

Bipolar Network News

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Meeting Highlights from the American College of Neuropsychopharmacology: Boca Raton, Florida, December 2007

A meeting of the American College of Neuropsychopharmacology (ACNP) was held in Boca Raton, Florida in December 2007. Researchers presented a number of new psychopharmacological developments pertinent to the clinical therapeutics of bipolar disorder.

Considerable new data were presented for two of the atypical antipsychotics quetiapine (Seroquel) and aripiprazole (Abilify).

Quetiapine (Seroquel)

Quetiapine is approved for the treatment of mania and depression, and multiple recent positive clinical trials indicate that it is also positive in the prevention of both manic and depressive episodes. In a two-year study by Suppes et al (2007), quetiapine and placebo were compared as adjunctive treatments added to either lithium or valproate. Quetiapine at dosages of both 400 mg and 800 mg was markedly effective in preventing both manic and depressive episodes. Those treated with quetiapine in addition to a mood stabilizer relapsed at a rate of 20.3% compared with 50.1% relapse in those treated with adjunctive placebo during the 2-year period. If quetiapine is approved for this use, it will be the first time that a single agent will be FDA-sanctioned for both acute treatment and prevention of manic and depressive episodes.

Melissa DeBello also presented a study in which 400 and 600 mg of quetiapine was more effective than placebo in childhood and adolescent-onset mania in youngsters aged 10 through 17. Response rates were 64% and 58%, respectively, for quetiapine doses, and 37% for placebo.

Several studies were all positive for quetiapine monotherapy in unipolar depression. In addition, there was a positive study of quetiapine

in generalized anxiety disorder, with 150 mg and 300 mg/day both yielding better results than placebo. These data, taken along with studies on the monotherapy of bipolar depression, in which prominent antianxiety and pro sleep effects were observed with 300 mg and 600 mg compared to placebo, suggest that quetiapine has notable effects in anxiety symptomatology across several different diagnoses, from unipolar and bipolar depression to generalized anxiety disorder.

Mechanisms of Action and Dosing

As described in a previous BNN, there are new data that an active metabolite of quetiapine is potent in blocking norepinephrine reuptake, similar to that of many more classical antidepressants, and is also a partial agonist of serotonin 5HT1A receptors, which are thought to be important for antidepressant and antianxiety effects. A partial agonist has a limited ability to activate a receptor, as opposed to a full agonist, which stimulates a receptor fully. In addition, the metabolite is a blocker of 5HT2C receptors, which results in increased dopamine and norepinephrine release in the forebrain. These effects compound the better-known effects of quetiapine as a weak blocker of dopamine receptors (of insufficient potency to increase prolactin) and as a blocker of 5HT2B receptors, which are associated with antidepressant effects and increases in deeper phases of slow wave sleep.

Quetiapine, which is administered only at night, can be highly sedating for some patients even the next morning. Some authorities, such as Joe Calabrese at Case-Western Reserve, have suggested beginning treatment with a test dose of 25 mg at night on a Friday or Saturday when an individual can stay home if he or she is too sedated

in the morning. While it is unusual for a patient to experience such strong sedation, it is probably worth taking this extra precaution. Many individuals are able to rapidly escalate the dose to 200-300 mg at night with minimal side effects. However, sedation and drowsiness are among the most frequent recorded side effects at these doses.

Aripiprazole (Abilify)

New data were presented on the efficacy of aripiprazole, both as a treatment for acute bipolar-I mania in youngsters ages 10 to 17 and as an adjunctive treatment for unipolar depression in adults.

The acute antimanic effects of aripiprazole on young patients were notable at both 10 and 30 mg/day, and the effects were sustained over the extended term of the trial. These data are consistent with findings in adults that aripiprazole is effective both in treating acute mania and in relapse prevention in those who were recently manic. When treating children (as well as most adults), it may be advisable to start out at very low doses of aripiprazole (2.5 mg/day) in order to avoid activating side effects such as akathisia (restless legs) and in children, nausea and more rarely, vomiting. All of these are much less likely to occur with initiation at lower doses.

Aripiprazole has just been FDA-approved for adjunctive treatment of unipolar depression in patients who have not responded adequately to a serotonin-selective antidepressant. The addition of aripiprazole was much more effective than placebo in helping patients achieve a good response or a clinical remission. These data are particularly important because aripiprazole

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College of Neuropsychopharmacology Meeting Highlights (cont.)

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(along with ziprasidone) is among the least sedating of the atypical antipsychotics (compared to others such as quetiapine and olanzapine, which can be sedating even when given at night), and thus provides an alternative for patients with reverse vegetative symptoms – that is, increased sleep and appetite and psychomotor slowing instead of the more classical picture of an agitated, insomniac, anorectic presentation of unipolar depression.

N-Acetylcysteine In Depression And Substance Abuse Prevention

The BNN has previously reported the remarkable findings of Mike Berk and colleagues from Sydney, Australia, that augmenting treatment as usual with N-acetylcysteine is more effective than placebo in long-term prophylaxis of bipolar patients. Results showed a particularly good effect on residual bipolar depression.

New findings show that N-acetylcysteine also appears effective in decreasing use of and craving for cocaine, heroin, and gambling in patients with these addictions.

The use of N-acetyl cysteine for cocaine avoidance emanated from preclinical laboratory

data by Peter Kalivas of South Carolina. He found that cocaine sensitization and proneness to relapse following a cocaine cue, a stressor, or a small cocaine challenge in rodents was associated with marked increases in glutamate release in the nucleus accumbens, the reward center of the brain associated with dopamine. N-acetylcysteine is effective because it affects the cysteine-glutamate exchanger, down-regulating the hypersensitive glutamate responsivity. This is associated with a decreased risk of relapse. This study is one of the best current examples of how laboratory work with animals can lead to new treatments for patients with a variety of neuropsychiatric conditions.

It is also noteworthy that N-acetylcysteine is a precursor to glutathione, which is one of the brain's main antioxidants. There is considerable evidence that every episode of bipolar illness, whether depression or mania, is associated with oxidative stress that produces free radicals and other toxins that inhibit normal cell function and can even cause cell death. Thus, it is possible that N-acetylcysteine also provides an antioxidant mechanism, which could contribute to its therapeutic effects.

The possible antioxidant role of N-acetylcysteine coincides with increasing evidence that inflammatory processes, particularly increased secretion of inflammatory cytokines, play a role in bipolar illness. One of the new findings presented in a poster session indicated that childhood-onset bipolar illness was associated with significant increases in inflammatory markers. Anti-inflammatory and antioxidant strategies may ultimately emerge as important approaches to the therapeutics of this early onset disorder.

New Conceptual Advance: DNA Itself Can Be Regulated

What is a new part of this story is that not only can environmental factors lead to changes in the gene expression for neurotrophic factors such as BDNF, but environmental stressors productive of depressive-like behaviors in animals are also associated with changes in the microstructure of DNA and histones around which the DNA is wrapped. BDNF is a neuro-protective peptide that is produced and secreted by cells. Its synthesis depends on whether DNA is read and transcribed to RNA, which enters the cytoplasm where the proteins are produced in the endoplasmic reticulum. How easily the DNA is read and transcribed is regulated by how tightly the DNA is wound around histones. Methylation makes DNA harder to transcribe, but when histones have an added acetyl group, DNA is more unraveled and open,

such that the gene sequences in the DNA can be easily turned on or transcribed. This provides a mechanism that explains the observations that early exposure to either maternal separation stress or defeat stress can change an animal's behavioral and biochemical reactivity for the rest of its life. The DNA sequences that encode specific genes are inherited genetically, and are invariant. However, the degree of DNA methylation based on early life experience can inhibit specific genes from being transcribed for the entire life of the animal.

While this appears to have particularly negative implications for therapeutics, evidence is emerging that treatment with histone d-acetylase inhibitors, which keep the DNA in a more open structure, can reverse some of the changes in DNA expression that would otherwise occur throughout an animal's life. There are 10 different subtypes of histone d-acetylase inhibitors, and both valproate and carbamazepine function as histone d-acetylase inhibitors. It remains to be seen how this aspect of these two drugs might be used to reverse long-term changes in DNA expression by modifying the openness of its structure.

These findings may be pertinent to the study of levels of neurogenesis and changes in BDNF, both of which can have a lifelong low set point in animals based on adverse early life experiences. Treatment with a histone d-acetylase inhibitor could induce more normal levels of BDNF and neurogenesis in the brain. Thus, environmentally induced vulnerability factors (low hippocampal BDNF and neurogenesis) leading to cognitive deficits and the onset of unipolar or bipolar depression could potentially be ameliorated with the appropriate therapeutic intervention aimed at histones and at DNA itself.

OTHER POTENTIAL THERAPEUTIC FINDINGS **Mementine**

A poster by Anand reported that the anti-Alzheimer's drug mementine (Nemenda), which in itself is not an antidepressant, augmented the antidepressant effects of lamotrigine when used in starting doses of 5 mg/day and increased weekly to 20 mg/day. However, this effect only occurred at the trend ($p < .10$) level and remains to be further systematically evaluated.

Left Plus Right rTMS

There was another positive study of repeated Transcranial Magnetic Stimulation (rTMS) when it was used bilaterally as a treatment

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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 summary or pre-publication 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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for unipolar depression compared with either unilateral or sham treatment. Bilateral treatment involved 10 Hz stimulation at 100% of motor threshold (MT) over the left prefrontal cortex and 1 Hz rTMS over the right cortex, and was associated with a 50.2% response rate, as opposed to left unilateral rTMS which produced a 27.9% response rate, and sham rTMS which produced 20.6% effect. Repeated TMS is not yet generally available in the community, although the FDA is considering such approval based on a large study by Riordon et al (2007) indicating that 10 Hz rTMS over the left prefrontal cortex at 120% of MT was more effective than sham treatment both acutely and in continuation. These studies have implications for bipolar depression as well.

Prazosin in PTSD

Raskin presented a poster indicating that 9 mg/day of alpha-1 noradrenergic antagonist prazosin, which is used for high blood pressure, was more effective than placebo in reducing the nightmares and sleep disturbance of patients in the general population with posttraumatic stress disorder. This was a replication of previous data from studies of military personnel that had suggested prazosin as a new intervention for those with residual sleep disturbances and nightmares.

Editor's note: PTSD is commonly treated with serotonin-selective antidepressants. There is only a small amount of data indicating that adjunctive anticonvulsants and atypical antipsychotics are helpful, but this editor would endorse those treatments in addition to serotonin-selective antidepressants in those without comorbid bipolar disorder, and anticonvulsants and atypical antipsychotics alone (in preference to serotonin-selectives) in bipolar patients with comorbid PTSD. If, after these treatments, nightmares and sleep disturbance remain, one might wish to consider the preliminary and off-label use of prazosin for this area of dysfunction.

Topiramate

Berlin and colleagues presented a poster with a new finding of therapeutic note for patients with obsessive-compulsive disorder. Topiramate compared with placebo was more effective as an adjunctive treatment added to SSRIs for the compulsive aspects of the syndrome in particular. This extends the potential range of topiramate for use in a variety of comorbidities that often accompany bipolar illness. While topiramate itself has no acute antimanic properties in monotherapy, evidence suggests that it may help with cocaine and alcohol abstinence, PTSD, weight loss and

bulimia, and now obsessive-compulsive disorder as well.

Editors Note: Several of the atypical antipsychotics, in particular quetiapine, have also been reported to enhance the effects of SSRIs more than placebo in those with primary obsessive-compulsive disorder. These are potentially important therapeutic approaches as well.

Lamotrigine Plus Quetiapine

Ketter reported critically important open data based on naturalistic treatment of bipolar patients. In those who remained symptomatic on quetiapine or lamotrigine in concert with 1.3 to 1.7 other medications, the addition of either quetiapine or lamotrigine to the other drug (with the other adjunctive agents left alone) was associated with the remission of symptoms in two-thirds of patients. While these data are open, they nonetheless suggest that these two drugs, which are widely used in combination clinically, may have a particularly important role to play in those with residual depression despite treatment with either agent alone and a variety of other substances.

Rapid Onset Antidepressant Effects: Ketamine And Sleep Deprivation

A series of papers indicated new approaches to the glutamate system with potential implications for the treatment of depression. There are now four different studies indicating that a sub-anesthetic dose of the dissociative anesthetic ketamine (0.5 mg/kg i.v. administered over a 40 min. period) is associated with a very rapid onset of antidepressant effects in even highly treatment-resistant depressed patients. The onset is notable in that it is evident some several hours after acute infusion, and in many patients, lasts 3-5 days or longer.

The preliminary data from Charney and colleagues at Mt. Sinai indicated that several patients who were given three additional intermittent ketamine infusions showed a more sustained duration of clinical improvement.

Several groups are attempting to follow the acute onset of antidepressant effects of ketamine in those with treatment-resistant depression with another agent that would sustain the response long-term, such as another glutamate-active drug called riluzole. Riluzole has been reported to be an effective antidepressant compared with placebo in patients with both unipolar and bipolar depression, although this drug is highly experimental and FDA-approved only for use in amyotrophic lateral sclerosis (Lou Gherig's disease).

W.E. Bunney presented data that sleep deprivation induced an acute overnight onset of

antidepressant effects in about 50% of severely depressed individuals. However, one night of sleep deprivation can be associated with a relapse following the next night's sleep. Bunney presented preliminary data that the sleep deprivation procedure could be associated with a sustained antidepressant effect in those responders who were given phase advance treatment and high intensity light with 7,500 Lux intensity. Phase advance treatment involves going to bed at 6 PM and waking up at 2 AM on the recovery sleep night, then proceeding to go to bed the next day at 8 PM and wake at 4 AM, then go to bed at 10 PM and wake at 6 AM the next day, then finally arriving at a normal sleep onset and offset. This procedure has been widely used in Europe to sustain the response to sleep deprivation, and this maneuver in the context of high intensity light appears helpful in sustaining the acute onset of antidepressant response achieved literally overnight with one night's sleep deprivation,

The sleep deprivation data taken in concert with the ketamine data indicate that the rapid onset of antidepressant effects within a day or less is now clinically and theoretically a feasible proposition, and that the old view that two to six weeks of treatment (with traditional antidepressant modalities) were required in order to achieve maximum therapeutic efficacy has now been invalidated. These data are also supported by evidence for relatively rapid onset of antidepressant effects in a few individuals who received deep brain stimulation. Helen Mayberg has stimulated Brodmann area 25 in patients' anterior cingulate cortex, and others in Europe have stimulated the nucleus accumbens. Rapid onset antidepressant effects have also been observed in some patients administered thyrotropin releasing hormone (TRH) via their spinal fluid. Together, these reports indicate that rapid onset antidepressant effects are possible via a variety of pharmacological and physiological procedures, even though most of our currently clinically available antidepressant modalities take much longer to work.

Editors Note: The field will now struggle with how to achieve and sustain these acute effects and the challenge of identifying who will be rapidly responsive. Given the highly ambiguous role of traditional antidepressants in bipolar compared to unipolar depression, one can also hope that some of the rapid onset modalities will be more clinically useful in bipolar depression than the older agents.

Clinical Neuroscience Update: Brain-Derived Neurotrophic Factor (BDNF) And Its Role In Bipolar Illness Vulnerability, Onset, Progression, and Treatment

BDNF Functioning And Common Variations

BDNF is a brain substance secreted by cells that aids in synapse formation and the growth and survival of neurons, and is necessary for long-term learning and memory.

It is a long, complicated molecule with common variations that affect the efficiency of its functioning. The replacement of a single amino acid is called a single nucleotide polymorphism (SNP), and is a genetic variation that is very common in the general population, as opposed to a gene mutation, which is rare, occurring in about one in a million individuals.

At the 66th position in its string of amino acids, there are usually two valines, yielding a highly efficient form of BDNF called val-66-val BDNF. However, in a substantial proportion of normal individuals, there is a methionine substitution for one of the valines, resulting in a val-66-met structure. People with this common val-66-met variation, who include normal volunteers in the general population and those with bipolar disorder or schizophrenia, exhibit minor deficiencies in some cortically based neuropsychological tasks that depend on working memory. A very small percentage of the population has a third variant, met-66-met BDNF, which functions least well.

Surprisingly, it is the best functioning variant (val-66-val BDNF) that is associated with the occurrence of bipolar illness or its early onset or rapid cycling features, according to more than 5 studies. Why this might be so is unknown, but could relate to the increased associativity (or loose associations) seen clinically in bipolar patients and the increased functional connectivity seen on their PET scans compared to controls. This could, in turn, relate to the findings of increased creativity in many individuals with bipolar disorder.

The Effect Of Environmental Stress On BDNF

In addition to common genetic variations, adverse environmental stressors can alter BDNF levels in the brain in a lasting way. Studies of rodents showed that repeated neonatal exposure to stressors decreased BDNF in the hippocampus and frontal cortex into adulthood. Repeated stress in adults also decreases BDNF in the hippocampus. Berton and colleagues (2006) found that repeated defeat stress (when an intruder rodent is attacked and defeated by the home cage resident)

also results in BDNF decreases and despair behaviors. If animals are given antidepressants or other treatments that prevent decreases in BDNF, defeat stress behaviors do not develop.

There have been interesting clinical parallels in humans. A research group in Brazil led by Kapczinski found that bipolar patients who experienced early life adversity have significantly lower levels of serum BDNF (or BDNF in their blood) than those who did not experience adversity.

They and others have also found that each episode of either depression or mania is associated with decreases in blood BDNF levels, which then return to normal after treatment and resolution of the affective episode. The degree of decrease in serum BDNF is proportional to the severity of the depressive or manic episode.

These data, replicated by several other laboratories in studies of unipolar depression, suggest that each affective episode may be associated with decrements in BDNF that could endanger the health and survival of neurons in the brain. This is all the more likely because Kapczinski and colleagues also observed that each episode of affective illness is associated with increases in oxidative stress (the release of toxic free radicals), which can further damage cells. Thus, there appears to be a dual mechanism for increased cellular vulnerability during affective episodes, i.e.

loss of neuroprotective factors and a simultaneous increase in destructive factors.

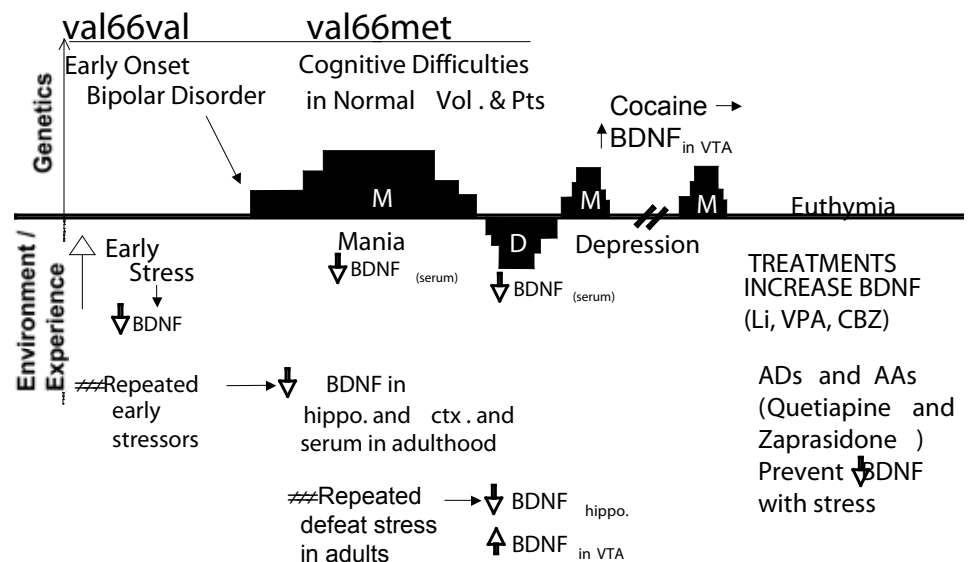
Taken together, these findings provide a plausible set of mechanisms to explain previous findings regarding stress and episode sensitization. This editor had postulated from the kindling model and the psychomotor stimulant-induced sensitization model that repeated stressors are associated with increased stress reactivity, and increased numbers of prior episodes convey greater vulnerability to episode recurrence, a phenomenon called episode sensitization. The literature on the course of affective illness is now generally supportive that this progression of episode sensitization occurs in those with untreated or inadequately treated affective disorders.

Brain Dysfunction And Episode Sensitization

Previous BNNs have outlined data indicating that in bipolar illness, the frontal cortex has deficits in its anatomy, biochemistry, physiology, and function, and even in number of brain cells (neurons and glia). At the same time, there is evidence for increased reactivity of the deeper emotional parts of the brain such as the limbic system and one of its key structures, the amygdala.

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BDNF is Involved in Onset, Course, and Treatment of Bipolar Disorder



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A number of these brain abnormalities in affectively ill patients are correlated with the number of prior episodes or the duration of illness. It now seems possible that episodes could adversely affect the brain, rather than the opposite hypothesis that preexisting brain alterations lead to a more severe course of illness.

The new findings that BDNF levels decrease and oxidative stress increases with every episode are clinically important because they provide one potential mechanism for how episodes could cause further brain dysfunction and vulnerability to episode recurrence, thus emphasizing the importance of early, long-term, effective preventive treatment. Each new episode could lead to further damage and dysfunction, with potential for a patient to accumulate vulnerability to episode

recurrence as a function of number of prior episodes. While there is not direct evidence that episodes are associated with increased amounts of brain damage and dysfunction, it is highly likely that this is the case. This mechanism would explain findings that increased numbers of depressions are associated with increased levels of psychosocial impairment, cognitive dysfunction, and incidence of dementia in late life.

Implications For Treatment

This new model may provide a new view of the potential role of many therapeutic drugs. Three of the mood stabilizers – lithium, carbamazepine, and valproate – all increase brain BDNF, and all antidepressants seem to as well. These findings are schematized in Figure 1 on page 4. Thus, if bipolar patients are adequately treated with appropriate mood stabilization and unipolar

depressed patients are adequately treated with long-term prophylactic antidepressants, it is highly likely that patients will reap dual benefits for themselves (experiencing fewer episodes) and their brains.

With good prophylactic treatment, not only will episodes be prevented, but BDNF and related neuroprotective and cell survival factors will also be fostered in two different ways. These treatments directly increase BDNF, and they can also prevent stress-induced and episode-induced reductions in BDNF.

New View of the Risk/Benefit Analysis Of Long-term Treatment of Bipolar Disorder Based on BDNF Findings

Given the new information about the role of BDNF in bipolar disorder and possible mechanisms of stress and episode sensitization, a new conceptualization of the risk/benefit ratio for long-term preventive treatment of recurrent unipolar and bipolar illness is needed.

It is clear to anyone with the slightest knowledge of bipolar disorder that its effects on patients' family, social and vocational lives are great. There is also considerable evidence reviewed elsewhere that an individual suffering from unipolar or bipolar depression is at about double the risk of suffering a heart attack or stroke compared with someone who is not depressed. Thus, there is a distinct increase in medical mortality that comes with the experience of untreated depression. The "BDNF" update above outlines the mechanisms by which episodes may also hurt patients' brains and leave them more vulnerable to future episodes.

Where previous schemas weighed only the potential good of preventing episodes against the potential adverse effects of the drugs, now one should consider that preventing episodes can have positive effects for the individuals' social and vocational functioning, their medical health, and their brain functioning as well.

While there are minor to moderate long-term risks of treatment with mood stabilizers (for bipolar illness) and antidepressants (for unipolar depression), these agents may, in fact, repair some

of the deficits associated with the illnesses or, at least, prevent their progression. There is, in fact, direct evidence of these potential helpful effects of drugs in patients with bipolar and unipolar illness. In bipolar patients, lithium has been shown to increase markers of neuronal integrity and to increase the volume of gray matter in the cerebral cortex in patients, but not in normal volunteers. In a parallel fashion, Annette Sheline from St. Louis has shown that patients with recurrent unipolar depression who remain on antidepressants more of the time do not have the decreases in hippocampal volume seen on MRIs of those whose depression was treated less often with antidepressants.

Taken together, all of these data suggest useful comparisons to the treatment of diabetes mellitus. The fatality rate from diabetes has decreased dramatically with the advent of insulin and related treatments. Patients with diabetes used to suffer premature deterioration of a variety of organ systems, yielding early onset of renal failure, congestive heart failure, and blindness. The dramatic shift in the treatment approach to diabetes over the past 20 years, with much more careful monitoring and control over patients' blood sugar, has yielded extraordinarily positive effects on long-term outcome, well being, and life expectancy.

We would make the parallel case that careful daily monitoring of mood, sleep, side effects, and comorbidities such as anxiety will

similarly facilitate more precise control over the mood and behavioral dysfunction associated with bipolar disorder. Multiple studies suggest that the minor emergence of depressed or manic symptoms are often the precursors to more major episodes; thus these minor fluctuations deserve careful treatment. The goal of treatment should be to achieve and maintain remission.

Pharmacotherapy typically also needs to be bolstered by focused psychotherapy and psycho-educational techniques with patients and family members who play critical roles in illness monitoring and medicating.

For too many patients with bipolar disorder, this is not a benign illness. However, with great care and attention, the effects of this illness, like that of diabetes mellitus, can be minimized so that one can lead a relatively normal and healthy life.

Instituting these new concerted therapeutic approaches will require a personal, scientific, and public health paradigm shift to see the adverse and progressive clinical and neurobiological consequences of affective episodes and act accordingly. Episodes are not benign or trivial, and may endanger one's well-being, functioning, and life itself either by suicide or the associated medical mortality. It is now also clear that episodes may subtly damage the brain, and therefore require the utmost care and treatment to prevent this possibility.

Clinical Research Highlights from the Australian Society for Bipolar Disorders Conference, September 2007

This conference in Sydney, Australia featured four plenary sessions with individual invited speakers including David Miklowitz, BNN Editor Robert M. Post, Mauricio Tohen, and Lakshmi Yatham.

Miklowitz: Family Focused Treatment for Bipolar Disorder

David Miklowitz presented a talk on Family Focused Treatment (FFT) for bipolar disorder in adults and youths. In 21 sessions of FFT over a period of nine months, three treatment components are emphasized. The first is psycho-education, which highlights signs, symptoms, etiology, treatment, and self-management of the disorder, and includes a relapse prevention drill. The second component is skills training for handling conflict in the family and increasing communication abilities. The third component is problem-solving skills training.

Two randomized studies have shown that combining family focused treatment with pharmacotherapy delays episode recurrences and reduces symptom severity over a two year period when compared with either a brief psycho-education program or even a comparably intensive individual psychotherapy program (plus pharmacotherapy).

A trial was recently completed in teens ages 13 to 17. In this trial, family-focused treatment and pharmacotherapy were associated with greater stabilization of depressive symptoms and less time in depressed states compared with treatment as usual. These promising data have led Miklowitz and associates to attempt a trial investigating secondary prevention, which would target those who are at high risk for bipolar disorder by virtue of having a parent with the illness and are beginning to show early signs of mood dysregulation.

Post: Role of BDNF in Bipolar Disorder

Robert M. Post presented another of the plenary sessions, emphasizing the new data that brain-derived neurotrophic factor (BDNF) is involved in vulnerability, onset, progression, and treatment of bipolar disorder (See Fig. 1). As reported in this and previous BNNs, these neurobiological data support clinical findings suggesting that early, effective, and sustained long-term preventive approaches to the illness are important in preventing many of the mechanisms of illness progression related to episodes, stressors, and substances of abuse.

Post stressed that lithium, carbamazepine, valproate, atypical antipsychotics and all antidepressants increase BDNF or prevent its decrement by stressors. Thus, in addition to preventing episodes, these treatments may help protect the brain, potentially either ameliorating previous neurobiological defects or preventing their progression.

Tohen: First mania recovery rates

In a third plenary session, Mauricio Tohen of Lilly presented data on 173 individuals hospitalized with a first episode of mania. While almost everyone achieved symptomatic and syndromal recovery, both reducing symptoms and reaching a point of not meeting criteria for an episode, only 35% achieved functional recovery after a follow up period of at least two years.

Predictors of relapse or recurrence of depression were the presence of psychotic features initially, a mixed episode, comorbidity with alcohol or substance abuse, and, paradoxically, previous high vocational status.

Yatham: Dopaminergic Hyperactivity and Mitochondrial Dysfunction in Mania

Lakshmi Yatham presented data from PET (positron emission tomography) brain imaging studies indicating evidence of dopaminergic hyperactivity and mitochondrial dysfunction in mania.

The dopamine excesses could lead to increased free radical production and oxidative stress that could further endanger mitochondrial function. Mitochondria are the chief energy factory within neurons and glial cells.

Yatham also presented information from studies of long-term prophylaxis and suggested such treatment should begin after the first episode of bipolar illness.

In addition to the plenary sessions, there were several oral presentations of particular interest, by Kapczinski, Berk, and Hallam.

Kapczinski: Pathophysiology Of Cognitive Impairment in Bipolar Illness

Investigators from Flavio Kapczinski's group presented information on the pathophysiology of cognitive impairment in bipolar disorders. Many studies have indicated that even euthymic bipolar patients experience ongoing mild cognitive impairments, and these correlate with number of prior episodes. New work from this laboratory

indicated that oxidative stress is increased in both manic and depressive episodes and not in the euthymic interval. This group had previously observed decreases in BDNF with each episode and recently found increases in glial cell line-derived neurotrophic factor (GDNF) and in neurotrophin-3 (NT3). Increases in GDNF and NT3 may be compensating for the decreases in BDNF.

In addition to increases in oxidative stress, a ten-fold increase in DNA damage has been found in bipolar depressed patients compared with controls. Since DNA damage and oxidative stress can lead to cell dysfunction and even programmed cell death, these findings (in the context of the episode-related decrements in protective factors such as BDNF) could contribute to the brain abnormalities found in bipolar disorder and contribute to cognitive impairment.

Berk: N-Acetylcysteine As Adjunctive Therapy

Michael Berk reported that the glutathione precursor n-acetylcysteine may be an effective addition to treatment as usual. In a double blind, randomized, placebo-controlled trial, patients received either 2 gm. of N-acetylcysteine per day or placebo as adjunct to treatment as usual. N-acetylcysteine, compared with placebo, was associated with decrements in severity of depression and increases in quality of life and functioning at the study endpoint. These findings were associated with moderate to large effect sizes. This trial is exciting because this new compound with few side effects led to substantial degrees of improvement, particularly in depression. The findings suggest that pathways of oxidative stress should be a target of therapeutics in bipolar disorder.

Editor's note: N-acetylcysteine has also been conceptualized by Peter Kalivas as acting at the glutamate-cysteine exchange mechanism in the motivations and reward area of the brain, the n. accumbens, and thus moderating glutamatergic excesses that occur with sensitization.

In line with these observations are other recent reports that N-acetylcysteine was found to be significantly more active than placebo in reducing cocaine and heroin consumption in two small studies, and pathological gambling in another.

It is not clear whether this anti-glutamatergic effect or the enhancement of glutathione and prevention of oxidative stress is the mechanism

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Research Forum of the American Academy of Child and Adolescent Psychiatry (AACAP): Protective and Risk Factors in Pediatric Bipolar Disorder

Robert Findling of Case-Western Reserve University, Gabriele Carlson of Stony Brook, and BNN editor Robert M. Post of the Bipolar Collaborative Network organized a one-day symposium prior to the beginning of the formal meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) in San Diego in October 2006. The goal of the Research Forum on Protective and Risk Factors in Pediatric Bipolar disorder was to help jump start the field of pediatric bipolar disorder and begin to better define optimal treatment strategies for those with childhood onset bipolar disorder and children at high risk.

The meeting began with a series of formal presentations in the plenary session and then five breakout groups to develop recommendations and consensus about the best ways of approaching each area. The breakout group topics included: 1) the prodrome, or early manifestations of the illness, 2) psychopharmacology, 3) brain imaging, 4) psychosocial treatments, and 5) genetics. A formal publication of the results and recommendations of this meeting will likely be published in the Journal of the American Academy of Child and Adolescent Psychiatry this year.

The plenary meeting began with a discussion of "risk and protective factors in the outcomes of depressed children" by Constance Hammen, Ph.D. She described the model presented by Goodman and Gottleib in 1999 for the risk of psychopathology in children of depressed mothers, which involves multiple and interacting risk factors, mechanisms, and vulnerabilities. Predictors of depression in high-risk offspring samples include: family history of depression, distal (past) or proximal (recent) stressful life events, family discord, cognitive and interpersonal dysfunction, and biological abnormalities. One mechanism highlighted in the recent reports of Weissman and colleagues (2006) is that behavioral

disorders in children of depressed mothers vary as a function of the completeness of treatment of the mother's depression. Offspring of mothers who were treated to remission had significantly fewer behavioral problems than offspring of mothers whose depression was only partially treated.

Editor's Note: A substantial collection of literature in unipolar depression now supports the utility of early intervention in children at high risk, with appropriate treatment of their symptomatology and that of their parents. A recent review states that the data show clearly that adolescent depression of either minor or major magnitude is continuous with and predicts depression in adulthood. The case is less clear with depression in pre-pubertal children, which may lead to a more diverse set of outcomes. There is evidence that one-third of these individuals will ultimately present with bipolar disorder. Retrospective data from the STAR-D, the practical clinical trial

network for depression, and other adult outpatient cohorts indicate that those depressed patients with the earliest onsets of symptomatology in childhood have the most adverse outcomes in adulthood. These data also speak to the importance of early effective intervention in hopes of changing this more difficult prognosis into a more benign one.

Steven P. Hinshaw next presented on risk and protective factors regarding the outcome of children with "externalizing disorders." His focus was on ADHD, oppositional defiant disorder and antisocial personality, and he suggested that many of the lessons learned from research in these children are readily applicable to those with bipolar patients. He made the point that bipolar disorder is an amalgamation of both externalizing and internalizing features and that this is also the case for

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Australian Society for Bipolar Disorders (cont.)

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of the therapeutic effects in bipolar illness and these compulsive syndromes, but in either instance the drug provides a potential new approach to clinical therapeutics.

Also supporting the utility of N-acetylcysteine in long-term treatment of bipolar illness are observations by Berk and associates that there are positive effects in schizophrenia, particularly on the negative symptoms of the illness (which heretofore had proven particularly resistant to treatment with more traditional antipsychotic agents).

Hallam: Melatonin And Light Sensitivity

Hallam and colleagues reported that bipolar patients exhibit more sensitivity to suppression of nighttime melatonin secretion with bright

light compared with normal volunteer controls. Melatonin secretion and light sensitivity are highly heritable (more closely related in monozygotic compared with dizygotic twins or other relatives). Altered sensitivity to melatonin's suppression by light could reflect an increased vulnerability to circadian rhythm dysregulation that could, in turn, induce mood dysregulation.

Editor's note: Others have suggested that treating depression with a melatonin agonist (a chemical that stimulates melatonin receptors) that also increases norepinephrine (NE) and dopamine (DA) in the forebrain, such as the antidepressant agomelatine, would produce good effects in both unipolar and bipolar depression. Hopefully this drug will be FDA approved in the near future.

Editor's Note: Information in the BNN

Here, as also noted in our masthead, we emphasize the fact that what is reported in the BNN consists of early versions of data based on abstracts and presentations at meetings, and must be taken as only highly preliminary. Patients should not proceed with treatment based on such data until effects are further clarified and validated in the literature, leading to ultimate FDA approval, and/or after thorough discussion with their own prescribing physician who takes responsibility for independent assessment of the risks and benefits of such a maneuver. The highly preliminary reporting of findings in this newsletter is a public service to patients and clinicians wishing to hear about some of the preliminary advances and findings in the field, but the accuracy and facts of the presentations cannot be validated because most have not yet been reviewed or published, and the statements and conclusions in the BNN need to be assessed independently by a treating physician. The editors of the BNN cannot be held responsible for errors of commission or omission, or for reporting early news of others' highly preliminary data. Treatment decisions cannot be based solely on the information provided in the BNN, which may be incomplete or even in rare instances erroneous.

Protective and Risk Factors in Pediatric Bipolar Disorder (cont.)

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ADHD, with hyperactivity on the one hand and an inattention component on the other perhaps reflecting internalizing problems.

Editors Note: The following review of his presentation is fairly technical, and particularly useful for investigators and clinicians designing clinical trials. Thus, many of our readers may want to skip this summary, but reading the "Political Action Commentary" on the following page is highly recommended for all.

Hinshaw noted important aspects of research terminology, where "risk factors" are those that precede and predict the outcome of interest, and that one should be particularly interested in risk factors that are malleable and treatable as opposed to those that might be fixed, such as one's genetic inheritance.

Hinshaw enumerated the many risk factors for childhood externalizing and conduct problems, as summarized in Hinshaw and Lee (2003). These included: perinatal risk factors, low IQ, lead toxicity, and later adolescent substance abuse. Family and parenting factors, and particularly parental psychopathology, were important, but also worth noting were the findings that maternal smoking predicted later ADHD and ODD independent of genetics. Coercive and inconsistent parenting discipline styles also were important risk factors along with young age of the parent or single parent. Neighborhood and peer factors as well as schooling factors were important. For example, if a child was old for their school grade, this increased the risk of antisocial personality disorder.

The take-home message is that the effects of the number of risk factors are cumulative and markedly increase risk. If one had more than three or four risk factors, the chances of externalizing and conduct problems occurring in the child were compounded. Thus, combinations and interactions of risk factors were critical predictors.

Hinshaw recommended that clinical trials focus on establishing factors that may modify the course of illness in those at high risk. In this regard, terminology was again important. He noted that moderator variables were those that were there at the baseline before a given clinical trial was undertaken, as opposed to mediators of outcome, which were variables that interacted with response to a specific treatment employed in the trial. If such mediators were found in an initial treatment trial, then the next clinical trial could then randomize patients based on this mediator

variable in order to attempt to assess and delineate causal mechanisms.

Hinshaw et al. presented data from a study of 579 youths with externalizing disorders who were randomized to one of four different treatments: (1) pharmacological (medication) management, (2) intensive behavioral treatment, (3) the combination of both 1 and 2, and (4) a community care comparison group receiving treatment as usual, including some medication. The researchers found that over a period of 14 months, combined treatment was superior to community care on most measures, including ADHD symptoms, oppositional aggressive behavior, anxiety, social skills, academic performance, and parent-child relationships. Medications alone were superior to community controls for ADHD symptomatology, oppositional aggressive behaviors, and social skills. In contrast, behavioral treatment was more effective than community controls only in the area of parent-child interactions.

The researchers also found that anxiety, comorbidity, and being on public assistance were significant moderator variables, associated with a worse outcome. In terms of medication variables, in children with anxiety disorder, combined treatment was better than medications alone when there was parental inattention. However, when there were parental internalizing symptoms, children with baseline anxiety showed positive effects with intensive behavioral treatment. In those with low socio-economic status, combined treatment was most needed in those who came from the most deprived backgrounds.

Many modulator variables appeared to work together, such that in the presence of parental depression, only 45% improved on combined treatment compared with 69% in the absence of parental depression. If one also includes severity of symptomatology and low IQ in the child, the chance for significant improvement even with combined treatment was reduced to 10%.

The first group, receiving medication management treatment, was highly successful. It consisted of a careful 28-day titration to ascertain optimal doses, monthly maintenance visits, daily treatment with stimulants including T.I.D. (three times a day) dosing (for the short-acting agents used at this period of time), a 30-minute office visit, and contact with the teacher. This contrasted markedly with the community controls, who were ostensibly provided medication management, but in reality had only one visit every five months for an average of ten minutes, medication only five days a week, B.I.D. (two times a day) dosing

only, and no teacher contact. The superior results gained from the intensive and careful monitoring in this clinical trial highlight the substandard care sometimes delivered in the community.

In terms of family mediators, negative or ineffective disciplining practices appeared to be a prominent adverse outcome measure. While only one-third of the families in intensive behavioral management showed notable improvement in their disciplinary practices, it was these 58 children whose parents did improve their disciplinary practices who showed the greatest degrees of improvement.

Hinshaw's conclusions for childhood-onset bipolar disorder studies from his epic study in childhood externalizing disorders were that: (a) one needs to use theory to select among potential risk and protective factors, (b) one must balance multi-informant, multi-method appraisals with the potential risk for respondent burnout, (c) statistical power issues and large Ns are critical for detecting interactions, (d) one needs to use clinical trials to serve conceptual as well as clinical practice ends (i.e. while ADHD is a highly heritable condition, the outcome is mediated by many family factors that are, in fact, malleable, and can make an extraordinary difference in the well-being of the child).

Boris Birmaher of Western Psychiatric Institute in Pittsburgh presented a paper entitled "Course and outcome of bipolar disorder in youth (COBY)," which began a series of talks directly on childhood bipolar illness. This study is particularly important because it describes the prospective outcome of 446 children, average age 12.7, with a mean age of onset of illness of 9.3 years.

Notably, 35% of the children presented with bipolar not-otherwise-specified (BP-NOS) and bipolar II (BP-II) in another 7% for a total of 42% of the children. While 68% consisted of those with bipolar I (BP-I), two-fifths of the sample were diagnosed in areas (BP-II & BP-NOS) where there is considerable controversy as to the precise diagnostic thresholds. The vast majority (86%) of those who were diagnosed with BP-NOS received this diagnosis because they did not meet the four-day durational threshold for BP-II or the one-week threshold for BP-I mania. These data reemphasize the issue that numerous children, particularly those with the youngest ages of onset, present with very rapid mood fluctuations, often several times within a day (called ultradian cycling). What is

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particularly disturbing about the controversies around BP-NOS diagnoses is that these children are as much impaired as those with BP-II and BP-I, and they also take the longest time to stabilize during naturalistic treatment, more than two and a half years compared with less than a year for those with BP-I and BP-II. In addition, 35% of BP-NOS children converted to the nagnostic category (BP-II or BP-I) during several years of follow-up, indicating that BP-NOS may be a precursor form of the illness, highly prevalent in the youngest children who are later destined to have longer duration hypomanic and manic episodes characteristic of BP-II and BP-I, respectively.

Childhood-onset bipolar disorder is highly associated with multiple other (comorbid) disorders. These include any anxiety disorder (40%), ADHD (60%), oppositional defiant disorder (ODD) (40%), conduct disorder (13%), substance use disorder (10%), and pervasive developmental disorder not otherwise specified (2%), as reported by Axelson et al. (2006, Archives of General Psychiatry).

Twenty-eight percent of the children in the Birmaher study presented with psychosis, 76% with suicidal ideation, and 31% with suicide attempts. Twenty-three percent had experienced physical or sexual abuse, as reported by the caregiver, and 52% already had a psychiatric hospitalization. Ninety-three percent were in psychopharmacological treatment. Birmaher noted, "If you see psychosis in a kid, you have to rule out bipolar disorder."

Editor's Note: This is likely true, especially since childhood-onset schizophrenia is an extremely rare disorder. Given this fact, if a child with extreme mood dysregulation also has psychosis, it would not be too far a stretch to suggest that bipolar disorder is, in fact, the most likely diagnosis and other entities only remain to be ruled out. (Since some clinicians and investigators do not even believe in the existence of prepubertal onset mania, this statement is likely to raise extraordinary consternation in some individuals; however, these critics are obligated to come up with an alternative diagnosis, and more importantly, an effective treatment.)

Birmaher also reported, as have others, that childhood-onset bipolar disorder has a

substantial degree of familial loading, with mania or hypomania in 38% of first degree family members, depression in 72%, anxiety disorder in 48%, conduct disorder in 24%, ADHD in 29%, substance use in 46%, suicide attempts in 25%, and schizophrenia in only 2%.

While 66% of the children recovered for a period of at least two months during the two years of follow-up, about 48% had at least one recurrence. Children remained symptomatic or subsyndromal for more than half the weeks of follow-up despite the range of available psychopharmacological and psychotherapeutic treatments.

These data are highly convergent with those of Geller et al. (2002, 2004) and DelBello et al. (2007), indicating the difficulties in stabilizing these children. In contrast to adults with BP-I reported by Judd et al. (2001) who experience few mood switches per year, children with BP-I experienced about 20 changes in polarity (mania to depression or depression to mania) over the course of a year. If one also considered the BP-II and

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Editor's Commentary:**Political Action Needed to Enhance Treatment Research in Pediatric Bipolar**

Hinshaw's large, comprehensive, multi-center trial in ADHD illustrates the kinds of interventions that need to be assessed and tested in randomized controlled clinical trials in the study of bipolar illness. Sadly, despite the extraordinary needs of the population with childhood-onset bipolar disorder, these kinds of studies are not being funded or conducted. In fact, even single-center treatment trials are not being funded to any substantial extent.

This is particularly egregious in light of the data emerging from most of the plenary presentations that early onset bipolar illness carries with it tremendous risks and disabilities throughout the child's lifetime into adulthood. The incidence of childhood-onset bipolar disorder appears to be very high in the US, and the lack of an adequate clinical trials database means that clinicians may not be treating children with the most appropriate approaches based on systematized information, but on the basis of their own best guesses. So far, naturalistic treatment in the community is proving highly inadequate, as seen in the treatment outcome data presented by Birmaher.

When this editor (RMP) approached Dr. Steven Hinshaw at the end of his remarkable presentation and asked how this large, successful

and highly informative study for the treatment of ADHD and related disorders was funded, Hinshaw indicated that it was only because of intense lobbying in Congress by another individual, Peter Jensen, who was an expert in the field and politically adept. His work resulted in a specific earmark whereby Congress mandated the money for this study to be conducted.

As we have emphasized elsewhere (Post & Kowatch, "The crisis in childhood-onset bipolar illness," Journal of Clinical Psychiatry 2006), not only are funding and funding mechanisms for childhood-onset bipolar illness inadequate, but the field of adult-onset bipolar illness has been understudied for the past three decades as well, resulting in further informational shortfalls about treatment of adults, many of whom had onsets in childhood. Given the difficulty of progress in the area of adult illness despite widespread public, academic, and National Institute of Mental Health (NIMH) acknowledgment of the portfolio deficits, it would appear that only some Congressional mandate like that achieved for the Hinshaw study will be sufficient to begin to move the field of childhood-onset bipolar illness treatment-related research forward at any reasonable pace.

Dr. Jensen is no longer at the NIMH, and it seems that no other individual with his unique set of skills and political savvy is available to chart a similar course for children with bipolar disorder. Since the lack of clinical treatment research on adult-onset bipolar disorder has not been fixed despite intensive efforts by many, there is little reason to believe that improvement in childhood-onset illness research will occur without extraordinary efforts by some individual or group directed at achieving a Congressional mandate or similar funding earmark. Many in Congress have families with adults or children suffering from bipolar disorder, and somehow their influence for better treatment-related research needs to be brought to the fore.

Constance Hammen began her presentation with the statement that "children with bipolar illness are impaired, denigrated, and ostracized." Without some new political/scientific initiatives, this situation is likely to remain unchanged for many years to come. We desperately need a political action hero for childhood-onset bipolar disorder like that played by Peter Jensen for children with ADHD and conduct disorders so that a solid database of empirical clinical trials can be generated and the best treatments delineated.

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BP-NOS children, this number of switches per year would increase dramatically.

One of the major predictors of which BP-NOS children would convert to longer duration forms of BP-II and BP-I illness was a positive family history of bipolar illness. In BP-NOS children with a positive family history of bipolar disorder in first-degree relatives, approximately 50% of the children converted to BP-I or BP-II compared with only 20% in those without a family history of bipolar disorder. These data further suggest the need for heightened suspicion of a bipolar diagnosis in those children presenting with extreme mood instability and a positive family history of bipolar disorders.

The next plenary paper was presented by Gaye Carlson, who reported that her sample of 15 to 20 nine-year olds led to findings similar to those of the COBY sample of children under age 12. Carlson's study found that the childhood-onset bipolar children took a longer time to achieve remission, and a smaller percentage achieved remission (40.7 to 56.1%) compared with those with adolescent and adult onsets (62 to 83% achieving remission).

Editor's Note: This theme was reiterated throughout many presentations – children with the earliest ages of onset of their bipolar disorder appeared to have a more adverse course of illness compared to those with adult onsets. However, if their treatment were more appropriate (mood stabilizers or atypical antipsychotics as per consensus guidelines of Kowatch et al. (2005)) and began more promptly, their outcome may have been more positive.

Hillary Blumberg of Yale University next presented neurobiological data on “Emerging neurodevelopmental models for bipolar disorder: risk related and treatment responsive brain regions.” She summarized evidence for volumetric decreases in the size of the amygdala and ventrostriatal areas of the brain measured with MRI in those with childhood-onset bipolar disorder. These areas are thought to serve critical aspects of affective regulation and motor activity and motivation, respectively. More than six investigative groups have reported deficits in amygdala volume, yet there is considerable evidence of amygdala hyperactivity and hyper-reactivity on measures of functional brain imaging. For example, there is an elevated amygdala response to looking at facial emotions, particularly negative emotions such as anxiety or anger, compared to well controls.

At the same time, there appear to be deficits in the reactivity of prefrontal cortical areas,

suggesting loss of cortical modulation of lower centers such as the amygdala. Several studies have indicated that children who are treated psychopharmacologically have a reversal of the volume deficits, raising the possibility that earlier, more effective treatment could not only produce improvement in the behavioral and emotional elements of bipolar disorder, but possibly also in its underlying neurobiology as well.

The next presentation was by Mauricio Tohen of Eli Lilly Co., entitled “Analysis of treatment efficacy and safety in adolescents compared with adults with bipolar disorder treated with olanzapine for acute mania.” In these controlled clinical trials, adolescents were highly responsive to olanzapine compared with placebo, just as in the adult acute mania studies. Interestingly, the magnitude of the decrease in the Young Mania Rating Scale (YMRS) and the effect size was larger in adolescence than in adults, although rates of remission were somewhat lower in adolescents (35.2% compared with 50% in adults).

While olanzapine has proven effective in the treatment of adolescent onset mania, it also appeared to cause more problematic side effects than it did in adults. These included increases in weight, prolactin, fasting lipids, and blood glucose. For example, 29% of adolescents reported increased appetite and weight gain compared with 5 to 7% of adults. Forty-one percent of the adolescents gained more than 7% of their body weight compared with only 11.3% of the adults. The only side effects that were less problematic in adolescents compared with adults were dry mouth and dizziness, side effects related to the anticholinergic effects of the drug.

Editor's Note: These findings by Tohen and colleagues illustrate the difficult tightrope that clinicians must walk in the treatment of childhood-onset bipolar disorder. Some of the most effective agents, such as olanzapine and clozapine, have problematic side effects in children including weight gain and risk of the metabolic syndrome (including three of the following five symptoms: hypertension, increased waist circumference, insulin insensitivity (or elevated blood glucose), elevated triglycerides, and elevated cholesterol). Quetiapine and risperidone also are associated with, at times, considerable weight gain in children, but less so than the first two drugs. Two of the newest antipsychotics, ziprasidone (Geodon) and aripiprazole (Abilify) are weight neutral in adults, but in children can still be associated with some weight gain, although this tends to be less with ziprasidone compared with aripiprazole according to some open anecdotal observations by several highly experienced clinicians in the field.

This editor's bias is to begin young children who require an atypical on these latter, relatively less problematic drugs (aripiprazole and ziprasidone), even though they are less well studied than olanzapine, in the hope of achieving a good effect without engendering a new set of medical problems in these youngsters.

Children with bipolar illness are at such great social and educational disadvantage to begin with, that adding a problem of being overweight, for which they may be severely teased resulting in further decrease their self-image, is particularly important to avoid. The potential medical consequences of being overweight are also highly problematic. Direct comparative studies among the atypicals for efficacy and tolerability, as well as comparisons of selective atypicals against lithium and the mood stabilizing anticonvulsants (carbamazepine, valproate, and even lamotrigine with the appropriate cautions for increased risk of serious rash) are needed to enlighten clinicians about the best treatment options for these often highly disabled children.

The next presentation was by Bob Findling of Case-Western Reserve clinics in Cleveland on “Comparison of maintenance responses between young and adult patients with bipolar disorder.” This was a particularly critical and in some respects disturbing study because of the demonstrated need for at least combination treatment. Forty-three percent of children were found to achieve four weeks of remission on the combination of lithium and divalproex and were thus eligible to be randomized to a long-term study of monotherapy with either lithium alone or divalproex alone (30 subjects in each group). Disappointingly, neither drug alone was particularly effective, with about 50% of the subjects discontinuing the study by 50 days, and about 80% by 200 days, indicating that neither monotherapy was sufficient to keep these children stabilized.

On the positive side, the vast majority of children restabilized once the combination of lithium plus valproate was re-administered, but this sometimes required other adjunctive treatments as well, and the majority of children were also on low-dose psychomotor stimulants for residual ADHD. Again, Findling reported that those who had a younger age of onset of bipolar illness were more likely to relapse to a mood episode on either monotherapy. Those with higher YMRS scores at study baseline were more likely to discontinue this study early. Only 15% of the children dropped out of the study for medication

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intolerance, but a higher number (27.3%) did so for study non-compliance.

Editor's Note: While Findling et al. took the optimistic perspective that a larger group of children initially stabilized on the lithium/valproate combination (43%) compared with the 25% of adults with rapid cycling disorder in the studies of Calabrese et al., the take-home message of this study would appear to be somewhat more sobering. That is, childhood-onset bipolar disorder is difficult to treat, and the vast majority of children treated in this academic center of excellence appeared to require at least combination therapy (with two of the better-studied drugs in adults--lithium and valproate) to maintain their improvement.

Comparative studies of these two drugs versus either of them with an atypical antipsychotic would be of great importance to the field in order to assess whether one of these drugs with an atypical would prove able to achieve a higher percentage response and remission rate over time.

A surprising finding from this study was that while depression remains the most difficult to treat phase in adults, in these children it was the manic phase which was most often problematic and evident in breakthrough symptomatology.

The last formal presentation was by Robert M. Post, formerly of the NIMH and now head of the Bipolar Collaborative Network, on "An excess of childhood bipolar illness in the U.S. Compared with Europe." He summarized data (Leverich et al., 2006) from adult outpatients with bipolar illness, average age 42, who reported the age of onset of illness and time of first psychopharmacological treatment for either mania or depression. Like data previously reported by the STEP-BD Network in 983 patients, the 519 patients in the Bipolar Collaborative Network (BCN) reported a high incidence of childhood-onset (prior to age 13) bipolar illness. Strikingly, these earliest onsets were not treated for more than an average of fifteen years, and this delay was associated with more severe symptomatology during adolescence and adulthood, as rated retrospectively and prospectively by clinicians. Adolescent-onset was also common, such that some 50-66% of all bipolar illness onsets occurred prior to age 19 in well-diagnosed adults in these two outpatient networks.

Thus, bipolar illness is largely an illness of childhood and adolescent onset, and yet, disturbingly, adults who are in their forties now experienced unrecognized or untreated illness for more than a decade on the average. This was associated with a difficult course of illness and a relatively poor outcome in adulthood. The hope

would be that earlier recognition and treatment of the syndrome would yield much more favorable courses of illness and long-term outcomes, and clinical trials of early intervention are desperately needed.

New data were reported on childhood onset bipolar illness in the US versus Europe (see Post et al. 2008, British Journal of Psychiatry). The Bipolar Collaborative Network consists of four sites in the U.S. (Los Angeles, Dallas, Cincinnati, and Bethesda) and three in Europe – one in Utrecht in the Netherlands, and two in Germany. Surprisingly, childhood-onset bipolar disorder prior to age 13 represented 22% of the U.S. cohort but only 2% of the European cohort, and adolescent onsets (from ages 13 to 19) represented 39% of the U.S. cohort compared with 28% of the European cohort. Together, these data suggest that child- and adolescent-onset bipolar illness is at least twice as common in the U.S. as it is in Europe (61% versus 30%), as gleaned from self reports on a questionnaire or from formal diagnostic interviews that asked well-diagnosed adults the age of onset of their first depression with dysfunction or their first mania or hypomania.

Surprisingly, two risk factors for childhood onset were also higher in the US than in Europe. A positive family history for both unipolar and bipolar affective disorders (and suicide) was significantly more common in the U.S. than in Europe. This was also the case for a positive history of childhood adversity, wherein some 22-27% in the U.S. reported sexual or physical abuse in childhood, while these figures were 11% and 12%, respectively, in the Netherlands and Germany.

These data on increased familial and environmental risk factors further suggest that the differences in incidence of childhood onset are not an artifact of diagnostic differences or understanding of the questions. Why there should be an increase in genetic vulnerability to bipolar illness in the US is not at all clear. Discerning what factors are involved in the increased vulnerability in the U.S. and the potential protective factors at play in Europe might lead to altered clinical practice and public health measures in an attempt to ward off early-onset bipolar illness in the U.S. Again, the hope would be that earlier and more effective recognition and treatment could ameliorate the otherwise adverse course of bipolar illness in those with the youngest ages of onset (who appear overly represented in cohorts in the U.S.).

BREAKOUT SESSIONS FOR PROBLEM SOLVING AND CONSENSUS RECOMMENDATIONS

The breakout groups were designed to reach consensus recommendations in each of the five focus areas, and each group included a portion of the 200 clinician/investigators registered for the research forum. The groups met and reported to the general session their consensus recommendations, which hopefully will be published in the *Journal of the American Academy of Child and Adolescent Psychiatry* later this year.

There was an overarching consensus across multiple groups about the need for a diagnostic consensus conference in order to deal with many of the diagnostic controversies in childhood-onset bipolar illness most effectively. Almost all groups also reported the need for greater degrees of clinical investigative trials and more grant support. This may be particularly problematic at a time of extremely tight budgets, and it is likely that many of the most highly prioritized studies will not be rapidly forthcoming. Thus, many groups talked about the need to raise money from other sources beyond the Extramural Program of the NIMH.

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