients aware of the multiple options and the diversity of opinions about treatment of PTSD might be a good place to start, and could give hope to patients who might believe they are untreatable. Using a series of targeted medications that are likely to improve specific aspects of the illness may be necessary. The sleep disturbances that accompany PTSD, while addressed differently by the three experts above, are a key element to treat, especially since the FDA-approved SSRIs for PTSD typically do not help much with this difficult symptom.

Perhaps the single most important thing is to let patients know that their physician will continue to work intensively with them using sequential treatments until good results are achieved. It is also important to convey that the use of multiple medications, virtually all of which may be off-label, will likely be necessary.

With complex combination therapy like the expert approaches described above, it is crucial that patients provide detailed and systematic feedback about any side effects they may experience and the impact of each drug on the targeted symptoms at each point in the treatment sequence. This allows the additions and combinations of drugs to be optimized for each individual.

Monitoring symptoms, treatment response, and side effects can be done using resources such as MyMoodMonitor/What's My M3?, a website and app that covers depression, anxiety, PTSD symptoms, alcohol and drug use, and suicidal ideation. Making daily ratings of mood, sleep, medications, side effects, anxiety, flashbacks, nightmares, etc. using a personal calendar such as those available for free on our website (bipolarnews.org, click on the tab for Mood Charting) would also be valuable.

Perhaps the single most important thing is to let patients with PTSD know that their physician will continue to work intensively with them using sequential treatments until good results are achieved. It is also important to convey that the use of multiple medications, virtually all of which may be off-label, will likely be necessary.

There is a moderately high incidence of PTSD and head trauma in patients with bipolar disorder, and approaching bipolar mood instability and PTSD symptoms at the same time is typically necessary.

Finally, patients must remember that treatment decisions should be based on discussions with their treating physicians. The BNN provides often preliminary or in some cases anecdotal information about drugs (such as the three expert opinions above). Only a treating physician is qualified to decide whether a given treatment would be appropriate for a given patient. The actions of physicians and therapists must be based on their own judgment, expertise, and review of the published literature rather than our reports here.

Revising Traumatic Memories in the Reconsolidation Window

We have previously described in the BNN how therapies can take advantage of the memory reconsolidation window to reduce the power of traumatic memories. **Five minutes to one hour following active emotional recall of a traumatic event, a 'window' opens during which therapies can revise or extinguish the traumatic memory.** A 2017 article by our Editor-in-Chief Robert M. Post and Robert Kegan in the journal *Psychiatric Research* describes how the reconsolidation window could theoretically be used to prevent recurring depressive episodes.

The theory is based on the idea that depressive episodes initially stem from stressors, but eventually become ingrained in the brain's habit memory system. Cognitive behavioral therapy during the memory reconsolidation window might be a good way to disrupt these habit memories.

The memory reconsolidation window has already been used successfully to reduce traumatic memories and even to reduce heroin and cocaine cravings in addiction. The idea in changing traumatic memories, in the words of researcher Göran Högberg in a 2011 article in the journal *Psychology Research in Behavior Management*, is to "change a reliving intruding memory into a more distant episodic memory." Post and Kegan suggest that work in depression would have a similar goal, to rework the triggering experience and render the depressive experience "less harsh, severe, [and] self-defeating (guilt-inducing)."

In exploring this new therapeutic approach, Post and Kegan suggest that it might be best to begin with patients whose depressive episodes are triggered by stressors.

The patient would be encouraged to recall the memory of the particular stressor and any emotions related to it. Then they would be prompted to reframe the memory, either by recognizing adaptive aspects of their response, focusing on their youth at the time of the stressor in the case of childhood memories, addressing any guilt the patient may feel, or other techniques used in trauma therapy. Evoking positive feelings during this period via relaxation exercises would be another useful practice.

In addition to targeting stressors that precede depression, the stress of the depressive experience itself could be a target of reframing during the reconsolidation window.

Questions remain, such as whether to target early or more recent memories, and whether this technique would be as useful in reducing manic episodes. Patient characteristics might also affect the success of this type of therapeutic intervention.

Post and Kegan also address how the therapy might be used in different stages of illness, and how it might be combined with other therapies, such as medications or procedures such as repeated transcranial magnetic stimulation (rTMS).

Antibiotic Doxycycline May Block PTSD Symptoms

A 2017 proof-of-concept study suggests that the antibiotic doxycycline can block the formation of negative thoughts and fear memories, perhaps offering a new way to treat or prevent post-traumatic stress disorder (PTSD).

In the study by Dominik R. Bach in the journal *Molecular Psychiatry*, healthy adults who received doxycycline had a lower fear response to fearful stimuli compared to healthy adults who received a placebo. The 76 participants received either doxycycline or placebo and then were taught to associate a color with an electric shock. Later, they were exposed to the color accompanied by a loud sound (but no shock), and their startle response was measured by tracking eye blinks, an instinctive response to sudden threats. Bach and colleagues found that **the fear response was 60% lower in those participants who received doxycycline, suggesting that the antibiotic disrupted the fear memory linking the color to a threat.**

The theory is based on evidence that doxycycline can inhibit metalloproteinase enzymes, which are involved in memory formation.

While in the study doxycycline was delivered before the fearful event occurred, there is hope that the antibiotic could also do some good after the fact. There is growing evidence that actively recalling a traumatic event can open a 'memory reconsolidation window' during which emotions associated with that event are open to change. Bach and colleagues hope to follow up with studies involving this reconsolidation window.

Another line of research is exploring how pain medications may reduce the emotional power of traumatic memories, because intense pain strengthens memory consolidation. See page 7 (above right) for a description of how the potent steroid dexamethonine can increase the effectiveness of memory extinction in people with PTSD.

Steroid Dexamethasone Facilitates Fear Extinction

A 2017 article by Vasiliki Michopoulos and colleagues in the journal *Psychoendocrinology* reports that the potent steroid dexamethasone reduced the fear-potentiated startle response in patients with post-traumatic stress disorder (PTSD) but not in healthy controls. Dexamethasone acts on glucocorticoid receptors to suppress the body's secretion of cortisol.

In the study, participants both with and without PTSD were taught to associate a picture of a blue square or a purple triangle with an uncomfortable short blast of air to the larynx (voicebox) and a loud burst of broadband noise in the participants' headphones.

Some participants were given a placebo the night before the study, while others received a 0.5 mg dose of dexamethasone. Those who received dexamethasone the night before the study acquired a startle response to the blue square or purple triangle as much as other participants.

People without PTSD were easily able to eliminate their fear of the visual symbol when it was no longer linked to the noise and the blast of air, regardless of whether they had taken dexamethasone. However, among those with PTSD, only those who received dexamethasone were able to eliminate this fear-potentiated startle response and properly discriminate between safe and unsafe signals. People with PTSD who received the placebo maintained the fearful response to the blue square or purple triangle and startled in response to safe symbols.

People with PTSD may have difficulty learning to inhibit their fearful responses to stimuli that are no longer dangerous. In this study, **the patients with PTSD continued to startle even after repeated presentations of the visual symbol without any accompanying air blast, while the controls showed excellent extinction of the response. After dexamethasone, but not placebo, patients with PTSD were just as successful in extinguishing the fear potentiated startle response as the controls.** The authors conclude that dexamethasone could help facilitate extinction-based interventions used in PTSD, such as exposure therapy delivered during cognitive behavioral therapy or virtual reality exposure therapy.

Different Types of Trauma Affect Brain Volume Differently

Post-traumatic stress disorder (PTSD) has been associated with decreased volume of gray matter in the cortex. Research by Linghui Meng and colleagues has revealed that the specific types of trauma that precede PTSD affect gray matter volume differently.

At the 2016 meeting of the Society for Neuroscience, Meng reported that PTSD from accidents, natural disasters, and combat led to different patterns of gray matter loss. PTSD from accidents was associated with gray matter reductions in the bilateral anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). PTSD from natural disasters was linked to gray matter reductions in the mPFC and ACC, plus the amygdala and left hippocampus. PTSD from combat reduced gray matter volume in the left striatum, the left insula, and the left middle temporal gyrus.

Meng and colleagues also found that severity of PTSD was linked to the severity of gray matter reductions in the bilateral ACC and the mPFC.

In a 2016 article in the journal *Scientific Reports*, Meng and colleagues reported that **single-incident traumas were associated with gray matter loss in the bilateral mPFC, the ACC, insula, striatum, left hippocampus, and the amygdala, while prolonged or recurrent traumas were linked to gray matter loss in the left insula, striatum, amygdala, and middle temporal gyrus.**

Successful Trial of N-Acetylcysteine for Veterans with PTSD and Substance Abuse

The antioxidant N-acetylcysteine (NAC) can improve a number of habit-related conditions, such as substance use disorders, gambling, and compulsive hair-pulling. It also aids in the treatment of depression and obsessive-compulsive disorder (OCD). A 2016 study by Susie E. Back and colleagues in the *Journal of Clinical Psychiatry* found that NAC can also improve symptoms of post-traumatic stress disorder (PTSD) in veterans who also had substance use disorders.

In the pilot study of 35 veterans, participants were randomized to receive an 8-week course of NAC (2,400 mg/day) or placebo, plus cognitive-behavioral therapy targeting their substance use disorder. PTSD and substance use disorders have some overlapping neurobiological features, such as impaired prefrontal cortex regulation of basal ganglia circuitry.

At the end of the 8-week trial, those veterans who received NAC showed improvement in PTSD symptoms, substance cravings, and depression compared to those who received placebo. Substance use was similar and low among both groups. Side effects were minimal.

Continued on Page 10

Dietary Supplements for Autism: Up-to-Date Research

A 2017 review article by Yong-Jiang Li and colleagues in the journal *Frontiers in Psychiatry* describes the current research on dietary supplements that may help improve symptoms of autism spectrum disorder.

Some of the most promising research was on vitamin D, folinic acid, and sulforaphane. Methyl B12 and digestive enzyme therapy had some positive effects, while gluten- and casein-free diets and omega-3 fatty acids did not seem to help improve autism symptoms.

Vitamin D

Li and colleagues described a randomized, controlled trial of vitamin D in 109 children with autism aged 3 to 10 years. The experimental group received doses of 300 IU/kg of body weight/day, not exceeding 5000 IU/day. By the end of the four-month study, vitamin D levels had significantly increased in the experimental group compared to the control group. Those who received vitamin D also showed significant improvement on all ratings of autism symptoms, which included general scales of autism symptoms and more specialized checklists that capture aberrant behavior and social responsiveness.

Folinic Acid

The review article also described a randomized double-blind placebo-controlled trial of folinic acid in 48 children with autism spectrum disorder and language impairment. Participants received high-dose folinic acid (2 mg/kg/day) or placebo for 12 weeks. Those who received folinic acid, a form of folic acid that can readily be used by the body, showed significant improvements in verbal communication and core autism symptoms compared to those who received placebo. Participants who tested positive for folate receptor alpha autoantibodies (FRAA), which disrupt the transportation of folate across the blood-brain barrier and are common in autism, showed greater improvements from taking folinic acid than those without this abnormality.

Sulforaphane

Sulforaphane is a phytochemical derived from cruciferous vegetables. It can create metabolic effects that resemble those of a fever, which can improve behavioral symptoms of autism. Sulforaphane also fights oxidative stress, inflammation, and DNA damage, which may play roles in autism. Li and colleagues described the first double-blind, placebo-controlled trial of sulforaphane treatment in 29 boys aged 13 to 17 years. The boys who received sulforaphane showed significant improvement in autism-related behavior, especially social interaction and communication, after 18 weeks compared to those who received placebo. Sulforaphane has low toxicity and is well tolerated.

Methyl B12

Methyl vitamin B12 is another supplement with some positive data in the review by Li and colleagues. They described results of a double-blind placebo-controlled trial of methyl B12 in 57 children aged 3 to 7 years with autism spectrum disorder. The children who received methyl B12 showed significant improvements in their autism compared to those who received placebo when rated by clinicians, but not when rated by their parents. The children in the experimental group also showed improvements in some metabolic measures (increased methionine, decreased S-adenosyl-lhomocysteine (SAH), and a better ratio of S-adenosylmethionine (SAM) to SAH) that were associated with the improvement in clinician-rated symptom scores.

Digestive Enzyme Therapy

Some studies described by Li and colleagues implied that probiotics and digestive enzymes could help in autism. One double-blind randomized controlled trial of digestive enzyme therapy in 101 children with autism spectrum disorder aged 3 to 9 years found that after three months, those who received the therapy had significant improvement in emotional response, general impression autistic score, general behavior, and gastrointestinal symptoms. Effects on core symptoms of autism were inconclusive, but gastrointestinal improvement was clear.

N-acetylcysteine

Editor's Note: N-acetylcysteine (NAC) was not included in the review by Li and colleagues, but three placebo-controlled studies have suggested that the antioxidant can be helpful in autism. One study used NAC as a monotherapy, while the other two paired NAC with the antipsychotic risperidone.

Less Effective Strategies

Two types of dietary changes that did not seem to help in autism were a gluten- and casein-free diet and supplementation with omega-3 fatty acids. Li and colleagues found no evidence that a diet free of gluten and casein improved autism symptoms, nor did supplementation with extra gluten and casein worsen symptoms. Among six randomized controlled trials of omega-3 fatty acids in autism spectrum disorder, five showed no effect of omega-3s on core symptoms of autism.

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

Autism Linked to Banned Chemicals

An explanation for the increase in autism rates over the past few decades has remained elusive in the years since researcher Andrew Wakefield fabricated a link between the disorder and mercury in vaccinations that was eventually completely debunked.

In 2016, researcher Kristin Lyall of Drexel University's A.J. Drexel Autism Institute published findings suggesting that **high exposure during pregnancy to chemicals banned in the 1970s increased risk of an autism spectrum disorder.**

The study looked at 1144 children born in southern California between 200 and 2003. Their mothers had participated in California's Expanded Alphafetoprotein Prenatal Screening Program, intended to identify birth defects during pregnancy. Second trimester blood samples from these women could be used to determine to what extent their children were exposed to the chemicals while in utero. The researchers found an association between the highest exposure levels and later autism diagnoses.

Lyall and colleagues measured levels of two different classes of organochlorine chemicals: polychlorinated biphenyls (PCBs), used as lubricants, coolants, and insulators; and organochlorine pesticides (OCPs), including DDT, which was banned in 1972. All production of organochlorine chemicals was banned in the US in 1977, but they remain in the environment and are absorbed in the fat of animals that humans eat. According to Lyall, people in the US generally have detectable levels of organochlorine chemicals in their bodies.

The study revealed that exposure to two compounds in particular—PCB 138/158 and PCB 153—was linked to dramatically higher autism rates. Level of exposure is key to autism risk. Those children in the top 25 percentile of exposure were 79% and 82% more likely to have an autism diagnosis than those with the lowest levels of exposure, respectively.

High exposure to two other compounds, PCB 170 and PCB 180, increased autism risk by 50%.

The findings by Lyall and colleagues were published in the journal *Environmental Health Perspectives*.

Editor's Note: See right for details of another study by Manish Arora and colleagues, which links autism risk to levels of lead, zinc and manganese absorbed in early life.

The myth that mercury in vaccines causes autism still lingers in our popular culture. Mercury is no longer used in vaccines, but autism rates are still increasing. Perhaps the new findings of a link between heavy metals and autism will help end the misinformation about the safety of vaccines and allow more parents to vaccinate their children without worry.

Study of Baby Teeth Links Autism and Exposure to Heavy Metals Such as Lead

Recent research has revealed that autism is linked to new onset genetic mutations (called 'de novo' mutations) that occur during early fetal development. A new study suggests that levels of heavy metals such as lead and zinc (but not mercury) may affect the likelihood that these mutations will occur.

The 2017 study by Manish Arora and colleagues in the journal *Nature Communications* included twins with and without autism, particularly twin pairs in which one twin had autism and the other did not. An international team of scientists collected naturally shed baby teeth from the twins. The researchers then used lasers to extract specific layers of dentine, the hard substance beneath tooth enamel, which correspond to different developmental periods, including before birth and in early childhood. The researchers then analyzed these dentine samples to determine the children's uptake of various heavy metals in early life.

The analysis showed that **children with autism had higher levels of lead (a neurotoxin) throughout development, but particularly right after birth. Children with autism also had lower uptake of manganese, an essential nutrient. Compared to children without autism, children with autism had lower zinc levels in utero, but higher zinc levels after birth.** Zinc is another essential nutrient. Lead and manganese levels were also linked to autism severity.

The method of analyzing teeth allows researchers to look back in time and measure what children were exposed to years earlier. This may help identify environmental factors that contribute to autism spectrum disorders.

Diuretic Looks Promising for Autism

Phase 2 clinical trials showed that the diuretic bumetanide can reduce the severity of autism spectrum disorders in children aged 3 to 11. A 2017 phase 2B trial assessed side effects and determined the dosage that maximizes benefits and minimizes side effects. Bumetanide will now move on to year-long phase 3 trials in five European countries and may be on the market by late 2021. Bumetanide is an unusually potent 'loop diuretic' (a diuretic that works at the loop of Henle in the kidney). In preliminary studies, it has also been used to prevent seizures in newborns.

The phase 2B study included 88 mostly male participants with autism spectrum disorder between the ages of 2 and 18. The participants were randomly assigned to receive 0.5 mg, 1.0 mg, or 2.0 mg twice daily of bumetanide or a placebo for three months.

Bumetanide improved core symptoms of autism such as social communication and restricted interest across all ages. Side effects were worse at higher doses, and included hypokalemia (low potassium), increased urine production, loss of appetite, dehydration, and weakness or lack of energy.

Researchers led by Eric Lemonnier determined that doses of 1.0 mg twice/day produces the most benefits while controlling side effects.

Brain Growth in Infancy Predicts Autism

A 2017 article in the journal *Nature* suggests that brain scans during infancy can predict which kids at risk for autism will go on to develop the disorder, leading to earlier treatment. Studies have shown that children with autism have enlarged brains. The new research zeroes in on the time period when this overgrowth occurs.

Researcher Heather Cody Hazlett and colleagues used magnetic resonance imaging (MRI) scans to measure brain growth in 106 high-risk infants with siblings who have autism spectrum disorder and 42 infants at low risk. The scans were performed when the infants were 6 months, 12 months, and 24 months old.

In 15 infants diagnosed with autism at 24 months, the researchers saw hyperexpansion of cortical surface area between 6 and 12 months and brain overgrowth between 12 and 24 months. The overgrowth coincided with symptoms of autism appearing, and with symptom severity.

The reseachers were able to create a computer algorithm that could predict whether an infant would develop autism based on images of brain growth. The algorithm corrected predicted autism 81% of the time.

Studies have suggested that starting interventions to treat autism early provides the best benefits, so using MRI to diagnose or predict autism before symptoms appear might allow for even earlier treatment that could be more effective.

The study also identified the sites of unusual brain development, which may help researchers determine what mechanisms lead to brain overgrowth in autism and eventually develop treatments that prevent these changes.

Reduced Functional Connectivity of Amygdala Linked to Autism in Pre-School Boys

A 2016 study in the *Journal of the American Academy of Child and Adolescent Psychiatry* found that preschool-aged boys with autism have weaker functional connectivity of the amygdala than typically-developing children of the same age. Researchers led by Mark D. Shen used resting-state functional connectivity magnetic resonance imaging (MRI) to measure how connected the amygdala was to other regions of the brain in 72 young boys (average age 3.5).

The boys with autism had weaker connectivity between the amygdala and regions linked to social communication, language deficits, and repetitive behaviors. These areas include the medial prefrontal cortex (mPFC), bilateral temporal lobe, striatum, thalamus, cingulate cortex, and cerebellum.

The weaker the connectivity between these regions, the more severe the boys' autism symptoms were. They showed impairments in overall cognitive ability and both verbal and nonverbal ability.

Treating PTSD in Veterans with Substance Abuse (continued)

Continued from Page 7

While these results were preliminary, they suggest that NAC could treat both PTSD and substance use disorders, which often occur together. Larger studies are expected to follow.

Editor's Note: These preliminary data add to the evidence that NAC has remarkably wide utility in addictions (cocaine, alcohol, nicotine, and marijuana), habits (including OCD, trichotillomania/hair-pulling, nail biting, skin-picking, and cutting), depression and anxiety in bipolar disorder and negative symptoms in schizophrenia.

IVIG Produces Long-Term Results in PANDAS

PANDAS, or pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, is an autoimmune condition that produces psychiatric symptoms that appear suddenly following a case of strep throat in children. These symptoms can include obsessive-compulsive symptoms, tics, and behavioral dyscontrol and regression. Treatments are still experimental, but those that target the immune system are expected to be most successful at improving PANDAS.

In 2015, Miro Kovacevic and colleagues published a case series describing the use of intravenous immunoglobulin treatment (IVIG) in twelve children with PANDAS in the *Journal of Child and Adolescent Psychopharmacology*. **One or in some cases two injections of IVIG brought about long-term remission in the children with PANDAS.**

IVIG consists of a wide range of antibodies from multiple individuals delivered via injection. This increase in the quality or quantity of antibodies in the recipient is thought to suppress the production of antibodies that attack brain cells, causing PANDAS. The case series was based on patients at a large clinical practice that specializes in the treatment of PANDAS. The practice used a dosage of 1.5g/kg divided into two daily doses of 750 mg/kg, meant to match twice the volume of the patients' own immunoglobulin G.

IVIG and other anti-inflammatory approaches are also effective in PANS, a more general variation on PANDAS in which psychiatric symptoms occur following an infection other than strep.

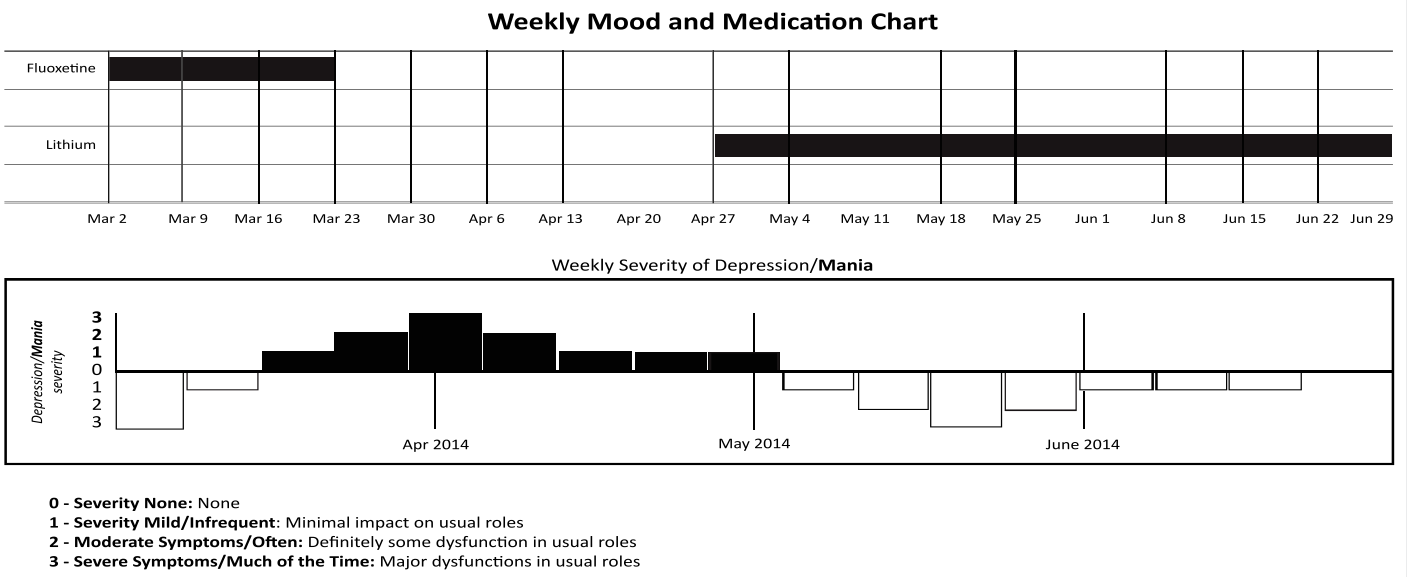
Is Your Child at Risk for a Mood Disorder? Join the Child Network!

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

Joining the Child Network could help families and doctors identify these illnesses earlier.

The Child Network is specifically for parents of children ages 2 to 12 who are at high risk for a mood disorder or have symptoms of a mood disorder. Parents assess their child weekly using a secure website. There is also a short demographic questionnaire and a more detailed symptom checklist to be filled out once a year. The network will collect information about which treatments children are already taking, how effective they are, and for which children.

We believe that this network will be helpful to its participants. Parents will be able to print out the ongoing weekly ratings in a graphic form so that the child's symptoms and responses to any treatments they receive over time can easily be visualized (as illustrated below).



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

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

Thank you for your time and interest in the Child Network.

Robert M. Post, MD and Michael Rowe, PhD
Bipolar Collaborative Network, and
Robert L. Findling, MD, MBA, Principal Investigator
This research study is IRB approved by the Johns Hopkins University School of Medicine
Research Study, Principal Investigator: Robert L. Findling, MD, MBA , IRB Study #00026940

BNN
PO Box 18
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED