

# Bipolar Network News

Published since 1995

The latest news on bipolar disorder research from around the world

bipolarnews.org

---

**Updates from the 2013 Meeting of the American Academy of Child and Adolescent Psychiatry**

Vol. 17, Issue 6, 2013

## Treating Substance Abuse: A Step Forward

New discoveries in neuroanatomy are helping clarify what addiction looks like in the brain. Peter Kalivas of the Medical University of South Carolina reported at the 2013 meeting of the Society of Biological Psychiatry that **most drugs of abuse alter glutamate levels and the plasticity of synapses in the nucleus accumbens, the reward area of the brain**. Glutamate is the main excitatory neurotransmitter in the brain, and compulsive habits may be associated with increased release of glutamate in this brain area.

During chronic cocaine administration, for example, the neurons in the nucleus accumbens lose their adaptive flexibility and their ability to respond to signals from the prefrontal cortex. Normally, low levels of stimulation would induce long-term depression (LTD) while high levels of stimulation would induce long-term potentiation (LTP). These are long-term changes in the strength of a synapse, which allow the brain to change with learning and memory. When long-term potentiation and long-term depression are no longer possible, memory and new learning in response to messages from the prefrontal cortex are diminished.

Given this absence of flexible responding, animals extinguished from cocaine self-administration (when a lever they had pressed to receive cocaine ceases to provide cocaine) are highly susceptible to cocaine reinstatement if a stressor is presented or if a signal appears that suggests the availability of cocaine. This cocaine reinstatement is associated with high levels of glutamate in the nucleus

accumbens, so Kalivas reasoned accurately that lowering these levels would be associated with a lesser likelihood of cocaine reinstatement.

The drug N-acetylcysteine (NAC), which is available from health food stores, decreases the amount of glutamate in the nucleus accumbens by inducing a glutamate transporter in glial cells that helps clear excess synaptic glutamate. In Kalivas' research, NAC prevented cocaine reinstatement, cocaine-induced anatomical changes in spine shape (bigger, stubby spines), and the loss of long-term potentiation and long-term depression in the nucleus accumbens.

The findings on NAC in animal studies led to a series of important small placebo-controlled clinical trials in people with a variety of addictions, and **positive results have been found using NAC in people addicted to opiates, cocaine, alcohol, marijuana, and gambling**. It also decreases hair-pulling in trichotillomania and reduces stereotypy and irritability in children with autism.

NAC also appears to be effective in the treatment of unipolar and bipolar depressed patients in placebo-controlled trials by Australian researcher Michael Berk. Thus, NAC could be useful for patients with affective disorders who are also having difficulties with comorbid substance use.

Some antibiotics (that are not commonly available) also induce the glutamate transporter in glial cells of the nucleus accumbens, offering a potential new approach to treating some addictions.

### Also in this issue:

Omega-3s for Depression	p. 2
Cognitive Behavioral Therapy for Youth with Depression	p. 3
Malnutrition's Effects	p. 4
Ketamine for Depression	p. 4-5
Course of Bipolar Illness	p. 6-7

## Depression in Youth Is Tough to Treat and Requires Persistence and Creativity

At a symposium on ketamine for the treatment of depression in children at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, David Brent, a professor at the University of Pittsburg, said in the opening that **as many as 20% of adolescents who are depressed fail to improve, develop chronic illness, and are thus in need of alternatives to traditional treatment**. Predictors of non-improvement include substance use, low-level manic symptoms, poor adherence to a medication regimen, low blood levels of antidepressants, family conflict, high levels of inflammation in the body, and importantly, maternal depression. In adolescents insomnia

*Continued on Page 2*

## Depression in Youth Is Tough to Treat and Requires Persistence and Creativity

*Continued from Page 1*

was associated with poor response, but in younger children insomnia was associated with a better response.

Brent suggested using melatonin and sleep-focused cognitive behavioral therapy for insomnia in youth, but not using trazodone (which is commonly prescribed). Trazodone is converted to a compound called Metachlorophenylpiperazine or MCPP, which induces anxiety and dysphoria. MCPP is metabolized by hepatic enzymes 2D6, and fluoxetine and

paroxetine inhibit 2D6, so if trazodone is combined with these antidepressants, the patient may get too much MCPP.

Surprisingly and contrary to some data in adults about the positive effects of therapy in those with abuse histories, in the study TORDIA (Treatment

of SSRI-Resistant Depression in Adolescents), if youth with depression had experienced abuse in childhood, they did less well on the combination of cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs) compared to SSRIs alone.

## Omega-3-Fatty Acids Promising For At-Risk Kids with Depression

Several studies in adults and children suggest that omega-3 fatty acid supplementation may have antidepressant effects. At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry in October, Melissa DelBello, a professor at the University of Cincinnati, reported on a new study of omega-3 fatty acids in depressed children who had a parent with bipolar disorder. **The children taking omega-3 fatty acids were more likely to improve than those taking a placebo, but the findings were only of marginal significance.**

Cold-water fish are a good source of omega-3 fatty acids, and DelBello said salmon is by far the best in this regard. People who live in countries where fish is consumed in greater quantities are less likely to suffer from depression. Other sources of omega-3 fatty acids include shellfish, plant and nut oils, English walnuts, flaxseed, algae oils, and fortified foods.

The omega-3 fatty acids from fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while the omega-3 fatty acids from plants are alpha-linolenic acid (ALA), which breaks down into EPA and DHA. All of these are anti-inflammatory, though one must consume much greater quantities of ALA to match the benefits of EPA and DHA. In contrast, omega-6 fatty acids, which are much more common in the typical American diet, are pro-inflammatory.

In DelBello's study of 56 depressed children of a parent with bipolar disorder, the participants were randomized to either 1.8 g of omega-3 fatty acids (1.2 g of EPA and 0.6 g of DHA) or placebo (olive oil). Those who received the omega-3 fatty acids had a 55.6% rate of remission versus 34.5% for those who received placebo, but while the odds ratio of 2.4 favored the omega-3 fatty acids, the difference in remission rates was not statistically significant, likely because of the small size of the study. However, improvement on the Children's Depression Rating Scale was significantly different across the two groups, with children taking omega-3s improving more. Omega-3 fatty acids are known to have an anticoagulant effect (preventing the clotting of blood), and four children in the study did have prolonged clotting times (but no clinical problems with bleeding).

*Editor's Note: Given the existing literature on omega-3 fatty acids and the trend seen in this study, omega-3s are worthy of consideration for the treatment and potentially for the prevention of depression in children. This later possibility is further suggested by findings from Australia that compared to placebo, omega-3 fatty acids significantly reduced the rate of conversion from prodromal (preliminary) psychotic symptoms to a full-blown diagnosis of schizophrenia.*

### Bipolar Network News

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

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

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

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

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

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.

bipolarnews.org

## Cognitive Behavioral Therapy Tailored For Children and Adolescents

At a symposium on early-onset depression at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, **Betsy Kennard described a course of cognitive behavioral therapy tailored to eliminating residual symptoms in children with unipolar depression who had no family history of a parent with bipolar disorder.** In the same study Graham Emslie discussed, the investigators considered cognitive behavioral therapy for the treatment of childhood- and adolescent-onset depression.

The therapy was aimed at achieving health and wellbeing and focusing on positive attributes and strengths in the child, and it was designed to be a shorter than usual course (i.e. four weekly sessions, then four every other week, and one at three months). This regimen typically also included three to five family sessions. Other key components of the therapy included anticipating and dealing with stressors, setting goals, and practicing all the skills learned.

On a visual timeline, children identified and wrote down past stressors, how they felt when depressed, their automatic cognitions, ways they would know when they were feeling down again (i.e. feeling isolated, angry at parents, etc.), their strengths and skills, what obstacles to feeling better existed and how to circumvent them, and their long-term goals.

The therapy was based on the research of Martin Seligman and Giovanni A. Fava, plus Rye's Six S's (soothing, self-healing, social, success, spiritual, and self-acceptance). The children participated in practice and skill-building

in each domain. Sleep hygiene and exercise were emphasized. The idea of "making it stick" was made concrete with phrases on sticky notes taken home and put up on a mirror. Postcards were even sent between sessions as reminders and for encouragement.

*Editor's Note: Most depressed kids don't get completely well (only about 20% after an acute course of medication). Something must be added. This kind of specialized cognitive behavior therapy works and keeps patients from relapsing. This study included only those children with unipolar depression whose parents did not have bipolar disorder. However, Emslie noted that depressed children of a bipolar parent also had an exceedingly low rate of switching into mania (2 to 4%) in his experience, so fluoxetine followed by*

*cognitive behavioral therapy might be considered for treating unipolar depressed children of a bipolar parent.*

*Once children have developed bipolar disorder, evidenced by hypomania or mania followed by depression, antidepressants are to be avoided in favor of mood stabilizers and atypical antipsychotics, since there is a higher switch rate in these youth when they are prescribed antidepressant monotherapy.*

*Since children with bipolar disorder are at such high risk for continued symptoms and relapses, the strategy of adding cognitive behavioral therapy to their successful drug treatment would appear appropriate for them as well as those with unipolar depression, especially since there is a large positive literature on the efficacy of cognitive behavioral therapy, psychoeducation, and Family Focused Therapy (FFT) in children and adults with bipolar depression. As noted previously, FFT is very effective for children at high risk because of a parent with bipolar*

*disorder and who are already symptomatic with anxiety, depression or BP-NOS.*

*Moral of the story: getting kids with unipolar or bipolar depression well and keeping them well is a difficult endeavor that requires specialized, combined medication and therapy approaches and follow-up education and therapy. This is for sure. The hope would also be that good early and long-term intervention would yield a more benign course of recurrent unipolar or bipolar disorder than would treatment as usual (which all too often consists of medication only).*

## Continuation Cognitive Behavioral Therapy Prevents Relapse in Kids

At a symposium on early-onset depression at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, Graham Emslie of the University of Texas Southwestern Medical Center discussed the role of cognitive behavioral therapy in the long-term treatment of child- and adolescent-onset unipolar depression.

In Emslie's research, the combination of the antidepressant fluoxetine and cognitive behavioral therapy reduced depressive relapses in children. Using the two treatments together did not speed onset of antidepressant response compared to fluoxetine alone, but **once children responded to the medication, the addition of cognitive behavioral therapy reduced relapses over the next year compared to fluoxetine alone** (even though the cognitive behavioral therapy ended after the first six months).

Emslie likened the use of cognitive behavioral therapy to the course of rehabilitation that often follows a major surgery and is meant to sustain or enhance the good effects of surgery. Getting patients to full remission (well and with no residual symptoms) was the key to staying well.

## Malnutrition Early in Life Has Lasting Effects on Mental Health

Severe malnutrition in the first year of life even when corrected for the rest of a person's life leaves a legacy of permanent cognitive deficits, marked deficits in attention, and increases in depression, conduct disorders, and medical disorders compared to carefully matched controls. Jamina Galler, a researcher at Harvard Medical School, gave a plenary talk at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry on the long-term effects of even short-term childhood malnutrition, including marasmus (calorie deficiency) and kwashiorkor (protein deficiency).

Galler's studies followed three generations of people born in Barbados and observed the consequences of prior malnutrition, which was completely eliminated in Barbados by 1980. **The consequences of malnutrition in the first year of life not only affected the first generation (G1), but subsequently their offspring in the G2 generation who also suffered an excess of attention-deficit hyperactivity disorder, low IQ, and low annual income into adulthood.** That is, the early malnutrition had transgenerational effects.

Malnutrition is a huge problem worldwide and is especially bad in sub-Saharan Africa and some parts of Asia. Globally, malnutrition accounts for 50% of the deaths of children under age five. However, even in the US hunger is a problem for one in four children, or about 16 million individuals, and the long-term consequences of hunger remain to be further studied.

Studies in animals indicate that early malnutrition has epigenetic effects that can be passed on to four future generations before they are reversed. Epigenetic effects refer to environmental factors that cannot change the sequence of DNA, but change how easily it is transcribed by adding or taking away acetyl and methyl groups on DNA and histones, the structures around which DNA is wound. Malnutrition (defined as 6–8% casein, a type of protein, in the diet instead of the normal 25%) in rodents affects cognitive abilities and blood pressure and can lead to diabetes, obesity, and other metabolic abnormalities. The next generation is also affected because a previously malnourished mother huddles too much with her

offspring, and they become obese as a result of these poor parenting skills. The second generation also exhibits epigenetic changes in the prefrontal cortex (such as too few glucocorticoid receptors due to methylation of the glucocorticoid promoter) and fewer neurons in the hippocampus.

*Editor's Note: Other data indicate similar long-lasting epigenetic and transgenerational effects of other types of childhood adversity, such as verbal, physical, or sexual abuse. These findings in humans are also paralleled by findings in animals, and give strong credence to the idea that the environment can have long-lasting effects on neurobiology and behavior via epigenetic effects that can be superimposed on whatever genetic effects are inherited.*

*Data from this editor (Robert Post) and colleagues on verbal abuse in childhood is striking; this supposedly less severe form of abuse is still associated with a more difficult course of bipolar disorder and an increase in medical comorbidities. Thus, the experience of early abuse, even just verbal abuse, appears to have long-lasting consequences for psychiatric and medical health into adulthood.*

## Intranasal Ketamine May Be an Alternative to IV in Refractory Depression

At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, Kyle Lapidus of Mount Sinai Hospital reviewed the literature from controlled studies on the efficacy of intravenous (IV) ketamine at a dosage of 0.5 mg/kg over a 40-minute infusion for adults with treatment-resistant depression (with consistent response rates of 50% or more), and suggested that intranasal ketamine may also be effective.

Ketamine is a strong blocker of the glutamate NMDA receptor. At high doses (6 to 12 mg/kg) it is an anesthetic, at slightly lower doses (3 to 4 mg/kg) it is psychotomimetic (causing psychotic symptoms) and is sometimes used as a drug of abuse, and at very low doses it is a rapidly acting antidepressant, often

bringing about results within 2 hours. **Antidepressant effects typically last 3 to 5 days, so the question of how to sustain these effects is a major one for the field.**

Murrough et al. reported in *Biological Psychiatry* in 2012 that five subsequent infusions of ketamine sustained the initial antidepressant response and appeared to be well tolerated by the patients. Another NMDA antagonist, riluzole (used for the treatment of ALS or Lou Gehrig's disease), did not sustain the acute effects of ketamine, and now lithium is being studied as a possible strategy for doing so.

The bioavailability of ketamine in the body depends on the way it is administered. Compared to IV administration, intramuscular (IM) administration is painful but results in 93% of the

bioavailability of IV ketamine. Intranasal (IN) administration results in 25-50% of the bioavailability of IV administration, while oral administration results in only 16-20% of the bioavailability of IV administration, so Lapidus chose to study the IN route. He compared intranasal ketamine at doses of 50mg (administered in a mist) to 0.5 ml of intranasal saline. Both were given in two infusions seven days apart. Lapidus observed good antidepressant effects and good tolerability. Papolos et al. had reported earlier that intranasal ketamine had good effects in a small open trial in treatment-resistant childhood onset bipolar disorder.

*Editor's Note: Further studies of the efficacy and tolerability of intranasal ketamine are eagerly awaited.*

## Rationale for Using Ketamine in Youth with Treatment-Resistant Depression

At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, Vilma Gabbay of the Mount Sinai School of Medicine reiterated the findings from the TORDIA (Treatment of SSRI-Resistant Depression in Adolescents) study that 20% of young people with depression remained resistant to treatment, childhood-onset depression was more likely to be recurrent and more difficult than adult-onset depression in the long run, and suicide was the second leading cause of death in 12- to 17-year-olds in 2010 according to a Centers for Disease Control report in May 2013. Anhedonia (a loss of pleasure in activities once enjoyed) was the most difficult symptom to treat in adolescents.

Gabbay carefully explained some of the rationales for using ketamine in young people with depression. The presence of inflammation is a poor

prognosis factor, and ketamine has anti-inflammatory effects, decreasing levels of inflammatory markers CRP, TNF-alpha, and Il-6. Given that ketamine has been widely used as an anesthetic for surgical procedures, its safety in children has already been demonstrated. Ketamine did not appear to cause behavioral sensitization (that is, increased effect upon repetition) in a report by Cho et al. in 2005 that included 295 patients.

As noted previously, Papolos et al. reported in a 2012 article in the Journal of Affective Disorders that intranasal ketamine at doses of 50 to 120 mg was well-tolerated and had positive clinical effects in 6- to 19-year-olds with the fear of harm subtype of bipolar disorder that had been highly resistant to treatment with more conventional drugs.

Gabbay reluctantly endorsed further cautious controlled trials in

children and adolescents, in light of ketamine's suggested efficacy and good safety profile, which stands in contrast to its popular reputation as a party drug or "Special K."

*Editor's Note: The discussant of the symposium, Neal Ryan of Western Psychiatric Institute and Clinic, added an exquisitely brief discussion suggesting that ketamine should ultimately be studied in combination with behavioral and psychotherapeutic procedures to see if its therapeutic effects could be enhanced. He made this suggestion based on the data that ketamine has important synaptic effects, increasing brain-derived neurotrophic factor (BDNF), which is important for healthy cells and long-term memory, and reverting thin dendritic spines caused by stress back to their normal mushroom shape. This editor (Robert Post) could not be more in agreement.*

## Intravenous Ketamine Superior to Intravenous Midazolam in Adults with Post-Traumatic Stress

In a recent study, ketamine performed better than an active comparator on several measures in adults with post-traumatic stress disorder (PTSD). **Since ketamine has noticeable dissociative effects, researchers have looked for another drug with mind-altering effects that would be a more appropriate comparator than placebo.**

At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry, Adriana Feder of Mount Sinai Hospital reported on the randomized study in those with PTSD, in which **intravenous ketamine was compared to intravenous midazolam, a potent benzodiazepine that produces anti-anxiety and sedating effects.** Murrough et al. previously showed that intravenous ketamine was superior to midazolam in treatment-resistant depression.

In the randomized study Feder described, the participants had suffered PTSD after a physical or sexual assault and had been ill for 12 to 14 years. Those who received ketamine improved more, in some instances for as long as two weeks (ketamine's blood levels disappear after a few hours, and its clinical antidepressant effects usually last only a few days). Reports of side effects included three patients with blood pressure increases requiring treatment, and four patients who each had a transient episode of vomiting.

These controlled data parallel previous open observations. When ketamine was used as a surgical anesthetic during operations on burn patients, only 26.9% subsequently reported PTSD compared to 46.4% who developed PTSD when an alternative to ketamine was used as the anesthetic.

## Extra Folate in Those Taking L-Methylfolate Could Be Counterproductive

While the nutritional supplement folate (also known as folic acid or vitamin B9) can be useful for depression, there appears to be one instance when augmentation with regular folate could be counterproductive.

In those with a transport defect associated with a MTHFR (methyl tetrahydrofolate reductase) deficiency, folate can compete with l-methylfolate for uptake into the brain. Folate would thus limit the beneficial effects of l-methylfolate supplementation, which is required for this 15% of the population.

## Irritable, Elated, And Combined Bipolar Disorder Subtypes in Children Are Similar

Research on early-onset bipolar disorder has often hinged on identifying the key characteristics of the disorder. At a symposium on the course of bipolar disorder in children at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Jeff Hunt of Brown University discussed findings from COBY, the Collaborative Child Bipolar Network.

Hunt described the course of illness in 446 children with bipolar disorder who participated in the study, including 10% who had irritability at baseline, 15% who had elated mood at baseline, and a majority (75%) who had both irritability and elation at baseline.

Most factors such as positive family history of bipolar illness and comorbidities including attention deficit hyperactivity disorder (ADHD) did not differ across the three groups. The three subtypes (irritable, elated, or mixed) did not remain stable, and **most of the children eventually converted to the combined irritable and elated subtype**. These data contrast with those of Ellen Liebenluft et al., who found that those with severe mood dysregulation or chronic irritability (but not other key characteristics of bipolar disorder) did not go on to receive a bipolar diagnosis and tended not to have a family history of bipolar disorder.

## Inflammatory Markers of Bipolar Illness Course

People with bipolar disorder often show signs of inflammation. These could eventually help clarify diagnosis, illness activity, and treatment response, and predict illness progression. Previous studies have shown increases in c-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) in adults with mood disorder. These high levels tend to improve with medications, are related to illness severity, and are also related to manic and mixed states.

At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Ben Goldstein reported on a study that examined levels of TNF alpha, IL-6, and high sensitivity CRP (hsCRP) in 123 adolescents with an average age of 20.4 years, who had been ill for an average of 12.7 years.

**CRP levels in adolescents with bipolar illness were equivalent to those with rheumatoid arthritis, and much higher than healthy controls. In children with bipolar disorder, higher levels of CRP were related to more time symptomatic.** High hsCRP was related to lower socio-economic status and to substance abuse disorders.

Increases in IL-6 were linked to a longer time to achieve remission and more weeks depressed. High IL-6 was related to duration of illness, positive family history of substance use, and family conflict.

High TNF alpha was related to low socioeconomic status (SES), self-injury, suicidal ideation, and positive life events.

Goldstein said studies of these markers could eventually lead to therapeutic advances, but the process would be long and would require several steps: proof of concept studies, prospective validation studies in independent samples, and demonstration of clinical gains over standard predictive markers, culminating in enhanced patient care and outcome through better, faster prediction of response.

*Editor's Note: Ideally clinicians could jump ahead by immediately attempting to determine whether adding a medication with direct anti-inflammatory effects could enhance therapeutic effects in children with elevated inflammatory markers. Treating inflammation could also theoretically help prevent cognitive deterioration and decrease the considerable risk for cardiovascular dysfunction in patients with bipolar disorder.*

## Worsening Comorbidities Relate To Adverse Bipolar Outcomes

Many children with bipolar disorder also present with other comorbid Axis I psychiatric illnesses. Now it seems that the worsening of these comorbidities, such as attention-deficit hyperactivity disorder (ADHD) or an anxiety disorder, can signal a more difficult course of bipolar illness itself. At a symposium on the course of bipolar disorder in children at the 2013 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Shirley Yen from Brown University discussed findings on comorbidities of childhood onset bipolar disorder from COBY, the Collaborative Child Bipolar Network. Upon study entry, 60% of children with bipolar disorder also had ADHD, 40% had oppositional defiant disorder (ODD), 39% had an anxiety disorder, 12.5% had both oppositional defiant disorder and a conduct disorder, and 9% had a substance abuse disorder.

**The prevalence of most of these comorbid illnesses increased over time (e.g. anxiety disorder rates increased from 39% to 62%). The illnesses were also related to the time it took participants to achieve recovery (eight consecutive weeks well), and the time until a recurrence of a depressive or manic episode.**

Increases in anxiety were linked to longer time to achieve recovery and a shorter time to a recurrence. Increases in ADHD were linked to a more rapid onset of a depressive recurrence. Increases in oppositional defiant disorder and conduct disorder had no relationship with either remission or recurrence. Increases in substance abuse disorders were linked to a longer time to recover from a manic episode. Thus, worsening of the comorbid conditions had definite consequences for both recovery and recurrence.

## Longitudinal Trajectory of Childhood Bipolar Disorder

Most children recover from an episode of bipolar disorder after a considerable period of time, but the majority eventually relapse. At the 2013 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Boris Birmaher of the University of Pittsburgh presented new data on the long-term prospective course of bipolar disorder in 255 children with bipolar I, 30 children with bipolar II, and 153 children with bipolar NOS (not otherwise specified), who together had an average age of onset of 9.3 +/- 3.9 years. The children participated in the study for an average of 8 years. **Most of the children (81.5%) recovered from their episode, but only after an average of 2.5 years of follow up treatment. Yet 62.5% of those who recovered experience a recurrence after an average of 1.5 years.**

*Editor's Note: It takes a long, long time to achieve recovery, and longer for bipolar NOS (more than 2 years on average) than for either Bipolar I or II (about 1.8 years).*

Have you  
visited us online?

**bipolarnews.org**

Find the latest  
research, plus  
downloadable  
mood charts.

*However, the high rate of relapse within 1 to 2 years is equally disturbing. These data are similar to those in many other prospective follow up studies of children, and suggest that it is important for parents to be aware that this illness is difficult to treat, and good results within weeks are not likely to be the norm. At the same time, 43% of the children with a bipolar diagnosis eventually achieved euthymia (wellness) in the longer term, so there is cause for some optimism.*

### Four Trajectories in Children with Bipolar Illness

Birmaher described four different long-term trajectories observed over an average of 8 years of follow up with 438 children with bipolar disorder.

1. Predominately euthymic (24%)
2. Ill early, then much improved (19%)
3. Mild to moderately ill – euthymic only 47% of the time (34.6%)
4. Predominantly ill – euthymic 11.5% of the time (20.3%)

### Predictors of Wellness

The predominantly well group (1) was associated in a univariate analysis with a later onset of illness, higher socio-economic status, less conflict, fewer stressors, less sexual abuse, fewer anxiety and ADHD comorbidities, and less medication (including stimulant use). In a multivariate analysis, this group was independently associated with less severe depression/mania, less suicidal ideation, less substance use, less sexual abuse, and less family history of mania and substance abuse.

This group had the best functioning, almost to 80 on the Children's Global

Assessment Scale (C-GAS). In comparison, despite considerable time euthymic for groups 2 and 3, these children still had considerable functional impairment, in the realm of 65 on the C-GAS scale. Even in Group 1, about half of the children had low C-GAS scores.

Birmaher suggested the importance of trying to find ways to delay the onset of the illness (to graduate more children into the good prognosis group) and allowing them time to develop socially and educationally and graduate from high school. Potential preventive strategies could include omega-3 fatty acids, more time spent exercising, good sleep hygiene, family focused therapy (FFT), dialectic behavior therapy, treating subsyndromal depression, and even treating parents with mood disorders to complete remission (which has been shown to improve behavioral health in offspring).

*Editor's Note: As this editor Post with Chang and Frye wrote in the Journal of Clinical Psychiatry in 2013, beginning to study the effectiveness of these kinds of early primary and secondary prevention strategies in children who can now be readily identified clinically as at risk for a mood disorder, should be given the highest priority.*

*Children who have at least one parent with a bipolar disorder, some further environmental risk factors (such as adversity in early childhood), and early symptoms of depression, anxiety, or prodromal bipolar disorder are at very high risk for bipolar disorder, and there is an urgent need for randomized studies (even open ones) of safe potential preventive strategies for these children.*

*Omega-3 fatty acids in particular have a strong record of safety, compelling rationale for use in bipolar disorder, and have already been shown to have significant preventive effects in decreasing the transition from early prodromal psychosis to full-blown schizophrenia.*

---

BNN  
PO Box 18  
Beltsville, MD 20704-0018

ADDRESS SERVICE REQUESTED