

Bipolar Network News

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Updates from the 2012 Meeting of the American Academy of Child and Adolescent Psychiatry

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Long Delays to First Treatment Are Crippling Many with Bipolar Disorder: What You Can Do

An article published by N. Drancourt et al. in the journal *Acta Psychiatrica Scandinavica* this year examined the duration of the period between a first mood episode and treatment with a mood stabilizer among 501 patients with bipolar disorder. **The time between a first episode of depression, mania, or hypomania and first treatment averaged 9.7 years. The authors conclude that more screening, better recognition of the early stages of the illness, and greater awareness are needed to decrease this long delay.**

Editor's Note: The article by Drancourt et al. replicates earlier findings of an average treatment delay of 10 years among bipolar patients from the treatment network in which this editor (Robert Post) is an investigator (formerly the Stanley Foundation Bipolar Network, now called the Bipolar Collaborative Network). The duration of the untreated interval (DUI) for patients with bipolar disorder is unacceptably long and carries a heavy price.

Those with the earliest age of onset experience the longest delay to first treatment. Early onset is associated with poor outcome compared to adult onset bipolar disorder, and the duration of time untreated adds a separate, independent risk of a worse outcome in adulthood, especially more frequent and severe depression, more episodes, and less time well.

What patients and doctors can do to shorten this interval to first treatment: Know the risk factors for early onset bipolar disorder so you can seek evaluation and advise treatment as appropriate.

Bipolar illness often runs in families (although half the time it occurs in those without a positive family history of bipolar disorder).

Know the risk factors in parents:

One or both parents with a bipolar disorder, especially if their illness is poorly controlled, they have made suicide attempts in the past, or they have substance abuse problems. These are risk factors that a child will develop early-onset bipolar disorder.

Know the risk factors in children:

Stress or adversity at a young age; other child psychiatric diagnoses, such as an anxiety disorder, ADHD, oppositional defiant disorder, or depression; early symptoms short of a diagnosis of bipolar disorder, which might include periods of elation or euphoria out of context with events, sleep irregularities (especially short sleep time without apparent fatigue), and very rapid and distinct changes in mood.

Symptoms

A bipolar diagnosis is likely in a child with ADHD who is suicidal, homicidal, hallucinating, delusional, or overtly hypersexual.

If a child is symptomatic and one or more of the above factors are present, the family should obtain a consultation with a doctor who specializes in child psychiatry. If that physician is not helpful, seek another opinion.

If your child's mood deteriorates, chart their mood on a daily basis and bring the mood chart to the child's physician. (We offer various mood charting calendars on our website bipolarnews.org. The Monthly Mood

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and more!

Chart Personal Calendar is the most comprehensive.) Also chart progress in order to have detailed information about which treatments are successful and whether side effects occur.

In a child who has a parent with bipolar illness and is symptomatic, Family Focused Therapy (FFT) can help moderate or prevent early symptoms of bipolar disorder. FFT was pioneered by David Miklowitz and involves education about the illness and its treatment, symptom recognition, and enhancing family communication and support.

Know that stigma may be involved in the diagnostic process and be persistent. Most parents are scrupulous about applying sunscreen to their kids when the risks of skin cancer are low and occur decades in the future. Be equally scrupulous about childhood psychiatric problems, which can have dramatic and more immediate adverse effects.

In this editor's 35 years at the National Institute of Mental Health, he saw patients with the most difficult to treat illnesses, many of whom

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Preventing Treatment Delays in Bipolar

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might have had a much easier course if they had received earlier and more consistent treatment. His many years in the field of treatment and research in the mood disorders has taught him that changes in public health attitudes do not come easily, and thus he suggests that patients and their families become proactive in educating themselves about psychiatric illness and seeking timely and appropriate intervention for their children with mood and behavioral problems.

Bipolar Network News

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

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

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

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

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It Appears Antidepressants and Stimulants Do Not Hasten the Onset of Bipolar Disorder in Kids

It is a common clinical assumption that early treatment of depression with antidepressants may be a risk factor for hastening the onset of subsequent bipolar disorder. Accumulating evidence indicates that this may not be the case. At a symposium at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) researchers in the field shared the latest findings on antidepressant-induced manic symptoms in youth (AIMS), and there was a surprising consensus that antidepressants do not increase the risk of subsequent bipolar disorder onset when used for the treatment of childhood-onset depression.

Symposium speakers Kiki Chang, Melissa P. DelBello, and David Axelson all agreed that **antidepressant treatment was not a risk factor for bipolar disorder.**

DelBello shared data from a study in which antidepressant treatment was associated with a lower likelihood of mania during follow-up. Antidepressants were typically discontinued if the patient switched into manic-like symptoms or increased irritability or aggression. These symptoms tended to occur in children who were younger, who had a smaller volume of the amygdala, and in those who had a positive family history for bipolar disorder in first-degree relatives.

Axelson indicated that his data represented only a "bird's-eye view," but suggested that antidepressants do not cause or hasten the onset of bipolar disorder when used for treating depression in children. He also reported results from a naturalistic study in which stimulants also did not increase the risk of subsequent bipolarity.

Several of the presenters discussed how they would treat children with an early-onset depression when there is a family history of bipolar disorder. DelBello indicated that there is not

enough data to give a definitive answer, but suggested the use of family focused therapy (FFT), omega-3 fatty acids (3g per day), and possibly the medications lamotrigine, atomoxetine, or asenapine.

Boris Birmaher, the discussant of the symposium, reiterated that there are few systematic data to guide therapeutics of childhood onset depression. However, he suggested first-line treatment with psychotherapy and second-line treatment with a selective serotonin reuptake inhibitor (SSRI) or bupropion. In addition he suggested that SSRIs not be used in cases of mixed presentations (where both manic and depressive symptoms are present) or when the patient experiences rapid cycling. He also suggested the possible use of high-intensity light or omega-3 fatty acids.

Editor's Note: The naturalistic data presented at this symposium, although preliminary, suggest that antidepressants do not increase the onset of mania in children. Limited data from Axelson and collaborators also suggest that this is the case for stimulant exposure, although these results were also based on naturalistic data rather than randomized controlled data, which would be preferable.

The other consensus describes a troubling phenomenon we have written about before. All of the presenters indicated that strategies for treating youth with early-onset depression cannot be derived from a systematic database based on controlled clinical trials, since these have not yet been conducted. Treatment strategies for children with depression, especially in the context of a family history of bipolar disorder, currently rely only on expert opinion, clinical intuition, and guesswork. The consensus of these researchers highlights the terrible dearth of treatment outcome studies for this important group of children, especially since childhood-onset depressive disorder carries a more difficult prognosis than the adult-onset variety.

Family Environment, Cognitive Functioning, and Quality of Life Among Depressed Adolescents with Bipolar Disorder

At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry, Arman Danielyan presented a poster on psychosocial, cognitive, and behavioral characteristics of youth in a depressive phase of bipolar disorder. These adolescents had lower scores on a variety of measures.

Adolescents with bipolar depression had significantly lower scores on 7 of 10 family environment scales measuring the quality of family interaction, communication, and emotional tone. They also exhibited significant impairment in cognitive function, particularly executive functioning, and all domains of psychosocial health were substantially lower than US normative data.

The authors concluded that **bipolar depression affects multiple domains of adolescents' lives including their cognitive, psychosocial, and family**

functioning. This suggests that the involvement of the whole family in the treatment process would be beneficial.

The impaired cognitive functioning these young people face is associated with lower quality of life, and ways of addressing this better are clearly needed.

Editor's Note: In a previous BNN we reported on the efficacy of Family Focused Therapy (FFT), which was pioneered by David Miklowitz. This therapy is effective for adolescents and adults with bipolar disorder and for adolescents who are at high risk for the disorder because of two factors: having a parent with the disorder and having preliminary symptoms of bipolar disorder not otherwise specified (BP-NOS), depression, or an anxiety disorder. Kiki Chang, a respected authority on child and adolescent psychiatry, recommends FFT for children and adolescents with bipolar disorder and those at high risk for it.

Cortisol, PTSD, and Sexual Abuse

Brooks R. Keeshin presented a poster on neuroendocrine function in recently sexually abused adolescent girls with and without post-traumatic stress disorder (PTSD) at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP). Average age of the girls was 15, and they had experienced the sexual abuse six months to one year before the study.

The researchers found that **morning cortisol awakening response was flattened in the girls, and this was associated with PTSD severity and the severity of intrusive symptoms.** Increased adversity prior to the sexual abuse experience was also associated with flattening of the cortisol awakening response.

The researchers suggest that alterations in the hypothalamic pituitary adrenal axis (HPA) appear around the time of the abuse and are associated with the severity of PTSD symptomatology in sexually abused adolescent girls.

Substance Use Among Canadian Adolescents with Bipolar Disorder: The Critical Need for Intervention and Prevention

At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Antonette Scavone presented a poster on correlates of substance use disorders among Canadian adolescents with bipolar disorder. Participants were 62 adolescents aged 14 to 19 with bipolar disorder. Twenty-three participants (37.1%) had a substance abuse disorder.

Those with a comorbid substance use disorder were more likely to have a comorbid panic disorder or an oppositional defiant disorder. They also had higher rates of police contact or arrest, were more likely to have been involved in assault, and were more impulsive. In addition they had experienced more stressful life events.

Editor's Note: These data from a Canadian sample replicate previous findings in the US and again indicate the critical importance of preventing the onset of substance abuse in adolescents at especially high risk because of their bipolar disorder.

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Anxiety and Depressive Disorders Often Precede the Onset of Bipolar Disorder in Those At High Risk Due to Family History

At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) meeting, Anne Duffy and Gabrielle A. Carlson sponsored a symposium on the association between anxiety and minor mood disorders and subsequent bipolar disorder in those at high risk. **There seemed to be consistency among all the researchers who presented at the symposium in finding that there was a sequence in which young people at high risk for bipolar disorder developed first anxiety, then mood disorders, then bipolar illness.** However, the incidence of childhood-onset bipolar disorders in those at high risk because a parent has the disorder was lower in Canada, Switzerland, and the Netherlands than it was in the US.

Duffy, a professor of psychiatry in Calgary, noted that **bipolar disorder is highly heritable** even though most adults with bipolar illness do not have a family history of bipolar illness among their first-degree relatives. She shared estimates that if one parent has bipolar disorder their offspring have a 5% lifetime risk of developing bipolar disorder. If both parents have bipolar disorder their offspring have a 25% risk of developing bipolar disorder and a 35% incidence of developing any affective disorder (although other data by Lapalme et al. suggest it may be as high as 60%).

Duffy found that **when parents responded well to lithium, their children tended to do the same.** Lithium-responsive patients tended to be those without anxiety disorder and substance abuse and who had classic bipolar episodes and clear well intervals between episodes.

In her sample of **Canadian** patients, Duffy found that a sequence of developing anxiety and mood disorders seemed to predate the onset of

bipolar disorder in those at high risk because a parent has bipolar disorder. Anxiety disorders were the first to occur, at a mean age of 8. These were followed by minor mood disorders in adolescence, then major depression in late adolescence or early adulthood, and finally bipolar disorder. Among the anxiety disorders, social phobia, panic, and generalized anxiety disorders were significant predictors of subsequent bipolarity and generalized anxiety disorder was an independent predictor of subsequent bipolarity.

Researcher Martin Preisig discussed a **Swiss** study of children at high risk for bipolar disorder due to having a parent with the disorder. The study took place in Lausanne and Geneva and included 134 offspring of a bipolar parent, 107 offspring of a parent with major depression, and 106 offspring of controls who had orthopedic medical problems. As expected, the incidence of any mood disorder was much higher in the offspring of parents with bipolar illness or major depression. A mood disorder was diagnosed in 34.5% of the offspring of the bipolar parents and 25.5% of the offspring of the parents with a major depressive disorder, and only 12.6% of controls.

Interestingly, there was a low and nonsignificant difference in the incidence of bipolar disorder, with 3.6% occurring in the offspring of parents with bipolar disorder, 2.7% in the offspring of parents with a major depressive disorder, and 0% of the controls. Preisig also found that anxiety preceded depression, which preceded the appearance of mania. Anxiety emerged at a mean age of 10, followed by depression and then mania at a mean age of 15. If a child developed an anxiety disorder, they were three times more likely to develop bipolar disorder. However,

depression was not a good predictor of bipolar disorder, and recurrent major depression seemed to occur more often in those with a parent with major depression compared to those with a parent with bipolar disorder.

Researcher David Axelson discussed a study of **US** children aged 6-18 from Pittsburgh, Los Angeles, and Providence. He compared 391 offspring of bipolar parents with 249 offspring of healthy parents. In contrast to the previous studies that were performed outside of the US, Axelson's study found significantly higher incidence of bipolar disorder in the offspring of bipolar parents compared to controls, with an illness on the bipolar spectrum (bipolar 1, bipolar 2, or bipolar not otherwise specified (NOS)) occurring in 18.7% of the offspring of parents with bipolar disorder. Also in contrast to the previous presentations, he found that depression multiplied the risk of subsequent bipolar disorder by 11.7. The presence of an oppositional defiant disorder or attention deficit hyperactivity disorder (ADHD) multiplied the risk by 2.4.

Axelson found a high incidence of anxiety disorder comorbidity in the offspring of bipolar parents, particularly generalized anxiety disorder and panic disorder. ADHD was comorbid in 50% of the offspring of bipolar parents compared to 27% of the controls.

Substance abuse also occurred in 29% of the offspring of bipolar parents, a much higher rate than in controls. Substance abuse emerged after the onset of bipolar disorder in the majority of cases. This provides a window of many years to attempt to head off substance use with education and other methods of prevention in those with early onset bipolar disorder.

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Anxiety and Depressive Disorders Often Precede the Onset of Bipolar

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Among the offspring of parents with bipolar disorder, 10.7% had bipolar NOS, 4.1% had bipolar II and 3.6% had bipolar I. However, approximately 40% of the children diagnosed with bipolar NOS converted to bipolar I or II over several years of follow-up. The diagnosis of bipolar NOS was typically given because symptoms of mania lasted only one day (43%), 2 days (28%), or 3 days (30%). Thus, in the United States, mania of brief duration or hypomanic bursts are a common way the illness initially presents. Given these data and previous evidence that bipolar NOS is highly impairing, attempts to treat it and prevent or slow the development of more full-blown manic episodes are important. In summary Axelson suggested that two-thirds of the offspring of bipolar parents who experience a major depression ultimately became bipolar.

Manon Hillegers discussed a **Dutch** study of a cohort of children at high risk for bipolar disorder because of a parental history of the disorder. Hillegers' research group also found that anxiety and depressive disorders occurred more commonly than bipolar disorder in the offspring of parents with bipolar disorder. Upon long-term follow-up, the researchers found that 19.5% of the offspring developed depression, while only 2.5% developed bipolar disorder, and of these, only four of the children developed the most severe variant, bipolar I. Following this cohort for 12 years, the researchers found that 54% of these children at high risk developed an affective disorder in that time.

Anne Glowinski discussed a study led by John Nurnberger that examined cohorts of **American** children at high risk for bipolar disorder. They found that 8.5% of these children at high risk developed a bipolar disorder compared

to 0% in the control population. The children also showed substantially greater anxiety disorders, disruptive behavioral disorders, and substance abuse disorders. In contrast to the much later onsets of mania in the non-US cohorts noted above, Nurnberger's research group found a mean age of onset of mania of 12.5 years. The presence of an anxiety disorder was a risk factor for earlier onset and higher incidence of onset of a bipolar disorder.

*Editor's Note: There was a great degree of agreement in these findings, although there were several important differences. **All of the studies indicated that anxiety and depression tended to emerge prior to bipolar episodes in children at high risk by virtue of having a parent with bipolar disorder.***

However, in contrast to the low to negligible incidence of bipolar disorder in very young offspring from Canada, Switzerland, and the Netherlands, there was a substantial incidence of bipolar disorder in the young offspring of parents with bipolar disorder in the US in the two cohorts studied by Axelson and Nurnberger and colleagues. These data are consistent with others that we have reviewed in previous issues of the BNN that indicate that there is an earlier age of onset of bipolar disorder in the US compared to many European countries.

This editor (Robert Post) asked the panel members how they would treat an eight-year-old child with a serious anxiety disorder and two parents with bipolar disorder. Carlson and most of the other panelists indicated that they would use an antidepressant such as a selective serotonin reuptake inhibitor (SSRI), but there are no controlled data to guide decision making. Hillegers indicated that in the Netherlands they would use psychotherapy and cognitive behavioral psychotherapy rather than medication in a very anxious child of this age.

Duffy suggested she would use the parental history of response to pharmacotherapy as a guide to treatment of the offspring – lithium for lithium responders; anticonvulsants or atypical antipsychotics for lithium non-responders. This editor cited Duffy's own data indicating that lamotrigine response runs in families and that this might be considered for anxiety/depression in a child at ultra-high risk for bipolar disorder by virtue of both parents having the disorder. Other options might be any of the other anticonvulsant mood stabilizers (valproate or carbamazepine), one of the well-tolerated atypical antipsychotics (quetiapine, aripiprazole, or lurasidone), the anti-anxiety drugs (clonazepam or gabapentin), or even omega-3 fatty acids and N-acetylcysteine.

The lack of any systematic data about the best treatment options for an anxious or depressed youth with a positive family history of bipolar disorder is another tragic example of the failure of funding agencies such as the National Institute of Mental Health (NIMH) and the Substance Abuse and Mental Health Services Administration (SAMSHA) to begin addressing the problems of children with or at risk for bipolar disorder.

Since all of the presenters agreed on the most usual sequence of anxiety followed by depression followed by bipolar disorder in children at high risk, the virtual absence of studies of treatments for these children or those who already have disabling bipolar NOS is disturbing. Throughout the entire AACAP meeting there was a general absence of studies on medications for any aspect of the recurrent mood and anxiety disorders, despite the recognition that most adult mood and anxiety disorders begin in childhood and adolescence. Getting youth with serious mood and anxiety disorders on the right track early in their course of illness could have life saving implications. What a shame that this opportunity is often lost because of a dearth of treatment research.

Long-term Outcomes for Several Childhood-Onset Disorders

A symposium at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) examined long-term outcomes of childhood onset disorders, including bipolar disorder, unipolar depression, ADHD, and anxiety disorder.

Course of Childhood Onset Bipolar Disorder

Researcher Boris Birmaher discussed the considerable differences in presentations of bipolar disorder in childhood versus in adolescence. In childhood there appeared to be a predominance of sub-syndromal symptoms or bipolar not otherwise specified (BP-NOS), mixed symptoms, hallucinations, worse course of illness, and comorbidities with ADHD, oppositional defiant disorder, and separation anxiety disorder being common. In contrast, in adolescence there was more bipolar I and bipolar II, major depression, mania with elation and grandiosity, substance abuse, and conduct disorder.

Birmaher reported that while most of the children with early-onset mania recovered within two years, roughly 80% showed recurrences over the next two to five years. Over a follow-up period of four years, 30% remained euthymic, 40% had continuing substantial symptoms, and 20% remained seriously ill. Birmaher's data indicate that those with childhood-onset bipolar illness remained symptomatic during 60% of the follow-up period.

Predictors of a more difficult outcome included a early onset, BP-NOS presentation, longer duration of illness, any comorbid illness, lower socioeconomic status, and a family history of bipolar disorder in first-degree relatives. Birmaher reported that these data in childhood-onset mania were consistent with earlier research by Judd and colleagues in a longitudinal follow-up study of adult patients with bipolar disorder.

However, there were three major differences. The proportion of time well was lower in children (41.1%) than in adults (52.7%). Time in mixed episodes or rapid cycling was higher in childhood-onset bipolar disorder (28.9%) than in adults (5.9%). Rapid changes in polarity were also more common in children (15.7%) than in adults (3.5%).

Birmaher and colleagues initially found that about 40% of children with BP-NOS converted to bipolar I or II upon follow-up. However, after longer follow-up, they have found that 50% of those with BP-NOS convert to bipolar I or bipolar II. Roughly two-thirds of those with a family history of bipolar illness convert from BP-NOS to bipolar I or II. These data provide very strong support for the view that BP-NOS is an early phase of bipolar disorder and should be treated early, as it is highly impairing and difficult to stabilize.

Birmaher also discussed substance abuse among this population of children with bipolar disorder. In 167 bipolar children initially presenting without substance abuse, 32% showed new onset of substance abuse, and in 76% of these individuals, it involved two or more drugs. There was an approximate 6-year lag between onset of bipolar illness at an average age of 12 and onset of substance abuse at average age 18, indicating a substantial therapeutic window for intervention and treatment.

Birmaher presented new data from a latent growth analysis separating youth with bipolar disorder into 4 groups based on the percent of time euthymic during the 90 months (or approximately 8 years) after onset. About 30% showed a course of persistent wellness, while 25% had persistent severe illness. Thirty percent experienced moderate illness throughout the follow-up period. Most interestingly, 15% showed a course of relatively severe illness for the first 30 months and then a relatively rapid progression to consistent wellness thereafter.

The reasons for this relatively sudden transition are not yet clear. However, Birmaher speculated that it could be related to changes in brain chemistry and maturity or diverse psychosocial issues such as leaving the home environment or perhaps deciding to avoid alcohol or other substances of abuse. This intriguing group of patients will be studied in more detail in order to ascertain the mechanisms involved in their improvement. This 15% of participants, along with the 30% who were consistently well, indicate that 45% of those with childhood-onset bipolar disorder do very well over long-term followup.

The Course of Childhood Onset Depression

Gabrielle Carlson presented Karen Wagner's work on unipolar depression, in which Wagner found a 15.3% incidence of unipolar depression in female adolescents, and 7.7% incidence in male adolescents. The overall incidence increased with age; from 8.4% in children aged 13, to 12.6% in children age 15 and 21.4% in children age 17. Average duration of a depressive episode was 17 months. While 85% recovered, 40% of those who recovered experienced a recurrence.

Carlson also presented data from Barbara Geller indicating that among children hospitalized with pre-pubertal onset of depression, 33% eventually were diagnosed with bipolar I disorder. If diagnoses of bipolar II and BP-NOS were included, the rate at which these children who got depressed before puberty eventually developing a bipolar disorder increased to an astonishingly high 49%. Thus, very early onset depression has a 50/50 chance of predicting an eventual bipolar disorder diagnosis.

Predictors of a more difficult course of depressive illness presentation

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Long-term Outcomes for Childhood-Onset ADHD and Anxiety Disorders

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were: earliest onset, more than 3 episodes, longer duration of depressive illness, and a positive family history. Those with early-onset depression had more suicidality, smoking, drug abuse, alcoholism, and an increased incidence of not having children when they became adults.

The Treatment for Adolescents with Depression Study (TADS) performed at the National Institute of Mental Health compared antidepressant response to fluoxetine, cognitive behavioral therapy (CBT), or the combination of fluoxetine plus CBT. Early in the study, the combination was most effective, with response in 39% of the children, compared to 24% for fluoxetine and 19% for CBT alone. However, after 3 years of follow up, all of the groups showed a relatively similar percent response: 60% for the combination; 55% for fluoxetine; and 64% for CBT.

Course of Childhood Onset ADHD

Lily Hechtman reported on the long-term difficulties of adolescents who had childhood onset of attention deficit hyperactivity disorder (ADHD). They often experienced: continued typical symptoms including restlessness and over-activity, decreased academic performance, deficits in social interactions, and decreased self-esteem. Twenty-five percent developed an antisocial personality disorder with 19-50% of these having difficulties with the legal system. There were again three distinct groups that showed different patterns of outcome. Thirty percent of the sample showed essential normality into adolescence and young adulthood. Sixty percent had continuous ADHD symptomatology, and 10% had serious psychiatric illness resulting in jail or hospitalization.

Other follow-up studies that extend as far as 40 years suggest that ADHD

persists in older adults at a rate of 36%, while antisocial personality persists in 10%, and substance abuse in 17%. Adolescent controls went on to experience these disorders in adulthood at respective rates of 13%, 0%, and 7%. Hechtman provided systematic data that treatment of ADHD was not a risk factor for the subsequent adoption of substance abuse.

In another study, a latent class analysis showed that about 52% of those with ADHD became well and stayed well. The predictors of this good outcome were: lack of maternal drug exposure in the prenatal period, a stable family, not being on welfare, not having a comorbid psychiatric diagnosis, not having a severe form of ADHD, and not having lower social functioning at baseline.

There is some evidence that treatment of ADHD in young adults can lead to psychosocial benefits. In one study performed in 1984, a group of college-age participants treated with stimulants for 3 to 5 years showed improvement in social skills and self-esteem, but surprisingly, no increase in academic performance.

Course of Childhood Onset Anxiety Disorders

Danny Pine presented a study of 191 adolescents with an anxiety disorder, among whom 36% showed no anxiety disorder in adulthood, while 62% continued to have an anxiety disorder. Among a control population, 390 adolescents without an anxiety disorder remained so in adulthood, while 36

developed new onset of an anxiety disorder in adulthood. Sixty-two of the 98 participants who had anxiety disorders in adulthood had had the disorder continuously from its onset in adolescence. Thus, it appears that approximately two-thirds of adults with an anxiety disorder show a persistence of their childhood onset anxiety disorder, while approximately 1/3 had a new anxiety disorder diagnosis.

While all of these major childhood onset psychiatric illnesses lead to long term difficulties in adulthood, it appears that the patients most severely impacted are those with bipolar disorder.

Editor's Note: While all 4 of these major childhood onset psychiatric illnesses (bipolar, unipolar, ADHD, and anxiety disorders) show long term difficulties into adulthood in the majority of instances, it appears that the most severely impacted are those with bipolar disorder. These data are also consistent with retrospective

data from multiple cohorts of adults with bipolar disorder, which indicate that those whose illness began in childhood fared more poorly in adulthood than those with adult-onset illness. Thus, while there has been a modicum of treatment research in childhood depression and anxiety disorder and a plethora of treatment studies in ADHD, the dearth of treatment studies in children with bipolar disorder is disconcerting.

Bipolar disorder is common, occurring in some 2 to 3% of children and adolescents, and carries a relatively grave prognosis into adulthood in the majority of instances, especially when it is inadequately treated. Virtually all of the investigators in the area of childhood-onset bipolar who presented at the AACAP meeting have pleaded for increased treatment research for bipolar disorder in children, and one can only hope that their message is soon heard.

News from Brain Imaging Studies in Children and Adolescents

Brain Imaging Finds Abnormalities that Appear Over the Course of Childhood-Onset Bipolar Illness

There is considerable evidence that children with bipolar disorder have smaller amygdalas, and the amygdala also appears to be hyper-reactive when these children perform facial emotion recognition tasks. A symposium on longitudinal imaging studies in pediatric bipolar disorder was held at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry to shed light on other brain abnormalities in these children.

Researcher Nancy Aldeman reported that **there is some evidence children with bipolar disorder have decreased gray matter volume in parts of the brain including the subgenual cingulate gyrus, the orbital frontal cortex, and the superior temporal gyrus, as well as the left dorsolateral prefrontal cortex and amygdala. At the same time there is evidence of increased size of the basal ganglia.** These abnormalities do not appear to precede the onset of the illness.

Some changes occur over the course of the illness. The basal ganglia seem to increase in volume in patients with bipolar disorder, but decrease in volume in those with severe mood dysregulation and comorbid ADHD. Moreover, parietal cortex and precuneus cortex volumes appeared to increase in children with bipolar disorder while decreasing or staying the same in normal volunteer controls.

A meta-analysis of brain imaging studies indicated that in general, the size of the amygdala appears to increase from childhood to adulthood in bipolar patients, starting out smaller than that of similarly-aged normal

volunteers, but becoming larger than that of adult normal volunteers as the patients age into adulthood.

Lithium treatment increases gray matter volume in a variety of cortical areas and in the hippocampus in multiple studies. In contrast, treatment with valproate for 6 weeks appears to decrease hippocampal volume.

White Matter Abnormalities in the Adolescent Brain Predict Onset of Psychosis

At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Carrie E. Bearden presented data from a study that predicted conversion to psychosis in at-risk youth (those who have prodromal symptoms or a particular genetic mutation that leads to psychosis) by observing white matter abnormalities.

Bearden found that **the degree of white matter abnormality seen during magnetic resonance imaging (MRI) was proportional to the degree of cognitive deficit in patients who subsequently developed a first episode of psychosis.** The white matter abnormalities were seen particularly in the superior longitudinal fasciculus (SLF) and were associated with increased severity of symptomatology. The overall degree of white matter alteration was also significantly related to clinical outcome 15 months later.

Editor's Note: The SLF is a major neuronal conduit between prefrontal cortical systems, which are responsible for cognition and planning, and the parietal cortex, which is responsible for spatial abilities. Disruption of this fiber track has been related to difficulties in social cognition and "theory of mind" concepts, like inferring what others might be thinking.

Amygdala Size Linked to Manic Symptom Severity

In two posters presented at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry, a research group led by Kiki Chang reported that **increased severity of manic symptoms is associated with increased size of the amygdala (especially the right amygdala) in adolescents who are at high risk for developing bipolar disorder.**

The amygdala is a crucial area for emotion regulation. The increasing size, either with more manic symptoms or as patients with bipolar disorder age into adulthood compared to normal volunteer controls (as we describe in the article on brain imaging at far left) could reflect increased use of the amygdala in bipolar disorder.

The increased amygdala size could be linked to increased emotion dysregulation, or it could be a compensatory mechanism in which the amygdala works harder to exert better emotion control.

Experience-dependent neuroplasticity describes a phenomenon in which the volume of a brain area increases as it gets more use (like a muscle that grows when it gets more exercise). One interesting example in which this may occur is London taxi drivers, who have larger hippocampi than the general public. (The hippocampus is responsible for some of the brain's spatial recognition abilities.) This could be explained in two different ways. The discrepancy in size between the hippocampi of taxi drivers and of the general population may exist because the taxi drivers' brains change over the course of their careers via experience-dependent neuroplasticity, or it may exist because those with excellent spatial recognition abilities and bigger hippocampi choose to become taxi drivers.

Primary Care Doctors Important in Detecting, Managing Childhood Mental Illness

The National Alliance on Mental Illness (NAMI) conducted a survey to determine ways that primary care providers can better communicate with parents about a child's mental illness. NAMI executive director Michael Fitzpatrick said, "Most Americans rely on family doctors and pediatricians for early detection of mental illness and in many cases treatment."

NAMI concluded that primary care providers could play a larger role in detecting mental illness in children. The organization found that in 63% of families, the first signs of behavioral or emotional problems were evident in children by age 7. More than half of families reported that their primary care physicians were not knowledgeable about mental health treatments or local resources to support families with mentally ill children.

NAMI suggests that primary care providers educate themselves about early-onset mental illness and local resources for families, provide screening tools for parents and youth in order to encourage discussion of mental health, emphasize that mental health is as important as physical health to a child's wellbeing, ask questions about mental health as a routine part of office visits, and listen to families' concerns without judgment.

Primary care providers are also encouraged to let families know that there is hope and that they are not alone in facing this difficulty, that mental illness in a child is not the parents' fault, and that their children have many strengths.

Primary care doctors should also be prepared to: refer a mentally ill child to psychiatrists, psychologists, and other specialists if needed; follow up, including collaborating with other healthcare providers to develop and implement a treatment plan; and encourage patients and their families.

Irritability and Unipolar Depression in Kids

At the 2012 Pediatric Bipolar conference sponsored by the Ryan Licht Sang Foundation, Graham J. Emslie gave a talk on irritable mood and unipolar depression in youth.

Irritability is common in unipolar depression. Emslie suggested that if a child's irritability is severe and the child destroys objects and denies being irritable, bipolar disorder might be likely. Irritable unipolar depressed children will generally acknowledge being irritable.

Emslie reported that 96% of youth in his randomized placebo-controlled studies of selective serotonin reuptake inhibitor antidepressants (SSRIs) recovered from their unipolar depression, but 46.6% relapsed. Those children with residual depressive symptoms were at double the risk for relapse into a depression compared to those who remitted completely. **In those without residual depressive symptoms, there were no relapses if the children stayed on their medications.**

Children were excluded from Emslie's study if they had a positive family history of bipolar disorder, and perhaps because of this, very few participants switched into mania with antidepressants.

MORAL: Treat to remission and stay on the antidepressants associated with the remission. This has previously been found to be important for adults as well. (Emslie added that he would advise that a child stay on an antidepressant for at least a year after a remission was achieved, and longer if the child had difficulties in academic performance or relationships at school.)

Children with unipolar major depression who had a few manic symptoms at a subsyndromal level had poorer outcomes in Emslie's study. The presence of subsyndromal manic symptoms in bipolar depressed adults is a risk factor for increased

switching into mania when antidepressants are added to a mood stabilizer.

Comorbid substance abuse is another risk factor for poor outcome in childhood depression.

Cardiovascular Problems in Bipolar Disorder May Begin in Adolescence

Adults with bipolar disorder have higher rates of cardiovascular disease and premature death from cardiovascular illness than the general population. At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry, Benjamin Goldstein presented a poster in which he showed that youth with bipolar disorder may also have abnormal cardiovascular function.

When a tourniquet is applied, blood vessels normally expand to make up for the period of oxygen deprivation. This does not happen as readily in patients with mood disorders. This lack of flexibility and compensatory response could be one of the reasons for increased cardiovascular difficulties in those with mood disorders.

In Goldstein's study, noninvasive ultrasound imaging was used to measure the thickness of the walls of the carotid artery and flow mediated dilation of the artery in adolescents with bipolar disorder and those without the illness. The data was collected by a certified ultrasound technologist who remained blind to the patients' diagnostic and symptom status.

Goldstein found highly abnormal results in 14 adolescents aged 14 to 19 with bipolar disorder compared to controls. He concluded that **reducing cardiovascular risk in bipolar disorder is a pressing clinical and public health challenge and that treating these patients while they are adolescents may offer considerable advantages both for prevention and for understanding the progression of cardiovascular problems in patients with bipolar disorder.**

High Rate of Mood Stabilization on Adjunctive Lamotrigine in Adolescents with Bipolar Disorder

At the 2012 meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), Melissa P. DelBello presented a poster on the design of a maintenance study in bipolar youth to determine characteristics of patients who stabilized on adjunctive lamotrigine. The study included children aged 10 to 17 who had been diagnosed with bipolar disorder. Of a total 244 potential subjects, **160 individuals or 66% stabilized on lamotrigine during the open (not blind) portion of the study.** Of these, 143 were randomized to either lamotrigine continuation or placebo.

Seventeen participants did not enter the randomized phase of the study, primarily because of withdrawal of consent, presumably because they were reluctant to be placed in the placebo group. The authors concluded that a study design involving randomization to medication continuation versus withdrawal with placebo substitution could underestimate the true level of treatment response.

However, the high stabilization rate of 66% using adjunctive lamotrigine in the open phase of the study suggests that the drug is effective. Clearly confirmation of this in the double-blind randomized phase is needed to confirm this prediction.

Memantine May Be Useful in a Variety of Conditions Including OCD, ADHD, and Autism

Memantine (Namenda) is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that is FDA-approved for the treatment of Alzheimer's dementia. Its use in other illnesses such as bipolar disorder and autism is currently being explored.

As we have written in previous issues of the BNN, A. Anand et al. reported in 2012 that in bipolar depression, memantine has an initial antidepressant augmentation effect when added to lamotrigine, an inhibitor of glutamate release. Koukopoulos et al. also reported in 2012 that in an open study, memantine had a large and sustained effect in previously treatment-resistant patients with bipolar disorder, producing an impressive 60-70% rate of excellent response at 6 months and again at 12 months of follow-up.

There is some evidence that memantine can be useful in obsessive-compulsive disorder (OCD). In a randomized double-blind placebo-controlled study of memantine combined with fluoxetine published by Ghaleiha et al. in 2012, patients with moderate to severe OCD taking memantine and fluoxetine were more likely to achieve remission after 8 weeks than patients taking placebo and fluoxetine.

Attention-deficit/hyperactivity disorder (ADHD) is another condition that memantine may be able to treat. Disturbances in NMDA receptor activity are thought to play a role in ADHD. Small, preliminary studies of memantine in ADHD have been promising.

New research has begun to explore memantine's effects in autism. In one recent randomized, double-blind, placebo-controlled study published by Ghaleiha et al. in the International Journal of Neuropsychopharmacology, **memantine produced improvement in children with autistic disorder when the drug was added to a treatment regimen that included risperidone**, which blocks dopamine D2 receptors and is FDA-approved for the treatment of schizophrenia and mania, as well as autism.

However, at the 2012 meeting of the American Academy of Child and Adolescent Psychiatry, Robert Findling presented a poster on extended release memantine (Namenda) in children with autism, a study with negative results. This was a monotherapy study, unlike the above studies in which memantine was added to treatment with another drug. Findling found that extended release memantine (at doses of 3mg to 15mg per day) was well tolerated in children with autism, but the drug on its own was not significantly more effective than placebo in these preliminary studies.

Editor's Note: Taken together, these data suggest an emerging role for memantine and possibly other drugs that work through NMDA receptor blockade in several disorders associated with repetitive behavior, like OCD and autism. The role of memantine augmentation in each of these syndromes deserves further exploration.

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An Animal Model of Poor Judgment in Adolescence: Previous Learning About Dangerous Environments May Be Suppressed

As young mice transition into adolescence, they experience a "sensitive" period in which their context-based fear memories are temporarily suppressed.

In a recent study, young animals learned to avoid an environment associated with a mild shock. Later, when they entered adolescence, this learning was temporarily forgotten or suppressed. However, when the same mice aged into adulthood, they re-

acquired this learned fear memory and began to again avoid the environment associated with the earlier shock. This temporary loss of fear memory differs in mice depending on their genes.

At the 2012 meeting of the Society of Biological Psychiatry, researcher Francis S. Lee reported that mice with a certain genetic variation display an impairment of this fear memory process. There are several common variants of the gene responsible for the production of brain-derived neurotrophic factor (BDNF), which protects neurons and is necessary for long-term memory. Mice with the poorer functioning variant known as Val66Met (as opposed to the better functioning Val66Val) fail to recall the earlier fear-related events not only in adolescence, but also in adulthood when the fear memory is usually retrievable again.

Editor's Note: In mice and humans, Val66Val is the most frequently occurring allele in the population, but Val66Met is also a fairly common variation of the BDNF gene. It is this Val66Met allele that is associated with not retaining earlier learned experience about a "dangerous" environment that should be avoided.

These data suggest an intriguing explanation for some of the "wild" behavior and poor judgment to which even the smartest adolescents are prone. This

Adolescents should be viewed with some sympathy--some unique physiological processes are occurring in them!

kind of behavior may be based in part on the temporary forgetting in adolescence of earlier learning about which situations or environments are safe versus which ones are dangerous.

Other data suggest that adolescent animals and humans are particularly prone to developing substance abuse. Are they temporarily forgetting or suppressing what they may have already learned about the dangerousness of drugs of abuse because they are in the critical adolescent period?

Other explanations for the chaotic behavior of adolescents are possible. According to the data of the famous neuroanatomist Pasko Rakic, adolescent primates prune back 100,000 synapses per second. (This editor's wild speculation: it is even possible that the two phenomena are related. It is possible that adolescents can't remember previously learned avoidance behaviors because their synapses are being pruned back so fast that their brain is scrambled. When the pruning reorganization finally slows down and excitatory synapses are largely replaced with inhibitory synapses, more effective brain processes return and the post-adolescent individual is again able to recall previous learning.)

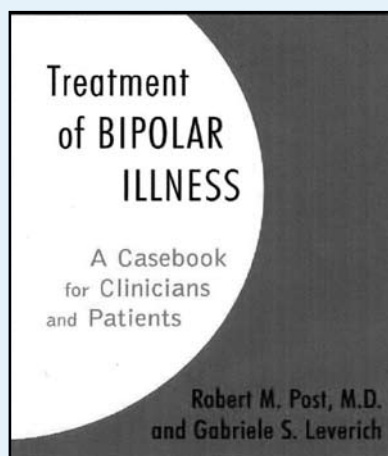
In any event, adolescents should be viewed with some sympathy because of the unique physiological processes occurring in them – light speed brain reorganization and the inability to remember previous learning about safe environments and actions.

Advertisement

From W.W. Norton & Company:

Treatment of Bipolar Illness: A Casebook for Clinicians and Patients

ROBERT M. POST, MD
and
GABRIELE S. LEVERICH, LCSW, BCD



BNN editors have written a book to provide physicians, patients and family members with the latest information about the illness and its treatments.

In a review in the *Journal of Psychiatric Practice*, Mark Frye of the Mayo Clinic gave the book 5 stars and wrote:

"This textbook by Post and Leverich is the most up-to-date, comprehensive visual teaching guide on the phenomenology, longitudinal course, and treatment of bipolar disorder currently available."

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