

## Clinical Trials Update

### Stanley Foundation Bipolar Network (SFBN)

The SFBN is in its fifth year of patient recruitment, with more than 500 patients enrolled in continuous longitudinal observation, study, and treatment.

In addition to the preliminary observations already completed on the newer anticonvulsants gabapentin (Neurontin®), lamotrigine (Lamictal®), and topiramate (Topamax®), the SFBN is proceeding with protocols for the study of two new anticonvulsants, levetiracetam (Keppra®) and zonisamide (Zonegan®). Based on their novel mechanisms of action the hope is that they might have additional benefit in patients with inadequately responsive bipolar illness.



The SFBN has randomized more than 80 patients into the protocol comparing omega-3 fatty acids (EPA, 6 grams) and placebo, and more than 135 into the protocol comparing the efficacy of bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®) added to a mood stabilizer for breakthrough depression.

In addition, the SFBN will be assessing the possible efficacy of new drugs targeted at different symptom components or comorbidities of the bipolar disorders. The European sites (Germany, The Netherlands) will be evaluating the potential efficacy of acamprosate (Campral®) in alcohol craving and its associated effects on mood stability. This compound is widely used in Europe for prevention of alcoholism in non-bipolar patients and has few serious side effects. Modafinil (Provigil®) is a newly approved agent for patients with sleep disorders such as narcolepsy, and will be studied as a possible approach to patients with bipolar illness who have increased fatigue and daytime sleepiness, either as a residual part of their depression or as a medication side effect. The SFBN will also explore the relative efficacy of sibutramine (Meridia®) and topiramate in treatment of both weight loss and mood stabilization.

### NIMH Patient Recruitment

The National Institute of Mental Health (NIMH) in Bethesda is exploring several novel treatment approaches with new protocols. If these new protocols yield promising results, they will be extended to the other SFBN sites.

- We are actively recruiting patients for a study of repetitive transcranial magnetic stimulation (rTMS) of the brain with higher intensities than we have previously used, anticipating that higher intensities may be more effective for treatment-resistant patients with unipolar and bipolar depression. A three-week comparison of low frequency (one stimulation/second) rTMS vs. high frequency (20 stimulations /second) rTMS vs. sham rTMS will be conducted.

- Our ongoing comparative study of lamotrigine and gabapentin also continues in a revised form. Given that the efficacy of lamotrigine exceeded that of both gabapentin and placebo in the first phase of the study (Frye et al., 2000; *J Clin Psychopharmacol* 20: 607-614), we are now directly comparing only the two active treatments lamotrigine and gabapentin (each for six weeks) without a placebo phase.

If you live in the vicinity of Los Angeles, Dallas, Cincinnati, Washington DC, Utrecht, The Netherlands, Freiburg, Germany, or Munich, Germany, and wish to be involved in any of these new SFBN or NIMH protocols, please call 1-800-518-7326 or (301) 496-6827 to speak with someone about the studies.

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## Clinical Trials Data

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Or you can visit the SFBN website for more detailed information about each participating research center, by going to [www.bipolarnetwork.org](http://www.bipolarnetwork.org). Many of the Network accomplishments and future goals have been summarized in a five-year prospectus, which is also available on the Web site.

### Bipolar Network News

#### Editors-in-Chief:

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The *BNN* is published four times a year by an international group of 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. The goal of the Network is to help develop new and more effective treatments for bipolar disorder.

Publication of the *BNN* is made possible by an unrestricted grant from Janssen Pharmaceutica (<http://us.janssen.com>), a division of the Johnson and Johnson company.



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*.

The opinions expressed in the *BNN* are solely those of the editors, and do not necessarily represent the views of the Stanley Foundation or the National Institute of Mental Health.

For any comments or suggestions you may have, or to be placed on the mailing list, please contact us at:

#### Bipolar Network News

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### Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

The National Institute of Mental Health has launched a nationwide study to improve the treatment of bipolar disorder. This study, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), is the largest, long-term, federally-funded project on bipolar disorder ever conducted. The main goal of this five-year effort, which is now recruiting 5,000 participants at 18 centers across the United States, is to improve treatment and outcomes for all people with bipolar disorder. While many treatments are used currently for bipolar disorder, including medications and psychotherapies, doctors are uncertain which of these treatments actually work best. Findings from STEP-BD will help improve the treatment standards used by doctors in everyday clinical practice.



STEP-BD offers participants long-term continuity of care. Participants will be followed and treated in a consistent manner throughout their involvement in the study, even when they are feeling well. STEP-BD is evaluating all the best-practice treatment options currently used for bipolar disorder: mood-stabilizing medications, antidepressants, atypical antipsychotics, monoamine oxidase inhibitors, and psychosocial interventions, including cognitive behavioral therapy, family focus therapy, interpersonal and social rhythm therapy, and psychoeducation. The study aims to find out which treatments, or combinations of treatments, are most effective for treating

episodes of depression and mania and for preventing recurrent episodes over time. Participants can stay on their existing treatment plan or can choose to change treatments at any time. At no point during the study will participants be assigned placebo alone. In addition to measuring improvement in illness symptoms, STEP-BD will evaluate how treatments influence other important issues such as quality of life, ability to work, and social functioning. The study also will assess the cost-effectiveness of different treatments and factors that affect how well people stay on their treatment plans.

Almost anyone who is age 15 or older and has a DSM-IV diagnosis of Bipolar Disorder or Cyclothymic Disorder (a less severe illness similar to bipolar disorder) can participate in STEP-BD. STEP-BD includes individuals who have more than one mental disorder diagnosis (for example, anxiety disorders or personality disorders) and those with physical illnesses.

Cities where the trial is being conducted include: Tucson, AZ; Stanford, CA; La Jolla, CA; Denver, CO; Chicago, IL; Louisville, KY; Boston, MA; Worcester, MA; Kansas City, MO; Buffalo, NY; New York, NY; Cleveland, OH; Tulsa, OK; Pittsburgh, PA; Philadelphia, PA; Houston, TX; and San Antonio, TX.

For more information on STEP-BD, call toll-free 1-866-398-7425 or visit the NIMH STEP-BD web page: [www.nimh.nih.gov/studies/STEP-BD.cfm](http://www.nimh.nih.gov/studies/STEP-BD.cfm). Questions also may be directed to the Massachusetts General Hospital coordinating center at (617) 724-6058. ■

## Research Update

### Variation in the COMT Gene as a Risk Factor for Schizophrenia: Implications for the Genetics of Bipolar Disorder

A large part of the human genome has been searched for robust association markers to bipolar disorder and schizophrenia, without finding any single gene with a sizable effect. Most authorities now agree that these serious psychiatric illnesses are probably multigenic, i.e., a variety of gene alterations likely act as vulnerability factors, and having a given threshold number of these genes is necessary for full-blown illness.

Dr. Daniel Weinberger, Chief of the Clinical Brain Disorders Branch at the National Institute of Mental Health (NIMH), and his staff have been searching for genes with small effects in patients with schizophrenia using a novel strategy. They decided to look at how genetic variation might relate to central nervous system processing defects as revealed on functional magnetic resonance imaging (fMRI), hoping that this method might give a more precise picture than using the entire syndrome of schizophrenia as the focus of the gene search.

Dr. Weinberger's group used a working memory task in which each person had to remember the position of a number on a card that had been shown two cards previously, called the "two-back test". This is a relatively easy task which normal volunteer controls and patients with schizophrenia are both able to complete with a high degree of accuracy.

As revealed by brain imaging with fMRI, the patients with schizophrenia activate a much greater area of the frontal cortex and cingulate gyrus than the controls without illness. This increased activation is considered evidence of inefficient processing of information involved in the task, because as one becomes proficient in a variety of motor learning and memory paradigms, lesser degrees of cortical activation are required.

It has long been thought that a deficiency of dopamine (hypoactivity) in the prefrontal cortex could account for many of the negative symptoms of schizophrenia, whereas dopaminergic hyperactivity in limbic and striatal areas of the brain could account for the positive symptoms of schizophrenia. Consistent with the view that decreased dopamine function in prefrontal cortex would be related to inefficient processing of the two-back test, patients with Parkinson's disease (who are dopamine deficient) were found to have this problem before but not after treatment with levodopa (the immediate precursor of dopamine).

The enzyme catechol-O-methyl-transferase (COMT) is required for the breakdown of dopamine and norepinephrine. Its activity is particularly important in regulating levels of dopamine in frontal cortex where the usual transporters for dopamine reuptake and inactivation are less prominent than in the striatum. High levels of COMT activity would thus decrease dopamine by rapidly converting it to methylated intermediates which are further oxidized by monoamine oxidases (MAOs). A gene variation in the DNA coding for COMT has been found which results in a four-fold increase in activity and, thus, decreases levels of dopamine.

Dr. Weinberger and colleagues also found that in another task that is critically dependent on dorsolateral prefrontal cortical function and one on which schizophrenic patients show deficiencies, that the variant of the COMT allele is, in fact, associated with poor performance in both controls and in patients with schizophrenia. These investigators have now found that the presence of this COMT variant confers a 1.5 times increased relative risk for developing schizophrenia. This is a relatively small effect, but Dr. Weinberger and associates

surmise that with sufficient numbers of such small genetic variations, each contributing a relatively small increased risk of illness, a robust effect could ultimately be produced.

This finding is much like the recent findings of a gene conferring vulnerability to diabetes, in which 75% of the normal population have the gene, but 80% of diabetics have it. Thus, the gene does not *cause* diabetes any more than the COMT variation causes schizophrenia. However, both appear to be risk or vulnerability markers which may be sufficient to push an individual over the gene threshold for active illness along with a variety of other vulnerability genes.

Should the findings with COMT be replicated by other groups (and the four linkage studies that have examined this association of the COMT variant with the presence of schizophrenia have all been positive), it would represent one of the first verified genetic vulnerability markers for a major psychiatric illness. At the same time, these findings illustrate the exquisite difficulty in finding and verifying such associations with polygenic illnesses such as schizophrenia or bipolar disorder, as opposed to some neurological illnesses like Huntington's chorea in which an alteration at a single gene locus determines whether, and at approximately what age, one is likely to develop that degenerative disorder.

#### Short Cuts in the Search for Gene Markers: Proteomics and SNPs

Although such a complicated process as described above would appear to put any impact of modern molecular genetics on clinical therapeutics many decades into the future, there may be some short cuts around this process. For example, the whole field of *proteomics* is focused on identifying pro-

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## Research Update: Genetics

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tein products that are abnormal in a given illness and then tracing back the genes that account for this abnormality. This method results in a much more focused search rather than having to look for linkages over the entire genome.

Perhaps the strategy most likely to be clinically relevant is one using single nucleotide polymorphisms (SNPs, pronounced “snips”) as markers for clinical response or side effects to a given treatment (Schork et al., 2000; *Clin Genet* 58: 250–264; Brookes, 1999; *Gene* 234: 177–186). With the advent of the sequencing of the entire human genome, it is estimated that there are many tens of thousands of these SNPs in each individual. SNPs are common variations in

the general population as opposed to gene defects or mutations which occur, by definition, more rarely.

In any given clinical trial, one would be able to compare the SNP profile of patients who respond to a given treatment versus those who do not, and establish this with a given degree of certainty. Then patients who are considering taking one drug compared with another might be able to have their SNP profile analyzed to see whether they are likely to be responsive or not. In this way individual clinical trials of medications could be more rationally sequenced based on this added information about the probability of being a responder.

The same profiling could be done with SNPs in relation to drug side effects, so that the likelihood of having a severe adverse side effect could be, in part, estimated in advance. Both of these processes of using the SNP profile to predict response or side effects could be done quite independently of the knowledge about the function of the array of SNPs that are involved in the clinical predictions. Given this ability to pass over the difficult steps of linking specific gene variants to differences in physiological function, the promise of SNPs for ultimate utility in clinical therapeutics is high, and this technology is likely to be clinically important for psychiatry in the very near future. ■

## Publication Update: The Evolution of Childhood Major Depression

### Bipolar Disorder at Prospective Follow-Up of Adults Who Had Prepubertal Major Depressive Disorder

B. Geller, B. Zimmerman, M. Williams, K. Bolhofner, J.L. Craney  
*Am J Psychiatry* 2001; 158: 125–127

**OBJECTIVE<sup>1</sup>:** The authors’ goal was to conduct an adult follow-up of subjects who had participated in a study of nortriptyline for childhood depression (Geller et al., 1992, *J Am Acad Child Adolesc Psychiatry* 31: 34–44; Geller et al., 1994, *J Am Acad Child Adolesc Psychiatry* 33: 461–468).

**METHOD:** The study group represented 100 (90.9%) of the original 110 subjects and included 72 subjects who had a prepubertal diagnosis of major depressive disorder and 28 normal comparison subjects. Subjects were assessed with semistructured research interviews given by research nurses who were blind to the subjects’ original diagnoses.

**RESULTS:** In the original study, the mean age of the children with prepubertal major depressive disorder was 10.3 years (SD=1.5); at adult follow-up the mean age of these subjects was 20.7 years (SD=2.0). At follow-up, significantly more of the subjects who had prepubertal diagnoses of major depressive disorder (N=24 [33.3%]) than normal comparison subjects (none) had bipolar I disorder. Subjects who had prepubertal diagnoses of major depressive disorder also had significantly higher rates of any bipolar disorder than normal subjects (48.6% [N=35] versus 7.1% [N=2]), major depressive disorder (36.1% [N=26] versus 14.3% [N=4]), substance use disorders (30.6% [N=22] versus 10.7% [N=3]), and suicidality (22.2% [N=16] versus 3.6% [N=1]). Parental and grandparental mania predicted bipolar I disorder outcomes.

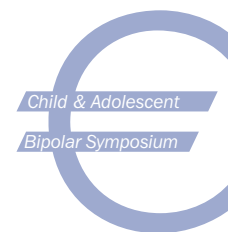
**CONCLUSIONS:** The rates of bipolar disorder in subjects who had prepubertal major depressive disorder were higher than those found in similar outcome studies of adults with major depressive disorder, consistent with the possibility that subjects first examined in adulthood (possibly after switching from prepubertal major depressive disorder to mania in childhood) would simply be counted as having bipolar disorder. High rates of switching to mania have implications for the treatment of depressed children because of concerns that antidepressants (such as desipramine or nortriptyline) may worsen childhood mania.

<sup>1</sup> Abstract compiled and modified from source listed above

**BNN SUMMARY:** The occurrence of prepubertal depression is a substantial risk factor for the subsequent occurrence of bipolar illness.

## Meeting Highlights

Satellite Symposium on Bipolar Disorder in Children and Adolescents  
Rotterdam, The Netherlands, September 20, 2000



The Second European Stanley Foundation Conference on Bipolar Disorder was held in Amsterdam, The Netherlands, from September 21–22, 2000. In conjunction, a satellite symposium on bipolar disorder in children and adolescents was held on September 20, 2000, in Rotterdam. We will present you with highlights of the satellite symposium in this issue, and highlights of the larger conference in the next issue.

### Plenary Session

Dr. J. Biederman of Harvard Medical School began the symposium with his presentation, "Pediatric Mania: a Developmental Subtype of Bipolar Disorder?" He noted that even though it was still controversial, the view that pediatric mania is rare or nonexistent is being increasingly challenged by case reports and systematic studies. The research suggests that pediatric mania may not be rare, but is difficult to diagnose, for a number of reasons, including comorbidities and overlap with other disorders.

Dr. Biederman gave a historical review and summary of his group's data set at Massachusetts General Hospital. He indicated that the earliest presentations of bipolar illness typically include affective symptom storms and dangerous, aggressive behavior, where the affective dysregulation is insidious in onset and mood lability is continuous as opposed to discretely episodic (see *BNN* Vol. 5, Issue 2). In a chart review of 427 referrals of children to his group's clinic since 1991, he found that of 291 with DSM diagnoses, 43 (15%) were manic. Forty-two of the 43 (98%) also had comorbid attention-deficit hyperactivity disorder (ADHD) symptoms, 38 (88%) had oppositional defiant disorder (ODD), 24 of the 43 (56%) had anxiety disorders of multiple types, and 16 (37%) met criteria for conduct disorder (CD).

In his retrospective chart review, he found that good responses were observed with mood stabilizers such as lithium, valproate (Depakote®), and carbamazepine (Tegretol®), but poor response to tricyclic antidepressants (TCAs), serotonin-selective reuptake inhibitors (SSRIs), and psychomotor stimulants. In his data set, risperidone (Risperdal®) showed an 82% response rate in mania, and olanzapine (Zyprexa®) was excellent in monotherapy at initial doses of 2.5 mg/day up to a maximum of 20 mg/day. However, side effects were prominent on these newer antipsychotics, with increased appetite in 61%, sleepiness in 44%, abdominal pain in 30%, increased weight in 30%, and depression in 26%.

Dr. Biederman discussed what he called the "parental exhaustion syndrome" in which these highly disturbed children are extremely difficult to manage and essentially exhaust all resources. He came to the conclusion that children with these extreme types of presentations should be treated with mood stabilizers first and only thereafter with psychomotor stimulants for residual ADHD. In his experience, adjunctive use of stimulants are less destabilizing in children with a history of bipolar illness than are SSRIs.

- There appears to be a mounting consensus among many of the authorities in the field, including our interpretation of the recommendations of Drs. Kutcher, Kowatch, Geller, and Findling, and many others, that these bipolar-like children require mood stabilization prior to the use of small adjunctive doses of psychomotor stimulants and often tend to deteriorate if they are treated with psychomotor stimulants alone.

Dr. C. Reichart of Academic Hospital Rotterdam-Sophia Children's Hospital, The Netherlands, discussed "Bipolar Disorder in Children and Adolescents: A Clinical Reality?" Dr. Reichart noted that among adolescents, bipolar disorder appears to be similarly prevalent in the U.S. and in The Netherlands. However, in her experience and that of many of her colleagues, the diagnosis of bipolar illness was extremely rare in children in The Netherlands. In her 15 years of work as a child and adolescent psychiatrist working in both inpatient and outpatient settings, she had observed only three children before the age of 12 who fulfilled the criteria of bipolar disorder, all of whom were male and had been treated with methylphenidate (Ritalin®).

A survey of 342 bipolar parents done by Dr. Reichart and her colleagues, inquiring about bipolar symptoms in their children, found that none of the children fulfilled the criterion of a bipolar disorder diagnosis before age 12, suggesting that bipolar disorder before puberty hardly exists in The Netherlands. This disparity between the two countries in childhood bipolar disorder led her to speculate that perhaps wider use of psychomotor stimulants in the U.S. in some 6–7% of the childhood population (10 million children exposed) compared to 1% use in The Netherlands (30,000 exposed) could be a factor in the different incidence rates. Perhaps U.S. children are mistakenly diagnosed as ADHD and given stimulants, resulting in full-blown mania. She hypothesized that stimulants, like antidepressants, may trigger a manic episode. In children genetically predisposed to develop bipolar disorder, using stimulants and related drugs may induce the expression of the illness before age 12.

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## Life Chart Highlight

### Adjunctive TRH for Prolonged Mood Stabilization in Treatment-Resistant Bipolar Depression?

#### Retrospective Mood History

The patient whose course of illness and treatment is shown in the life chart at right is a middle aged, married white female. Her hyperthymic (energetic) temperament switched to dysthymia during long-term butalbital (Sedapap<sup>®</sup>) treatment of her migraines. Major depressions began to emerge (1987–1988) with six hospitalizations in the next 5 years (Figure 1). These depressions did not adequately respond to: **mood stabilizers** (lithium, or valproate [Depakote<sup>®</sup>]); **antidepressants** (desipramine [Norpramin<sup>®</sup>], fluoxetine [Prozac<sup>®</sup>], bupropion [Wellbutrin<sup>®</sup>], nortriptyline [Pamelor<sup>®</sup>], or venlafaxine [Effexor<sup>®</sup>]); **benzodiazepines** (temazepam [Restoril<sup>®</sup>], oxazepam [Serax<sup>®</sup>], diazepam [Valium<sup>®</sup>], lorazepam [Ativan<sup>®</sup>], or clonazepam [Klonopin<sup>®</sup>]); **neuroleptics** (trifluoperazine [Stelazine<sup>®</sup>] or thioridazine [Mellaril<sup>®</sup>]); or adjunctive estrogen and levothyroxine (Synthroid<sup>®</sup>, T<sub>4</sub>), .

#### Prospective NIMH Treatment

In many instances the patient showed evidence of initial response to a variety of protocol treatments at the National Institute of Mental Health (NIMH), only to slowly develop treatment resistance in an apparent tolerance pattern (loss of efficacy while maintaining appropriate treatment doses and blood levels) over a period of weeks to 1–2 months (Figure 2). These treatments included: rTMS (20Hz) daily, then twice daily; thyrotropin-releasing hormone (TRH) 500 µg daily, intravenously and sub-

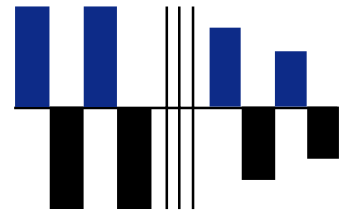
cutaneously (see euthymic period in late 1994); lamotrigine (Lamictal<sup>®</sup>); lamotrigine and bupropion; lamotrigine, bupropion, liothyronine sodium (T<sub>3</sub>, Cytomel<sup>®</sup>) and T<sub>4</sub>; and lamotrigine, bupropion, T<sub>3</sub>, T<sub>4</sub>, and TRH 500 µg in the morning.

She was readmitted in 1996 after a near lethal suicide attempt as her depression returned again. In consultation with Drs. M. Szuba, A. Winokur, and M. Frye, and based on the observations of Philpot (1993; *J Neuropsychiatry* 5: 349–350), we decided to use small doses of TRH (25 µg) subcutaneously at night rather than 500 µg in the morning. With this regimen the patient's mood has remained relatively stable without incapacitating depression for almost 5 years. The patient gave oral and written informed consent for the studies noted here and the publication of this case report.

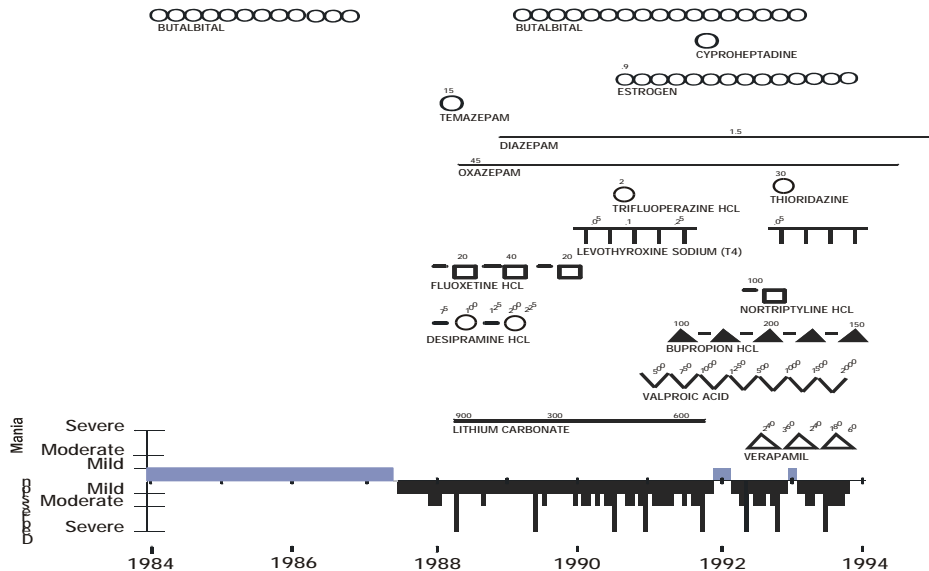
#### Therapeutic Lessons

This case and that of Philpot (1993) are the only instances of which we are aware, suggesting the possible utility of low dose parenteral TRH as an adjunctive treatment. Essentially the same treatment regimen without the TRH (i.e., lamotrigine, bupropion, T<sub>3</sub> and T<sub>4</sub>) was associated with a severe breakthrough depression in early 1996. It was only after low doses of TRH (25 µg subcutaneously) were administered in the evening that her mood remained normal or only mildly depressed. Whether the low doses or evening doses of TRH were

the critical ingredient remains to be ascertained. Systematic double-blind clinical trials should be performed to document or refute these preliminary case observations. Moreover, it also remains for further exploration to ascertain whether a positive mood response to 500 µg TRH during an endocrine challenge TRH test (as shown by this patient) is predictive of a positive response to low-dose adjunctive TRH. ■

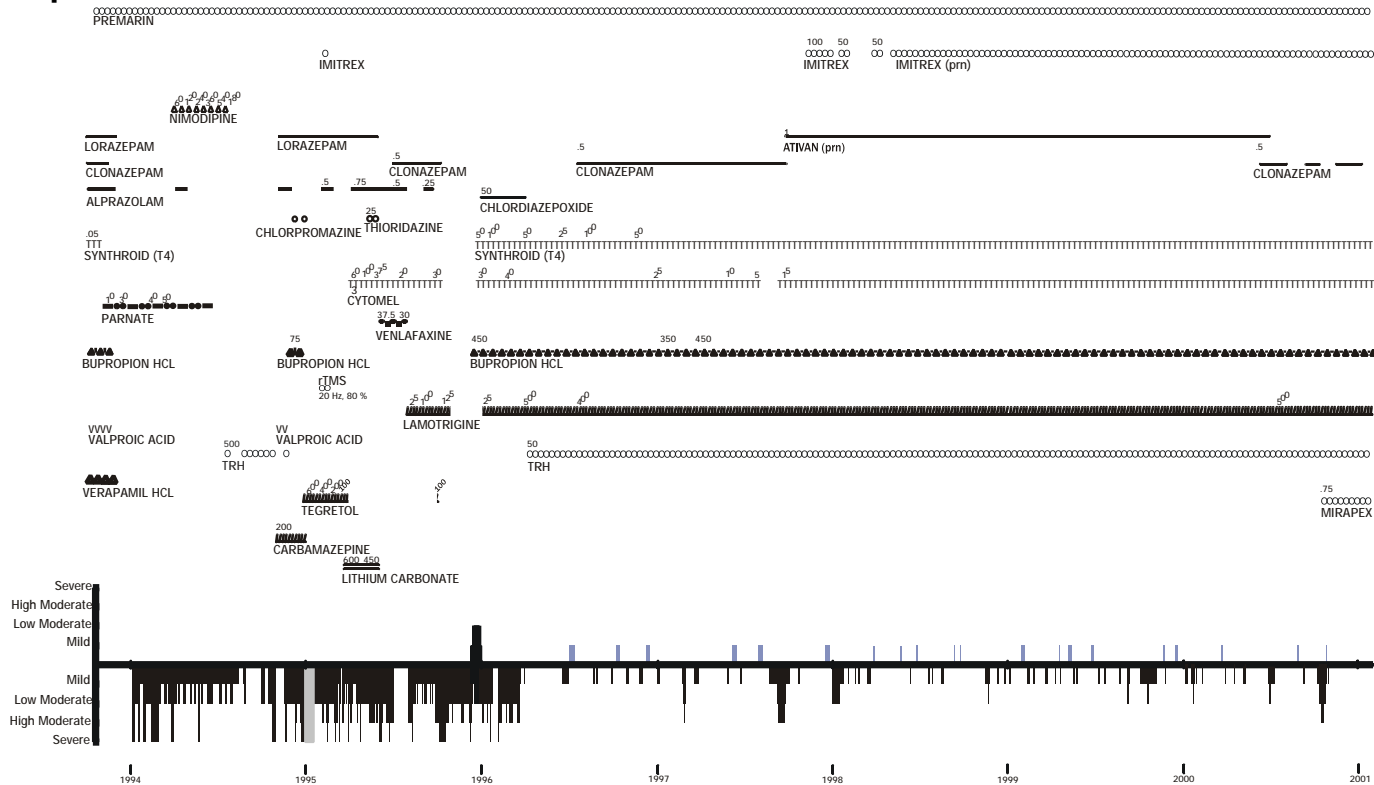


### Retrospective Life Chart



**Figure 1:** Retrospective life chart showing a long pattern of treatment-resistant depression and a failure to respond to a variety of drugs from many different classes.

### Prospective Life Chart



**Figure 2:** Prospective life chart showing sustained therapeutic response to a regimen of lamotrigine, bupropion, T<sub>3</sub>, T<sub>4</sub>, and TRH after eight years of almost continuous depression.

## Meeting Highlights: Satellite Symposium

(Continued from page 5)

Dr. R. Findling of the Stanley Clinical Research Center at Case Western Reserve University discussed "The Rationale, Design, and Progress of Two Novel Maintenance Treatment Studies in Pediatric Bipolarity." Dr. Findling noted that there are no proven acute or maintenance medication treatments for pediatric patients with bipolar illness, and no mood stabilizers are approved for use in the treatment of children and adolescents with bipolar disorder in the U.S.

Dr. Findling and his colleagues have been conducting a randomized, blind trial at Case Western Reserve University, comparing lithium or valproate monotherapy as maintenance treatment for stabilized pediatric patients with bipolar I or bipolar II disorder. Patients were 5–17 years old and met diagnostic criteria for bipolar I or II. Patients in phase I are treated with both lithium and valproate simultaneously in an open design for up to 20 weeks, and doses of both drugs are titrated to reach therapeutic levels and maximize clinical response. After four consecutive weeks of mood stabilization, patients enter phase II, where either valproate or lithium is tapered off over eight weeks in a double-blind fashion. The patients may receive blinded monotherapy on either drug for up to 76 weeks.

So far, 66 patients (50 male, 16 female) have received lithium/valproate combination therapy (phase I), 34 (52%) of whom had a history of rapid cycling; 24 are in phase II. Dr. Findling found in phase I of his trial of lithium and valproate that most children were euthymic in approximately the first four weeks of treatment with the combination. He noted that the children and adolescents in phase I were much more responsive to treatment than the adults in the series of Bowden et al. (2000; *Arch Gen Psychiatry* 57: 481–489) in which very few patients (less than one quarter of the initial intent-to-treat cohort) were able to be adequately stabilized on the combination.

However, in phase II, 19 (79%) of the 24 children stabilized on dual treatment with lithium or valproate who had been randomized to one of the drugs in monotherapy were withdrawn from the study, suggesting that monotherapy with these agents is not as effective as combination treatment.

Dr. Findling and his colleagues have also begun a study of youths (ages 5–17) who are manifesting subsyndromal symptoms of bipolar disorder and who have at least one parent with bipolar illness (and thus are at greater risk for developing full-blown illness). This second study is an attempt to identify a pharmacological intervention that might prevent the development of full-blown bipolar disorder in those youths at highest risk. Patients are randomized to receive either valproate or placebo for up to 5 years in a double-blind design. So far, 32 patients (24 male, 8 female) have received blinded study medication, and nine have left the study due to inadequate mood stabilization (although none have left due to adverse side effects). Completion of this study on the relative efficacy of valproate versus placebo in this high risk population is eagerly awaited.

Dr. M. Wals of the Altrecht Institute for Mental Health Care in Utrecht, The Netherlands, presented data from his work on the "Prevalence of Psychopathology in Children of Bipolar Parents." Problem behavior in 140 offspring (ages 11–21 years) of 86 bipolar parents was assessed using a variety of scales and checklists by interview of adolescents, parents, their spouses, and teachers. Although parental reports revealed significantly higher rates of problem behavior on 3–4 syndrome scales of the Child Behavior Checklist (CBCL), self-reports and teacher reports did not show any significant differences in scores for the adolescent offspring versus a Dutch normative sample, and the prevalence of DSM-IV diagnoses in the offspring (29%) was comparable to offspring

of parents with no mental disorders in a meta-analysis of many other studies (Lapalme et al., 1993; *Can J Psychiatry* 42: 623–631).

Dr. R. Kowatch of the University of Texas Southwestern Medical Center summarized the results of his two studies: "Acute and Continuation Pharmacological Treatment of Children and Adolescents with Bipolar Disorders." As previously reported (Kowatch et al., 2000; *J Am Acad Child Adolesc Psychiatry* 39: 713–720), 6–8 weeks of acute treatment with lithium, divalproex sodium, or carbamazepine in 42 bipolar I or II patients 6–18 years of age during a mixed or manic episode revealed response rates of 38–53%, with no significant differences among the three medications.

Thirty-five patients entered the continuation phase, of which 20 were responders in the acute phase and 15 were nonresponders. Thirty (85%) of the 35 patients in the continuation phase were classified as responders, including 10 of the 15 nonresponders in the acute phase. However, many children required either a combination of mood stabilizers, a mood stabilizer and a stimulant, or a mood stabilizer and an antidepressant.

### Poster Presentations

Several posters concerning child and adolescent bipolar disorder were presented during the Second European Stanley Foundation Conference on Bipolar Disorder from September 21–22, 2000, and are briefly summarized:

Dr. N. Austin of New York Presbyterian Hospital found that children 6–12 who were diagnosed with childhood onset bipolar disorder had nonverbal learning difficulties out of proportion to their verbal difficulties, as measured by an IQ test.

Dr. R. Graef of Graef & Enos Psychological Associates, Glenview, Illinois, presented guidelines for adapting psychotherapy for

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## Meeting Highlights: Satellite Symposium (Continued from page 8)

treating bipolar children and adolescents, including three major issues: 1) the importance of current knowledge of the disorder; 2) learning how to effectively pass this knowledge on to patients, families, and schools; and 3) a willingness to provide extraordinary support needed by children and their families.

M. Hellander of The Child and Adolescent Bipolar Foundation (CABF; [www.bpkids.org](http://www.bpkids.org)) described their website and its many opportunities for all interested in bipolar disorder in children and adolescents, including full-text medical journal articles, an on-line database of professional members, on-line support groups, and many other resources.

Dr. Y. Osher of Ben Gurion University of the Negev, Beer Sheva, Israel, compared the children of parents without bipolar illness to children of parents with bipolar illness using the Rorschach Inkblot Test. Compared to the 14 controls, the 14 children of bipolar parents showed fewer cognitively-mediated affective responses, fewer Human Movement responses, and significantly more severe thought disorder, and gave significantly fewer conventional responses.

Dr. J. Frazier of Harvard Medical School and colleagues found that olanzapine was an effective monotherapy for juvenile (ages 5–14) bipolar disorder; 14 (61%) of 23 patients responded with a reduction in mania scores. ■

### Circulation Note:

This issue is the most current issue of the *BNN*. The Winter 2000 and Spring 2001 issues should be published rapidly in the next 2–3 months.

## //www: bipolar

[www.bpkids.org](http://www.bpkids.org)

### The Child and Adolescent Bipolar Foundation

As noted in the article at left, The Child and Adolescent Bipolar Foundation is a community of people who care about children and adolescents with bipolar disorders. The Learning Center section of the website has many articles on early-onset bipolar disorder, research findings, and interviews. The heart of CABF is the Community Center, where there are message boards, chat rooms, and on-line support groups that will connect you with others in similar circumstances. The Community Center also features an on-line searchable database of professionals, a fine arts gallery of works by bright and creative children, a listing of research studies, and a bookstore. Visiting the Resource Center of the website will provide you with essential resources (such as Social Security Disability information and a directory of in-person support groups) right on the CABF Web site.

[www.bpsso.org](http://www.bpsso.org)

### Bipolar Significant Others

The BPSO website is intended to provide information and support to the families, friends and loved ones of those who suffer from bipolar disorder. The BPSO mailing list was formed in 1995. It is an informal organization whose members exchange support and information about bipolar disorder by e-mail, and discuss issues related to the impact of the illness on families and intimate relationships. "Significant Others" includes, but is not limited to, spouses, boyfriends, girlfriends, partners, parents, children, siblings, and other loved ones of those who have bipolar disorder. Sections of the website such as Medications; Current Research and New Trends; Coping, Job, and Legal Issues; and BP in Children and Adolescents provide a wealth of information for significant others of those with bipolar illness.

[www.nimh.nih.gov/publicat/childmenu.cfm](http://www.nimh.nih.gov/publicat/childmenu.cfm)

### NIMH Child and Adolescent Mental Health

This website of the National Institute of Mental Health has links to many NIMH reports related to bipolar disorder, including "Child and Adolescent Bipolar Disorder: An Update from the NIMH," and "Treatment of Children with Mental Disorders," as well as many other topics related to mood disorder research in children and adolescents.

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## **Bipolar Network News**

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### **In This Issue:**

Clinical Trials Update: SFBN, NIMH, STEP-BD  
Research Update: Genetics and Psychiatric Illness  
Life Chart Highlight: Adjunctive TRH in Refractory Depression  
Meeting Highlights: Child and Adolescent Bipolar Illness

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