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Fall 2002

Bipolar Network News

Meeting Highlights

NIMH Pediatric Bipolar Disorder Conference
March 22, 2003, Washington, D.C.

On Saturday, March 22, 2003, the National Institute of Mental Health (NIMH) sponsored a conference on pediatric bipolar disorder in Washington, D.C. The meeting was called to increase the exchange of information on the diagnosis, pathophysiology, and treatment of pediatric bipolar illness. Over 25 researchers and clinicians gave presentations or presented posters at the meeting.

Oral Presentations

Dr. J. Biederman (Massachusetts General Hospital) opened the conference with a talk on a **prospective follow-up study of pediatric bipolar disorder**, and emphasized that the criteria needed for the definition of a clinical syndrome had been met for pediatric bipolar illness in terms of: 1) clinical characteristics; 2) family history; 3) treatment response; and 4) course and outcome characteristics.

With respect to the characteristics of pediatric bipolar illness, Dr. Biederman noted in his study: 1) the high incidence of irritable presentations with a chronic course; 2) an increased incidence of relatives with bipolar illness in those with, compared to those without, childhood onset mania; 3) mood stabilizers appeared effective, whereas the stimulants were not; and 4) the course of pediatric bipolar disorder was highly variable and at times difficult, with 60% achieving syndromic remission at the end of one year, but only 20% achieving symptomatic remission, and only 10% achieving true euthymia in this period.

• *These discouraging outcome data to some extent parallel those of Dr. B. Geller's recent data of patients with pediatric bipolar disorder treated naturalistically in the community (Geller et al., 2002; Am J Psychiatry 159 [6]: 927–933). However, Dr. Biederman's data conflict with studies of Dr. Chang (Chang and Ketter, 2000; J Child Adolesc Psychopharmacol 10 [1]: 45–49), Dr. M. DelBello (DelBello et al., 2002; J Child Adolesc Psychopharmacol 12 [4]: 323–330), Dr R. Kowatch (Kowatch et al., 2000; J Am Acad Child Adolesc Psychiatry 39 [6]: 713–720), and Dr. R. Findling (Findling et al., 2002; Int J Neuropsychopharmacol 5 [Suppl. 1]: S57–S58) where the use of one and often two mood stabilizers in combination were highly effective in treating early onset acute mania. Thus, if the illness is treated aggressively, the outcome may be much more favorable than that suggested in several naturalistic studies in the literature.*

Dr. A. Nierenberg (Massachusetts General Hospital) discussed preliminary data on the **childhood illness presentations of 500 adult patients** studied in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Of the 491 patients with evaluable data, Dr. Nierenberg found that 50% of patients reported bipolar illness onset prior to age 18; 13% had a lifetime diagnosis of attention-deficit hyperactivity disorder (ADHD), and those who did were less likely to have 8 weeks of recovery (20%) compared with those without ADHD (35%). Moreover, the patients with a history of an ADHD comorbid diagnosis with bipolar illness had an earlier age of onset, a more adverse illness course (more depressions, manias, suicide attempts, violence, and problems with the legal system) as well as more comorbidities (an increased incidence of panic anxiety, agoraphobia, social phobia, generalized anxiety disorder, post-

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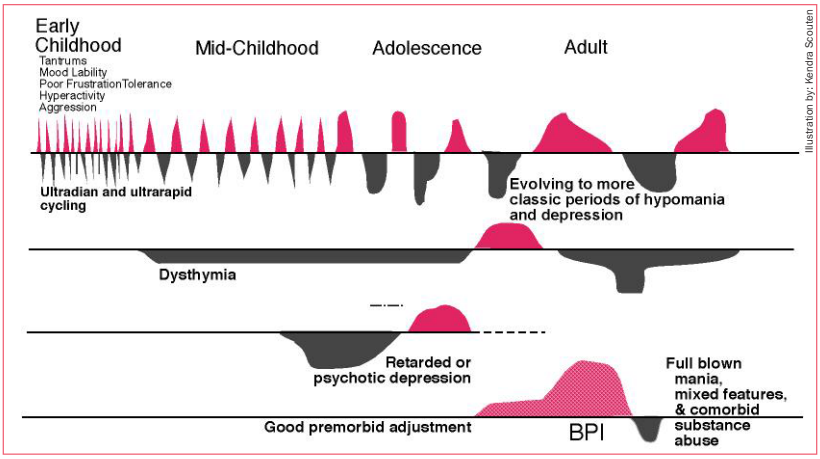

Potential differential presentations of childhood onset bipolar illness

Meeting Highlights: Pediatric Bipolar Disorder

(Continued from page 1)

traumatic stress disorder [PTSD], and alcohol and drug use).

The clinical features of children presenting with **bipolar depression** compared with those presenting with unipolar depression were compared by Dr. J. Wozniak (Massachusetts General Hospital); those children with bipolar depression versus children presenting with unipolar depression had a higher incidence of sad/low mood (69% vs 50%), conduct disorder (60% vs 12%), and oppositional defiant disorder (63% vs 30%). The bipolar children also had more anxiety disorders and relatives with anxiety disorder family histories.

". . . the patients with a history of an ADHD comorbid diagnosis and bipolar illness had an earlier age of onset, a more adverse illness course . . . as well as more comorbidities."

Dr. P. Davanzo (University of California at Los Angeles) reported a higher level of the **choline/creatine ratio** in children with a bipolar diagnosis compared to children with intermittent explosive disorder or controls. Moreover, scores on the Young Mania Rating Scale (YMRS) were directly correlated with the ratio.

Dr. M. DelBello (University of Cincinnati) reported her functional magnetic resonance imaging (fMRI) findings of **decreased thalamic volumes** in those with pediatric bipolar disorder, but increased thalamic volumes in adults with bipolar disorder. Dr. DelBello's study was a comparison of 12 control subjects, 13 first-episode bipolar patients, and 8 multiple-episode bipolar patients. Patients with either type of bipolar presentation had increased activity in anterior limbic structures, but those with multiple episodes had higher levels of activity in the dorsolateral prefrontal cortex in the anterior cingulate, as well as hippocampal activation, which Dr. DelBello thought was attributable to these patients having to work harder and recruit other structures for increased use of memory processing to do a task that others did more automatically. The task the patients performed during fMRI was a block design test for sustained attention. The multiple episode patients also had more performance deficits in this task, suggesting the possibility that those with repeated episodes of bipolar illness may be at risk for altered brain activation patterns and some degree of psychological dysfunction.

An **early age of onset** of bipolar illness might be a heritable trait, suggested Dr. S. Faraone (Massachusetts General Hospital), and he found three potential genetic loci associated with it. These loci were on chromosomes 12, 14 and 15, and are at different loci than others have found for the vulnerability to bipolar illness itself.

- *So far, the hope for breakthroughs in the diagnosis and identification of vulnerability factors for bipolar illness based on traditional gene searches has not been highly productive. It is likely that there will be multiple genes of small effect and these may differ among different ethnic groups or even families.*

Dr. E. Leibenluft (NIMH) reviewed her **neurophysiological findings** in children with bipolar illness; she found that children with bipolar illness had problems with delayed spatial memory rather than immediate spatial memory, and that they had problems with response inhibition on attentional tasks. Most interestingly, she found that children had no problems recognizing facial emotion in pictures of adults, but they had a considerably increased number of errors in recognizing facial emotion in children. In particular, those children with bipolar disorder mistook neutral and other affective facial expressions for anger.

Dr. M. Pavuluri (University of Illinois at Chicago) and Dr. M. Fristad (Ohio State University) outlined their **psychotherapeutic programs** for children with bipolar disorder (Child and Family-Focused Cognitive Behavior Therapy [CFF-CBT] and Multifamily Psychoeducation Groups [MFPG], respectively) that sequentially involve education around symptoms and medication, developing a treatment team system for dealing with negative family interactions, and then building coping skills, problem solving techniques, and communication skills. There are also components in their programs for helping with nonverbal skills such as misreading a person's expression of anger.

A **family-focused treatment program** for bipolar adolescents was reviewed by Dr. D. Miklowitz (University of Colorado). He presented data that showed family-centered treatment approaches clearly decrease

(Continued on page 11)

Bipolar Network News

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The *BNN* is published three times a year by investigators working with patients with bipolar disorder to better understand the long-term course and treatment of the 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 summary or prepublication form, and therefore cannot be taken as verified data. The *BNN* can thus assume no liability for errors of fact, 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*.

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Meeting Highlights

41st Annual American College of Neuropsychopharmacology (ACNP) Meeting
December 8–12, 2002, San Juan, Puerto Rico

The 2002 meeting of the American College of Neuropsychopharmacology (ACNP) was a landmark meeting with regards to many of its findings, as well as to a substantial focus on findings pertinent to bipolar illness. Three different areas of evidence from the meeting indicated a shift in our understanding of bipolar disorder and schizophrenia; these three areas were: (a) brain microstructure; (b) genetic vulnerability factors, and (c) glial cell pathology.

Glia and Bipolar Disorder

Dr. P. Hayden (University of Pennsylvania) gave a talk on the **tripartite synapse**, indicating that glial cells are a crucial component of the synapse, which also includes pre-synaptic and post-synaptic neurons. Dr. Hayden described the three types of glial cells in the brain. First, astrocytes are the critical third member of the tripartite synapse and increase uptake of potassium neurotransmitters (particularly glutamate), release neurotrophic factors, and provide metabolic support. He indicated that there are ten billion neuronal cells in the brain, and humans have a 10-to-1 ratio of glia to neurons (rodents have a 1-to-1 ratio); therefore, human brains have 100 billion glial cells. With each glial cell participating in about 140,000 synapses, astrocytes thus participate in zillions of synaptic connections necessary for normal neuronal function, learning, and memory. These astroglial cells participate in the glutamine-glutamate shuttle, as well as regulating lactate, blood flow, and neurotrophic factors. Glial failure to clear synaptic glutamate or lactate could account for some of the neuropathological disturbances seen in these major psychiatric illnesses (see Dr. Renshaw, below). In this way, deficits in glial cell number and activation, as measured by glial fibrillary acidic protein (GFAP), could not only have important effects on synaptic function, but also on the neuronal cell loss and elevated lactate levels seen in bipolar disorder and schizophrenia.

The second type of glial cell makes myelin. In the central nervous system they are called oligodendrocytes and those that make myelin in the peripheral nervous system are called Schwann cells. There is evidence of disturbances of myelin, not only in the classic demyelinating illness of multiple sclerosis, but now also in schizophrenia and major depression.

The third major type of glial cells are called microglia, and participate in phagocytosis (eating microbes and other cells), in the release of cytokines, and in providing the immune mechanisms of the central nervous system.

In this same symposium, Dr. G. Rajkowska presented data on the neural and glial deficits that she has found in both bipolar illness and schizophrenia and Dr. K. Davis described the multiple lines of evidence that implicate altered oligodendrocyte function in schizophrenia. There is clear evidence that glial cell pathology plays an important role in bipolar disorder and schizophrenia; this has now been almost unequivocally documented for schizophrenia, and to a slightly lesser extent for bipolar illness as well.

Neuroanatomy

Dr. L. Altshuler (University of California at Los Angeles) presented data showing an **increased size of the amygdala** in patients with bipolar illness. This finding has now been replicated by five other research groups. Dr. Altshuler reported that age and the size of the left amygdala were normally correlated in volunteers, whereas in similar adolescents with bipolar illness, age was positively correlated with size of the left amygdala.

- *These data, along with Dr. Altshuler's previous observations that the number of manic hospitalizations was correlated with increased size of the left amygdala, suggests a developmental alteration in the size of the left amygdala in patients with bipolar illness, and one that could be affected by illness-related variables.*

Dr. A. Kumar (University of California at Los Angeles) presented data from a study using a new neuroimaging technique, called **magnetization transfer** (MT). MT allows researchers to examine the biophysical characteristics of specific brain regions using magnetic resonance methods, and provides an MT ratio image (MTR) that reflects demyelination and axonal damage in neuropathological studies. In a study of eight patients with late life major depression versus eight nondepressed controls, there were significant reductions in MTR in the basal ganglia and occipital white matter, as well as in the genu and splenium of the corpus callosum. These same patients with late-life depression had white matter and subcortical nuclei that appeared normal using traditional magnetic resonance imaging (MRI) techniques.

- *Major meta-analyses consistently indicate that patients with bipolar illness have increased white matter hyperintensities on MRI compared with controls. This new study suggests that even when the brain looks normal on MRI, it may have evidence of demyelination and axonal damage with MT. Clear evidence of white matter hyperintensities is seen in the demyelinating disease of multiple sclerosis and are associated with altered motor function and a high incidence of affective disturbances as well. These new data suggest the possibility that a component of demyelination that had been*

(Continued on page 4)

- **What is the importance of a loss of normal glial function in bipolar patients?**
- **How is lithium involved in glial growth?**
- **What are the different ways that lithium is beneficial to your health?**

For the answers to these questions, along with a useful illustration of the tripartite synapse

and a table outlining the potential neurotrophic and neuroprotective effects of bipolar illness, lithium, valproate, and the antidepressants, visit the Research News section of our website, www.bipolarnews.org, under the section "ACNP Meeting."

Meeting Highlights: ACNP

(Continued from page 3)

subthreshold for detection, could be relevant to bipolar affective disorder and late life major depression.

Dr. J. Lieberman (University of North Carolina) studied the effects of **antipsychotic drugs** (the typical antipsychotic haloperidol [Haldol®] or the atypical antipsychotic olanzapine [Zyprexa®]) on the progression of **brain pathomorphology** in 167 patients with schizophrenia, using structural magnetic resonance imaging (sMRI). After 12 weeks of treatment, there was evidence that olanzapine had greater brain sparing effects than haloperidol in whole brain volume, total gray matter, and lateral ventricular volume; these results suggest the possibility that illness progression can be prevented with atypical antipsychotic medication.

"...the combination of olanzapine and fluoxetine produced the best rates of response and remission in patients with bipolar depression after eight weeks of double-blind treatment..."

- *It would appear warranted to have a controlled study of atypical antipsychotics with and without lithium augmentation to see if lithium could help prevent schizophrenic-related relapse as well as neuropathological progression, given the new evidence of neuroprotective and glial protective effects of lithium.*

Dr. P. Renshaw (McLean Hospital, Massachusetts) reported that after 12 weeks of treatment, **olanzapine reduced** frontal lobe **lactate levels** in proportion to the degree of treatment response in patients with first episode psychoses, on proton magnetic resonance spectroscopy (^{1}H-MRS). Lactate is a neurochemical that increases with mitochondrial dysfunction. Dr. Renshaw also found that lactate appeared to be a chemical marker for frontal hypometabolism and suggested that strategies to reduce brain lactate levels may offer novel therapeutic approaches to treatment of both schizophrenia and bipolar disorder, as he has also found elevated brain lactate levels in depressed, unmedicated bipolar subjects.

- *High plasma levels of lactate achieved with experimental lactate infusions are associated with the induction of panic attacks in patients with panic disorder. The link between the brain and plasma lactate levels, and each to psychopathology, remains to be further explored.*

Mechanisms of Action

Dr. H. Einat (NIMH) found that in rodents, both lithium and valproate (Depakote, Depakene®) upregulated signaling in the **extracellular signal-related kinase** (ERK) pathway, which is utilized by the neurotropins.

- *These data support the view that not only lithium, but also the mood stabilizer valproate, can promote neuronal growth and regeneration, as well as protect neurons against trophic factor deprivation and amyloid beta peptide toxicity.*

Dr. L. Santarelli (Columbia University) noted that antidepressants usually have a delayed onset, which suggests that their action results from slowly developing changes in the brain. Many antidepressants have been found to increase neurogenesis (birth of new neurons and integration into the hippocampus) in the dentate gyrus of an adult animal. In Dr. Santarelli's study with mice, he showed that **disrupting antidepressant-induced neurogenesis** with x-irradiation prevented the behavioral effects of two different classes of antidepressants in animal models. He also found that animals that had their 5-HT_{1A} receptor removed did not experience the usual effects of the serotonin-selective antidepressant fluoxetine (Prozac®) on neurogenesis and rodent behavior in pertinent animal models.

- *These data for the first time raise the possibility that stimulation of neurogenesis could account for some of the behavioral effects of chronic antidepressant treatment.*

Pharmacotherapy

Dr. D. Robinson (Melbourne, Florida) examined the long-term safety of the formulation of **selegiline** (Eldepryl®, a selective monoamine oxidase-B inhibitor) as a **transdermal patch** for use in major depression. In 312 patients randomized to either the selegiline patch or placebo, relapse rates after one year were 16.8% for those treated with selegiline versus 30.7% in the placebo-treated subjects. This transdermal (absorbed through the skin) delivery of a monoamine oxidase inhibitor was safe, as there were no acute hypertensive crises or serious drug-drug interactions. The most common side effects were irritation at the application site (15.5% with selegiline, 3.7% with placebo), headache (12% vs. 9.8%), and insomnia (10.1% vs. 6.7%).

Dr. R. Baker (Eli Lilly) found that the combination of **olanzapine and fluoxetine** produced the best rates of response and remission in patients with bipolar depression after eight weeks of double-blind treatment, versus treatment with olanzapine in monotherapy or with placebo. Treatment-emergent mania did not differ between the groups (5–6%).

In a retrospective study, Dr. A. Metz (GlaxoSmithKline) found that the combination of **lamotrigine** (Lamictal®) **and valproate**, *with the recommended reductions in the titration schedule of lamotrigine*, was effective and well-tolerated in 201 patients with bipolar I disorder.

Dr. G. Sachs (Massachusetts General Hospital) studied the effects of **quetiapine** (Seroquel®) or placebo in 91 bipolar I manic patients, used as an adjunct to a mood stabilizer (either lithium or valproate). He found a superior efficacy of quetiapine as an adjunct to lithium or valproate over treatment with a mood stabilizer

(Continued on page 10)

The Child and Adolescent Bipolar Foundation has an excellent, well-organized web site (www.bpkids.org) with a large amount of useful information for parents of bipolar kids. Membership in the foundation is free to parents, guardians, and others caring for children with early-onset bipolar disorder. Listed below are the many categories of information available on the site.

FRONT DESK

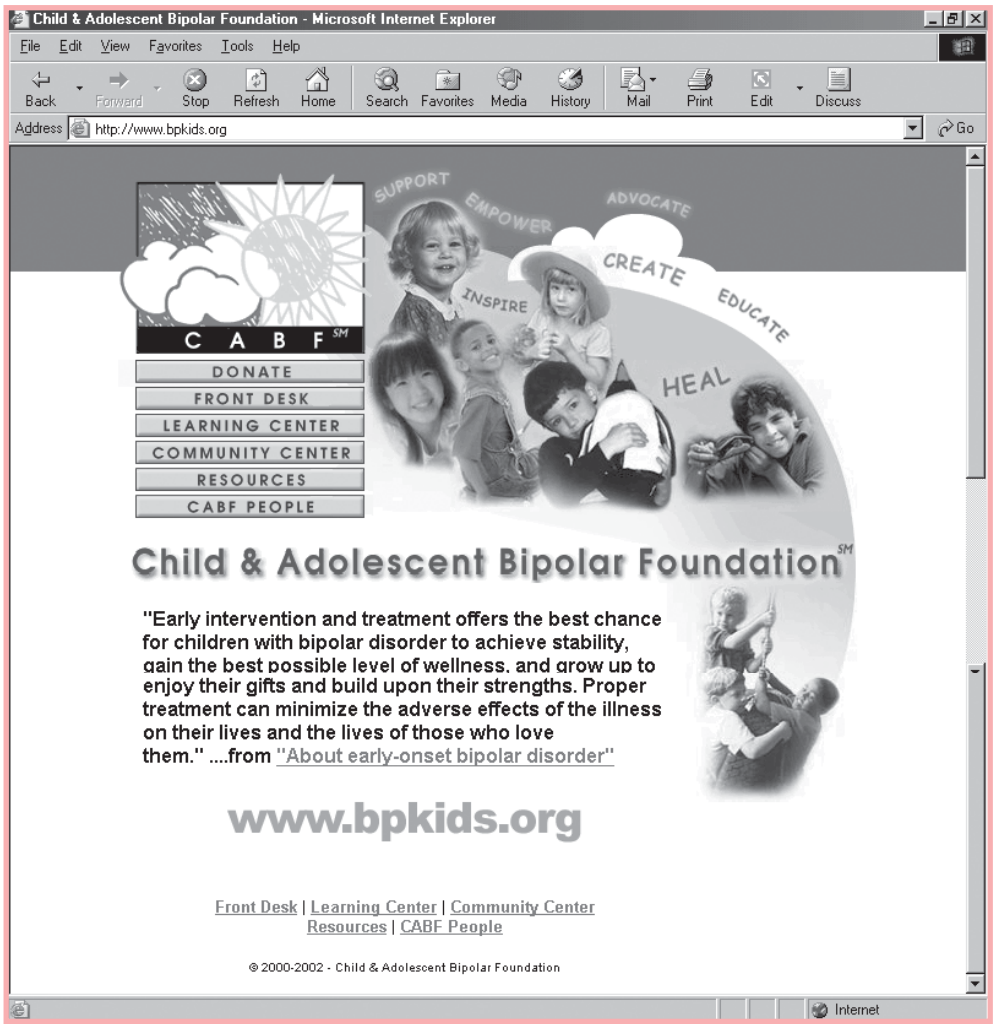
- Welcome
- About CABF
- Breaking News
- Mission
- Goals
- Printed Materials
- Mailing List Sign-up
- Join CABF
- Become a Donor
- Become a Sponsor
- CABF Web site Tour
- Web Site Map
- Calendar
- Press Room
- Suicide Hotlines

LEARNING CENTER

- About Early-Onset Bipolar Disorder
- Timeline
- Educating the Child With Bipolar Disorder
- Legal Issues
- Newsletter
- References
- Research Studies
- Mood Charts
- Brain Images
- Glossary
- Reference Room

COMMUNITY CENTER

- Message Boards
- Chat Rooms
- Chat Abbreviations
- Support Groups
- Find a Doctor
- Newsletter
- Gallery
- Bookstore
- Giftshop
- Research Studies
- Suicide Hotlines
- Mood Charts



RESOURCES

- Printed Materials
- State Resources
- Supplemental Security Income
- International Resources
- Bookstore
- Research Studies
- CABF Message Boards
- Directory of CABF Professional Members
- Directory of Support Groups
- Reference Room

CABF PEOPLE

- Members
- Board of Directors
- Professional Advisory Council
- Staff and Team Leaders
- CABF Teams
- Donors
- Organizational Donors
- Photo Album

Research Update

Conference on Pediatric Bipolar Disorder
Boston, Massachusetts, March 2002

Biological Psychiatry, Vol. 53, Number 11, June 1, 2003

The special June 1, 2003, issue of the journal *Biological Psychiatry* has 16 articles that were derived from presentations given at a conference on pediatric bipolar disorder in March of 2002. The following are direct excerpts from that issue (with the exception of words in brackets *[example]*, added by the *BNN* for clarity). To read the abstracts of all 16 articles, go to the following website: www.sciencedirect.com/science/issue/4982-2003-999469988-433221.

"The delay in research on bipolar illness in children for almost 50 years after lithium became available for treatment of mania in adults is a tragic chapter in the history of child psychiatry. Emil Kraepelin himself described mania in young children and adolescents in 1921, and more than 400 case reports have appeared in the medical literature since the middle of the 19th Century...

"Research on childhood mania and bipolar disorder remained largely unfunded at the federal level until the mid-1990s, while youth with bipolar disorder continued to suffer and die from an illness that, according to some leaders in child psychiatry, was exceedingly rare in children, if it existed at all... A breakthrough occurred when a consensus conference of child psychiatry researchers convened by the NIMH agreed, at last, that bipolar illness could, in fact, be diagnosed in children before puberty.

"Bipolar disorder with onset in childhood derails mood, energy, cognition, and behavior just when external social networks—as well as neural networks within—are undergoing crucial development, and learning is at a premium...Parents of children currently being diagnosed are in the unenviable position of learning the name of the medical disease assaulting their children's brains and threatening their lives and then being informed that there are no medications approved for children by the U.S. Food and Drug Administration (FDA) to prevent these tragic outcomes... Doctors asked to treat a child with severe depression and a family history of bipolar disorder must weigh the risk of triggering mania with antidepressants against the risk of brain damage and suicide incurred by *not* treating the child's depression.

"Families affected by bipolar disorder in children have reason to celebrate increased investment by the NIMH in research. This issue of *Biological Psychiatry* heralds the first in a series of annual scientific conferences at which researchers will gather to share findings, develop a common language, and forge collaborative relationships."

Martha Hellander, Child & Adolescent Bipolar Foundation
"Pediatric Bipolar Disorder: The Parent Advocacy Perspective," pp. 935–937

"...since structured diagnostic interviews are usually administered by trained raters, questions have been raised regarding their reliability for accurately identifying complex conditions such as juvenile mania... one approach to deal with this issue is to directly compare information on childhood-onset bipolar disorder derived from a structured diagnostic interview administered by trained rater with that of an expert clinician.

"We separately and independently assessed 69 youths recruited for a study of mania in childhood, all but 2 of whom experienced mania, with a structured diagnostic interview administered by trained psychometricians and a clinical assessment by a board-certified child and adolescent psychiatrist (JW) who was blind to the structured interview results... The expert clinician interview confirmed the structured diagnostic interview–derived diagnosis of mania (Bipolar I) in all but two cases (97% agreement).

"These results indicate that structured interview–derived diagnoses of pediatric bipolar disorder are very likely to be corroborated by clinician assessment and support the utility of structured interviews as diagnostic aids for the identification of pediatric bipolar disorder... as much of the controversy surrounding the diagnosis of pediatric-onset mania arises from the definition and threshold for endorsing symptoms such as euphoria, irritability, and grandiosity in children, the field will benefit from structured interviews that better exercise the definition of these symptoms."

Janet Wozniak, Michael Monuteaux, Jennifer Richards, Kathryn Lail, Stephen Faraone, and Joseph Biederman, Massachusetts General Hospital (JW)
"Convergence Between Structured Diagnostic Interviews and Clinical Assessment on the Diagnosis of Pediatric-Onset Mania," pp. 938–944

"In a series of studies, our group attempted to delineate the relationship between bipolar *[BPD]* and conduct disorder *[CD]*... Symptoms of CD were almost identical in CD children irrespective of the comorbidity with BPD, and the same was true for manic symptoms. Patterns of psychiatric comorbidity with other disorders also supported the conclusion that the diagnostic overlap between BPD and CD was true psychiatric comorbidity rather than a lack of differentiation of the current diagnostic system: children with CD had correlates of CD, children with BPD had correlates of BPD, and children with CD+BPD had correlates of both. Familial risk analyses also supported this conclusion: CD and BPD bred true in families of children with either disorder, with increased family risk for both disorders in children with both disorders. More specifically, our studies show that the comorbid condition may share a specific familial etiology.

"Our data suggest that when BPD and CD co-occur in children, both are correctly diagnosed. In these comorbid cases, CD symptoms should not be viewed as secondary to BPD, and manic symptoms should not be viewed as secondary to CD."

Joseph Biederman, Eric Mick, Janet Wozniak, Michael Monuteaux, Maribel Galdo, and Stephen Faraone, Massachusetts General Hospital (JB)
"Can a Subtype of Conduct Disorder Linked to Bipolar Disorder Be Identified? Integration of Findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program," pp. 952–960

"The diagnosis of a manic or hypomanic episode in a child requires not only that the child can experience manic symptoms but also that these symptoms can be reported accurately. The gradual development of meta-cognition, that is, children's ability to reflect on their own thoughts, constrains their ability to report some of the key symptoms of mania... Moreover, young children's ability to give accurate accounts of past problems and of how long they lasted is limited. This means that studies of mania in young children often have to rely on accounts from parents... or on accounts from parents corroborated by children. By contrast, studies of adults will usually obtain information about the patient's mental state by a direct interview (although in severe cases this will often need to be corroborated by information from a close relative or friend).

(Continued on page 7)

Research Update

(Continued from page 6)

"... the available data suggest that preadolescent mania is less common than adult mania and differs in that it shows a male preponderance and a greater degree of comorbidity with disruptive behavior disorders."

Richard Harrington and Tessa Myatt, Royal Manchester Children's Hospital, UK
"Is Preadolescent Mania the Same Condition as Adult Mania? A British Perspective," pp. 961–969

"The familial aggregation and genetic transmission of bipolar disorder has been consistently demonstrated through family, twin, and adoption studies. These studies show that early onset of the disorder confers a greater familial risk to relatives, but relatively little is known about genetic transmission in families having juvenile-onset cases.

"Although there are few genetic epidemiologic studies of juvenile-onset bipolar disorder, the evidence from extant studies is clear: this form of bipolar disorder aggregates in families and appears to be highly heritable. It is not yet known if this aggregation is due to genetic or environmental sources, as twin studies of juvenile-onset bipolar disorder are lacking; however, twin and adoption studies of broad-spectrum bipolar disorder clearly demonstrate the high heritability of the disorder, with a minority of disease risk attributable to shared and unique environmental experiences."

Stephen Faraone, Stephen Glatt, and Ming Tsuang, Massachusetts General Hospital (SF)
"The Genetics of Pediatric-Onset Bipolar Disorder," pp. 970–977

"The purpose of this study was to develop prospective data on the effectiveness of combination pharmacotherapy of children and adolescents with bipolar disorder during a 6-month period of prospective, semi-naturalistic treatment. Thirty-five subjects, with a mean age of 11 years, were treated in the extension phase of this study after having received 6–8 weeks of acute treatment with a single mood stabilizer. The extension phase of this study lasted for another 16 weeks, for a total of 24 weeks of prospective treatment. During this study phase, subjects were openly treated, and they could have their acute-phase mood stabilizer switched or augmented with another mood stabilizer, a stimulant, an antidepressant agent, or antipsychotic agent, if they were assessed to be a nonresponder to monotherapy with their initial mood stabilizer.

"During the extension phase of treatment, 20 of 35 subjects (58%) required treatment with one or two mood stabilizers and either a stimulant, an atypical antipsychotic agent, or an antidepressant agent. The response rate to combination therapy was very good, with 80% of subjects treated responding to combination therapy with two mood stabilizers after not responding to monotherapy with a mood stabilizer... A significant proportion of these pediatric bipolar subjects required treatment of comorbid ADHD before they became improved in overall functioning—mood and attention... Our experience in this study was that the addition of a low-dose stimulant to this subject's mood stabilizers would in many cases markedly improve the child's ADHD symptoms without exacerbating the mood disorder. This finding runs against the prevailing clinical wisdom, which holds that stimulants may exacerbate manic symptoms in bipolar patients... The critical issue appears to be the sequence of treatment, with the patient's bipolar disorder treated before stimulant medication is added or reintroduced."

Robert Kowatch, Gopalan Sethuraman, Judith Hume, Michelle Kromelis, and Warren Weinberg, University of Cincinnati Medical Center (RK)
"Combination Pharmacotherapy in Children and Adolescents with Bipolar Disorder," pp. 978–984.

"Initially, we developed two versions of psychoeducational intervention. One was a 1-hour workshop for parents of children psychiatrically hospitalized for any major mood disorder. This brief format was conceptualized to cover the "basics" (i.e., long enough to provide meaningful information but brief enough that already stressed parents of acutely ill inpatients would find time to attend)... First, we evaluated the impact of 1-hour psychoeducational workshops... Participants were 25 parents of 20 patients, 25% of whom had bipolar disorder... We found that workshop participants, especially fathers, experienced significant knowledge gain after attending the 1-hour workshop.

"The second version was multifamily psychoeducation groups (MFPG), designed for outpatient children with any major mood disorder and their parents. MFPG initially was administered in six 75-minute sessions in a manual-based, multifamily group format... Based on feedback received in our randomized, controlled pilot study, we expanded MFPG to eight 90-minute sessions... Each of the eight sessions is highly formatted with specific content to be taught and skills to be practiced. Thus, MFPG is not the same as a support group, the focus of which is often more on exchanging stories of success and frustration.

"... we completed a small, nonrandomized program evaluation of the six-session MFPG program for nine parents and children, three of whom had bipolar disorder... all eight subscales improved in the predicted direction from pretreatment to posttreatment (mothers and fathers each reported increased positive attitudes and behaviors toward their children and decreased negative attitudes and behaviors toward their children...

"Third, we conducted a small-scale randomized, controlled trial of the six-session MFPG with 35 families of children aged 8 to 11 with mood disorders... MFPG parents demonstrated significantly more knowledge than the wait-list control (WLC) families immediately after intervention, *[and]* this gain was sustained at the 6-month follow-up. Multifamily psychoeducation group children reported a significant gain in social support from their parents and a trend toward increased gain from their peers at the 6-month follow-up, compared to WLC children."

Mary Fristad, Stephen Gavazzi, and Barbara Mackinaw-Koons, Ohio State University (MF)
"Family Psychoeducation: An Adjunctive Intervention for Children with Bipolar Disorder," pp. 1000–1008

"A possible explanation for the ongoing controversy surrounding pediatric bipolar disorder is that differences in assessment methodologies lead to conflicting results. One way to address methodological differences in assessment across studies is to use a single standardized assessment of psychopathology to calibrate the findings reported in different studies.

"To this end, we conducted a meta-analysis of several studies that have employed the Child Behavior Checklist *[CBCL]* in the assessment of children with a diagnosis of bipolar disorder... The CBCL is one of the best-studied, empirically derived, checklists available that measure psychopathology... the CBCL is completed by parents and is scored according to precise algorithms defined in reference to published norms; therefore, it is not susceptible to interviewer biases or variability in assessment and ascertainment methodology. The CBCL and its clinical subscales are also independent of criteria from the Diagnostic and Statistical Manual of Mental Disorders and not limited by the same preconceptions regarding the mood and behavior associated with bipolar disorder in children.

(Continued on page 11)

Meeting Highlights

Anticonvulsants in Psychiatry Meeting
April 3–5, 2003, Elmau, Germany

Dr. H. Grunze of the Stanley Foundation Research Center at the Psychiatric University Hospital of Munich hosted a meeting on recent advances in anticonvulsants in psychiatry from April 3–5, 2003, in Elmau, Germany. Highlights of the meeting included the following presentations

Dr. M. Trimble (University College London) reviewed the anticonvulsant drugs from the perspective of their behavioral effects in epilepsy. He noted that the **drugs that increase gamma-aminobutyric acid** (GABA), such as gabapentin (Neurontin®), tiagabine (Gabitril®), and topiramate (Topamax®), all have the possible side effect of depression, suggesting that these agents may not have positive effects on mood in affectively ill patients. In contrast, lamotrigine (Lamictal®) has a much more positive antidepressant profile that even exceeds that of carbamazepine (Tegretol®), which was one of the earliest anticonvulsant drugs noted to have antidepressant effects in patients with epilepsy. Lamotrigine also exceeded the positive antidepressant profile of valproate in positive effects on mood as rated on a common mood state rating instrument.

Dr. Trimble noted that when topiramate was combined with lamotrigine there was a decrease in the number of adverse psychiatric events in patients with epilepsy compared with topiramate alone. Levetiracetam (Keppra®) also had a substantially lower rate of adverse effects than topiramate and these effects were further reduced with adjunctive lamotrigine.

- *These data further suggest the potential utility of lamotrigine in combination with other anticonvulsants in patients with inadequately responsive primary mood disorder.*

Dr. H. Emrich (Hannover Medical School, Germany) reviewed the data on the antimanic efficacy of **oxcarbazepine** (Trileptal®) based on his earlier studies and those of Muller and Stoll (1984). The response rates to oxcarbazepine were 50–80% and equal to those of haloperidol (Haldol®) and lithium in double-blind randomized studies. Oxcarbazepine has a chemical structure very similar to carbamazepine, yet oxcarbazepine is less likely to induce enzymes or have pharmacokinetic interactions, which are sometimes prominent with carbamazepine. Oxcarbazepine is therefore easier to use and has fewer side effects, with the exception of a possible substantial lowering of serum sodium levels (hyponatremia). No white blood cell count monitoring is needed for oxcarbazepine as it is for carbamazepine. As such, oxcarbazepine is increasingly being used as an alternative to carbamazepine.

- *For a more complete review of the use of oxcarbazepine in bipolar disorder, see our web site at www.bipolarnews.org.*

Dr. R. Post (NIMH; *Editor-in-Chief, BNN*) presented data from the Stanley Foundation Bipolar Network (SFBN) revealing that a high percentage of patients in the SFBN continued to have **substantial illness morbidity**, in particular a three-fold greater amount of depression than mania, despite ongoing treatment. Lithium and anticonvulsants were widely used in this patient cohort, and more drugs were used in those with rapid cycling. In the first look at the data from a levetiracetam study in 32 patients with affective disorder, the results did not show a high percentage of responders. However, the early zonisamide (Zonegran®) data show robust antimanic effects in the first week of treatment (see below).

Dr. Post noted that for the first time, within a class of psychotropic compounds, there are a range of **drugs with positive effects on weight**. Topiramate is associated with weight loss, as is zonisamide; lamotrigine is weight neutral, as is oxcarbazepine. Modest degrees of weight gain can occur on carbamazepine and gabapentin, with more prominent weight gain in patients on valproate (Depakote®, Depakene®), in parallel with weight gain on lithium (see table, p. 9).

Despite promising open trials with adjunctive topiramate, four recent, large, **controlled studies of topiramate** in acute mania indicate that it is **not an acute antimanic agent**. Nonetheless, it may have utility in assisting with weight loss. The drug may also be particularly useful in post traumatic stress disorder (Berlant 2001; *J Clin Psychiatry* 62 [Suppl. 17]: 60–63) and in **helping to decrease alcohol abuse** (Johnson et al., 2003; *Lancet* 361 [9370]: 1677–1685).

In a recent randomized study in the SFBN, topiramate and sibutramine (Meridia®, a weight-loss drug) showed parallel degrees of weight loss (Frye et al., 2003). This weight loss averaged about a third of a pound per week, very similar to the weight loss achieved by zonisamide. Whether adjunctive topiramate will emerge as more of a mood stabilizer than sibutramine (which was originally developed as an antidepressant) remains to be examined in the next round of data analysis.

Dr. C. Normann (University of Freiburg, Germany) presented data from a clinical trial in mainly unipolar patients of **lamotrigine versus placebo**. All patients received paroxetine (Paxil®) as well. Lamotrigine had a more rapid onset of antidepressant effects in unipolar depression than in those patients on placebo.

Dr. G. Goodwin (University of Oxford, UK) reviewed the literature on **treatment of bipolar depression** and emphasized the great lack of data, par-

(Continued on page 9)

Meeting Highlights: Anticonvulsants

(Continued from page 8)

ticularly in comparison to studies in unipolar depression. He noted the recent large, controlled studies of Dr. J. Calabrese and Dr. C. Bowden, which indicate that lamotrigine has better antidepressant prophylactic effects than lithium, but that lithium has better antimanic effects than lamotrigine. Dr. J. Calabrese explored these prophylactic studies in more detail, emphasizing the overall excellent tolerability of lamotrigine for prevention of depression in those who were recently manic or recently depressed.

The data of Dr. M. Frye (University of California at Los Angeles) and Dr. G. Obrocea (University of Southern California) was presented by Dr. R. Post; these data compared randomized **monotherapy with lamotrigine to gabapentin and placebo** for six weeks, with subsequent crossovers so that each patient received each of the three drug phases. Lamotrigine was superior to gabapentin and placebo for depression and overall illness. Lamotrigine improved subjective and cognitive components of depression, including guilt and pessimistic outlook for the future; lamotrigine also decreased somatic concerns, but was not significantly different from the other two phases (gabapentin or placebo) on improving sleep disturbance (lamotrigine is slightly activating). Four of seven patients who had a greater than two week exposure to the lamotrigine/gabapentin combination improved, suggesting that these two drugs with highly complementary mechanisms of action (lamotrigine is largely antiglutamatergic and gabapentin is largely pro-GABAergic) may be a clinical useful strategy. The combination was well tolerated.

Dr. K. Oedegaard (University of Bergen, Norway) noted the high rate of comorbidity between **bipolar II illness and migraine**, and suggested that depressed patients with comorbid migraine had a clinical presentation more like bipolar II than unipolar patients. Lamotrigine may also be a particularly useful anticonvulsant for those needing augmentation treatment with clozapine (Clozaril®), because it would not add to clozapine-induced weight gain like valproate would be more likely to do. In a preliminary open study, lamotrigine did not appear to be as effective in augmenting the antipsychotics risperidone (Risperdal®), olanzapine (Zyprexa®), or haloperidol treatment, as it was for clozapine.

Dr. C. Bowden (University of Texas Health Science Center) noted data showing that **valproate's efficacy** is independent of the number of prior depressions, as opposed to lithium, wherein more than three prior depressive episodes appear to render it less effective. At least ten studies suggest that patients with more prior episodes do not respond as well to lithium prophylaxis. In a randomized study in India, valproate proved superior to carbamazepine both in reduction of mania scale scores and in fewer adverse effects.

- *These data indicate another important reason for initiating lithium pharmacoprophylaxis as early as possible in the treatment of bipolar illness.*

Dr. J. Calabrese (Case Western Reserve University School of Medicine) commented that in contrast to his rapid cycling adult patients where response to the **lithium/valproate combination** is quite low (about 25%), **in childhood onset bipolar** illness this combination is highly and rapidly effective in the majority of patients (as seen by Dr. R. Findling et al.).

- *These data are of considerable importance in relation to several naturalistic studies suggesting that childhood onset bipolar illness has a poor prognosis. It may be that childhood onset bipolar illness is often inadequately treated in the community and that more aggressive, combination mood stabilizing therapy is needed and highly effective. The data also suggest that interventions early in childhood illness may yield higher responsiveness than later interventions in adulthood after many more episodes have occurred.*

(Continued on page 10)

Global Assessments of Anticonvulsants in Bipolar Illness Based on SFBN[1] Studies and the Literature

Category of Episode Efficacy	Drug	Mania	Depression	Prophylaxis	Weight Gain
Mania = Depression	ECT	+++	+++	"	0
Mania > Depression	CBZ	+++	++	+++	+
	OXC	(+++)	?	?	0
	VPA	+++	+	+++	++
	ZON	(++)	(+)	(+)	— —
Depression > Mania	LTG	"	+++	+++	0
Anti-manic? (High-potency BZs)	KLZ	+	+	+	0
	LOR				
Non-antimanic (GABAergic)	GPN	0,-	"	+	+
	TIA	0	"	"	?
	TOP	0	+	+	— —
To be determined	LEV	?	(+)	?	0

[1] Stanley Foundation Bipolar Network

Key: +++ = excellent; ++ = very good; + = good; " = equivocal; ( ) = preliminary; 0 = none; ? = unknown; — — = negative weight gain (weight loss)

Abbreviations: ECT, electroconvulsive therapy; CBZ, carbamazepine; OXC, oxcarbazepine; VPA, valproic acid; ZON, zonisamide; LTG, lamotrigine; KLZ, clonazepam; LOR, lorazepam; LEV, levetiracetam; GPN, gabapentin; TIA, tiagabine; TOP, topiramate; BZs, benzodiazepines; GABA, gamma-aminobutyric acid

Meeting Highlights: Anticonvulsants

(Continued from page 9)

Dr. T. Aamo (St. Olav's University Hospital, Norway) reviewed prominent **pharmacokinetic interactions** among the anticonvulsant drugs. He emphasized that fluvoxamine (Luvox®) was a potent *inhibitor* of most hepatic microsomal enzyme systems and thus could very substantially raise levels of drugs that are normally metabolized by the enzymes 2C9, 2C19, 1A2, and 3A4. Carbamazepine is a potent *inducer* of cytochrome 3A4 and will markedly decrease estrogen levels in oral contraceptives (as will oxcarbazepine and topiramate, necessitating the use of higher estrogen dosages). Carbamazepine will also approximately halve the blood levels of lamotrigine. In contrast, valproate markedly increases lamotrigine levels. There are new data that suggest valproate may increase lamotrigine levels by a factor of 3 or 4 to as much as 10, instead of the accepted figure of a factor of 2, thus suggesting the importance of measuring lamotrigine levels during valproate co-therapy.

"...zonisamide may emerge as an alternative weight loss agent with mood stabilizing properties in those patients unable to tolerate topiramate."

- *Using valproate with lamotrigine is also a risk factor for developing severe lamotrigine-induced rashes, and when the two drugs are given in combination, the rate of lamotrigine titrations should be slowed by at least half or more.*

Dr. E. Vieta (University of Barcelona, Spain) reviewed the literature on **combination therapy**, indicating that while it is clinically routine in bipolar illness, relatively few systematic studies guide its conduct. A number of studies have been done with atypical antipsychotic agents as adjuncts to either lithium or anticonvulsants which have demonstrated the utility of these atypicals compared with placebo. A discussion of maintenance electroconvulsive therapy (ECT) ensued with a number of meeting participants suggesting it could be maintained during anticonvulsant prophylaxis. Some patients appear to require weekly ECT, but others only once-a-month ECT to maintain efficacy.

Dr. Vieta also noted that a variety of **psychotherapeutic and cognitive behavioral techniques** have been shown in randomized controlled studies to be highly effective adjunctive treatments of bipolar illness, including early symptom recognition (Perry et al., 1999; *BMJ* 318 [7177]: 149–153); family based therapy (Miklowitz et al., 2003; *J Clin Psychiatry* 64 [2]: 182–191); cognitive behavior therapy (Scott and Tacchi, 2002; *Bipolar Disord* 4 [6]: 386–392); cognitive therapy for relapse prevention (Lam et al., 2003; *Arch Gen Psychiatry* 60 [2]: 145–152); and group psychotherapy (Colom et al., 2003; *Arch Gen Psychiatry* 60 [4]: 402–407).

G. Leverich (NIMH) presented new data on **zonisamide** from 63 patients in the SFBN. There was an 80% (24/30) response rate in acute mania, with the majority of effects coming in the first week of treatment. In contrast there was only a 33% (7/21) antidepressant response rate, with the majority of improvement occurring after week three of treatment. There was substantial weight loss on the drug, suggesting that zonisamide may emerge as an alternative weight loss agent with mood stabilizing properties in those patients unable to tolerate topiramate.

Dr. M. Carta (University of Cagliari, Italy) summarized data on **gabapentin and tiagabine** suggesting that these GABAergic drugs were not effective in monotherapy for achieving acute antimanic or mood stabilizing effects in patients with bipolar illness.

Dr. H. Grunze (Psychiatric University Hospital of Munich) reported data from a study of **levetiracetam** given as an adjunct to antipsychotic agents in bipolar patients. In an on(drug)-off-on(drug) study, levetiracetam appeared to be associated with some improvement, mild exacerbation in the "off" phase, and then renewed improvement on the drug, suggesting potentially positive, but delayed antimanic effects of this compound.

Dr. R. Belmaker (Ben Gurion University of the Negev, Israel) reviewed his new data on an older drug (**phenytoin**, Dilantin®) which is a potent blocker of sodium channels (as is carbamazepine, oxcarbazepine, lamotrigine, zonisamide, and to some extent valproate and topiramate). His preliminary acute and prophylactic studies suggest potential efficacy with occasionally robust antimanic responses in bipolar patients. ■

Meeting Highlights: ACNP

(Continued from page 4)

alone; quetiapine was well tolerated, with mostly only mild and transient side effects.

A double-blind, placebo-controlled, 3-week study of the new antipsychotic **aripiprazole** (Abilify®), conducted by Dr. S. Strakowski (University of Cincinnati) in 262 patients with acute mania showed a statistically significant improvement in mania scores and response rates with aripiprazole versus placebo.

Dr. J. Goldberg (Hillside Hospital) examined characteristics of **suicidal ideation** in the first 500 patients enrolled in the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). At study entry, 21% of the patients had suicidal ideation; current suicidal ideation was associated with a history of prior attempts and a history of alcohol abuse/dependence. The presence or absence of suicidal ideation was similar for patients who were, or were not, taking lithium, valproate, carbamazepine (Tegretol®), lamotrigine, topiramate, or antidepressants, but gabapentin use was associated with a greater presence than absence of suicidal ideation. ■

Meeting Highlights: Pediatric Bipolar Disorder

(Continued from page 2)

relapse in adults compared to other programs; related psychotherapeutic approaches will now be tested in children as well.

Conclusions

There are many highly effective psychotherapeutic treatment approaches for children with bipolar illness, and these approaches need to be added in the context of adequate psychopharmacological interventions in order to be optimally effective. The emerging psychopharmacology suggests children and adolescents with bipolar illness often require one or more mood stabilizers in order to bring their illness under control, and after mood stabilization has been achieved, sometimes the addition of small amounts of psychomotor stimulants for residual ADHD can also be helpful. However, there is a growing consensus that initial treatment with antidepressants and psychomotor stimulants for children presenting with bipolar illness can not only be ineffective, but in some cases can exacerbate illness course. Thus, children with a presumptive diagnosis of ADHD, who show a variety of signs and symptoms more consistent with bipolar illness, should be carefully reevaluated.

It should be noted that an irritability/dyscontrol factor in the symptomatology of children may be the first sign of bipolar illness (ages 3–5) prior to the development of typical manic and depressive symptoms at ages 8 or 9. Thus, children presenting with symptoms of extreme irritability, prolonged temper tantrums, and severe aggression may be among the first signs that one is not dealing with uncomplicated ADHD. Certainly, a whole variety of other symptoms should further suggest the diagnosis of bipolar illness. Each of these symptoms has a very low incidence rate in ADHD, and a moderate to high incidence rate in bipolar illness; these symptoms include: suicidal thoughts or acts; grandiose delusions; auditory or visual hallucinations; pressure of speech; homicidal threats or acts; prolonged periods of tearfulness and withdrawal; and extreme emotional lability.

In the presence of these symptoms with or without accompanying ADHD symptoms, we suggest parents keep a life chart of their children's symptoms on a daily basis in order to provide this detailed record for clinicians involved in the diagnostic process and also for clarifying the degree of treatment response to the therapeutic modalities employed. The "kiddie" NIMH-LCM forms and instructions are available in *BNN* Vol. 8, Issue 1, which is accessible from our web site (www.bipolarnews.org). ■

Research Update

(Continued from page 7)

"Children with bipolar disorder had scaled scores of >70 in the Aggression, Attention Problems, and Anxious/Depressed subscales of the Child Behavior Checklist. The Child Behavior Checklist was useful in distinguishing bipolar from attention-deficit/hyperactivity disorder subjects."

Eric Mick, Joseph Biederman, Gahan Pandina, and Stephen Faraone, Massachusetts General Hospital
"A Preliminary Meta-Analysis of the Child Behavior Checklist in Pediatric Bipolar Disorder," pp. 1021–1027

"Subjects were referred to our pediatric psychopharmacology outpatient clinic at the Hospital de Clínicas de Porto Alegre (HCPA), Brazil. We performed a retrospective chart review of all patients with a diagnosis of *[bipolar disorder]* BD under 15 years of age who were evaluated and treated in our clinic from 1998–2001. For comparison, we obtained demographic and clinical data from all children and adolescents with *[a]* diagnosis of ADHD without BD who were assessed in our clinic during the same period.

"The prevalence of juvenile BD in our sample was 7.2%... The mean...age of the BD sample was 9.6 years... We found a high rate (42%) of family history of bipolar disorder in the sample of children with BD... We found that 42% of the subjects presented only with irritability (without elated mood), 8% described only elated mood (without irritability), and 50% presented both symptoms... The most common comorbid disorder was ADHD, detected in 21 (58.3%) subjects... Children with BD had significantly higher rates of abnormally elevated CBCL scores in the externalizing dimension, anxiety and depression, delinquent behavior, and aggressive behavior scales than did ADHD subjects... In the sample of patients with BD, the rate of response (clinical improvement > 50%) was of 75%. Only 22% of these patients achieved a clinical improvement > 50% when in monotherapy with mood stabilizers or antipsychotics. Thus, most of the patients (78%) used a combination of drugs to achieve symptomatic control... Our results replicated previous findings demonstrating that juvenile BD is not a rare disorder in clinical samples."

Silza Tramontina, Marcelo Schmitz, Guilherme Polanczyk, and Luis Rohde, Federal University of Rio Grande do Sul, Brazil (ST)
"Juvenile Bipolar Disorder in Brazil: Clinical and Treatment Findings," pp. 1043–1049

"Relatively low levels of brain N-acetylaspartate *[NAA]*, as measured by magnetic resonance spectroscopy, may indicate decreased neuronal density or viability... NAA is an amino acid found in high concentrations within neurons, and not within glial cells, and therefore may serve as a marker of neuronal density or integrity... Dorsolateral prefrontal *[DLPF]* levels of N-acetylaspartate have been reported to be decreased in adults with bipolar disorder. We used proton magnetic resonance spectroscopy to investigate dorsolateral prefrontal N-acetylaspartate levels in children with familial bipolar disorder.

"Subjects were 15 children and adolescents with bipolar disorder, who each had at least one parent with bipolar disorder, and 11 healthy controls. Mean age was 12.6 years for subjects and controls. Subjects were allowed to continue current medications.

"Bipolar subjects had lower N-acetylaspartate/Creatine ratios only in the right dorsolateral prefrontal cortex... An overall regional decrease in NAA/Cr may indicate lower neuronal density or viability and therefore dysfunction in the DLPF. The DLPF has been suggested to have a role in mediation of affect and has been implicated to have a role in the pathophysiology of mood disorders in general and BD specifically."

Kiki Chang, Nancy Adleman, Kimberly Dienes, Naama Barnea-Goraly, Allan Reiss, and Terence Ketter, Stanford University School of Medicine
"Decreased N-Acetylaspartate in Children with Familial Bipolar Disorder," pp. 1059–1065

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