

Clinical Trials Update

The Year in Review

Antidepressant Trial

Seventy-three patients with bipolar disorder have been randomized to bupropion (Wellbutrin®), sertraline (Zoloft®), or venlafaxine (Effexor®) in the Network's ongoing controlled trial of three different antidepressants for the treatment of breakthrough depression. Forty-three (59%) of these 73 patients have acutely responded to one of these drugs and elected to enter a 1-year phase of continued prophylaxis. Thirty-three (77%) of these 43 patients responded to the first drug in the 10-week trial, 8 (18%) responded in the second crossover phase, and 2 responded in the third phase. The remaining 30 (41%) of the 73 patients finished or are still in the 1 year prophylaxis trial and we hope to ascertain which of the 3 drugs is the most effective in preventing depression without inducing mania.

New Drug Evaluations

Open clinical trials have been performed with 4 new drugs to gain information about their potential range of efficacy in patients with bipolar disorder. These new drugs are: (1) the atypical neuroleptic **olanzapine** (Zyprexa®), and the new anticonvulsants (2) **lamotrigine** (Lamictal®), (3) **gabapentin** (Neurontin®), and (4) **topiramate** (Topamax®). Olanzapine has a positive side-effects profile and a recent double-blind randomized comparison with placebo indicates it has acute efficacy in mania. As reviewed in BNN Vol. 4, Iss. 2, considerable evidence supports the use of the new (atypical) neuroleptics such as clozapine (Clozaril®), risperidone (Risperdal®), olanzapine, quetiapine (Seroquel®), and ziprasidone (Zeldox®, soon to be approved) in the acute and long-term treatment of psychosis in patients with schizophrenia and schizoaffective illness. There are many benefits to using these atypical neuroleptics instead of the

typical neuroleptics whenever possible for treating bipolar illness. The older (or typical) neuroleptics are liable to induce acute extrapyramidal side effects as well as long-term difficulties, such as tardive dyskinesia in 10-40% of bipolar patients treated with these neuroleptics. Intermittent treatment does not appear to lessen the risk of tardive dyskinesia, and may even enhance it.

(1) In our Network trial, 8 (57%) of 14 patients responded to **olanzapine**, at a mean dosage of 15 mg/day for an average trial duration of 117 days (see p. 6). The most problematic side effects of olanzapine appear to be weight gain and sedation (despite nighttime dosing). Use of this and the related atypical agents in bipolar illness (noted above) and in affective illness with psychotic depression would appear warranted based on the current preliminary data.

(2) The Network open trial of **lamotrigine** indicated moderate or marked response on the Clinical Global Impressions scale in 11 (65%) of 17 patients at a mean dosage of 187 mg/day for an average trial duration of 159 days (Suppes et al., 1999; in press). These results are highly convergent with data from 2 unpublished, double-blind, controlled

(Continued on page 2)

In This Issue:

Clinical Trials Update:	
The Year in Review.....	1
Meeting Highlight:	
Neurobiology of Psychiatry.....	3
Life Chart Highlight:	
Childhood Bipolar Disorder.....	4
Around the Network:	
Affiliated Site in Germany.....	7

Clinical Trials Update

(Continued from page 1)

clinical trials. The first trial, a randomized, crossover study at the National Institute of Mental Health (Frye et al., 1998) indicated a 52% response rate to 6 weeks of lamotrigine monotherapy compared with 27% response to 6 weeks of gabapentin monotherapy and 23% response to 6 weeks of placebo. Lamotrigine was significantly more effective than either gabapentin or placebo (using Cochran's Q statistic). The drug was well-tolerated, although one individual experienced a severe rash that progressed to exfoliative dermatitis, requiring hospitalization. In a second multicenter trial (Calabrese et al., 1999;

J Clin Psychiatry 60: 79–88), treatment with lamotrigine (50 mg/day or 200 mg/day) was more effective than placebo in depressed patients with bipolar disorder. Lamotrigine was well-tolerated and effective in approximately 50% of patients in that study as well.

Based on these data from controlled trials, in conjunction with our Network data from an open trial, and the open trial data from a variety of other investigators including Dr. Calabrese and associates, it is likely that lamotrigine will play an important role in treatment of depression in bipolar disorder. An important precaution in using this drug is to begin with a low dose (12.5 to 25 mg/day) and increase the dose very slowly to lower the incidence of a potentially serious rash (see BNN Vol. 4, Iss. 1). A benign rash occurs in approximately 10% of individuals, and a severe rash in approximately 1 in 500.

(3) In contrast to the low response rate for **gabapentin** in our double-blind, monotherapy study in treatment refractory inpatients at the NIMH (see above), adjunctive gabapentin therapy was effective in 20 (72%) of 28 outpatients in the Bipolar Network. Typical dosages ranged from 1200 to 1800 mg/day (Altshuler et al., 1999; in press). These data parallel a number of open add-on studies and suggest that gabapentin may have an adjunctive role in the treatment of patients with bipolar disorder. Gabapentin's target symptoms may include helping sleep, decreasing anxiety, improving mood, and treating paroxysmal and chronic pain syndromes. A double-blind trial of gabapentin in social phobia was positive, but another in acute mania was not. Given the benign side-effects profile of this agent and a lack of interactions with other psychotropic medications, gabapentin may come to play a role in the pharmacotherapeutics of patients with bipolar disorder despite negative results in double-blind

monotherapy studies. In the NIMH study, younger patients with shorter illness durations were among those who responded best to the drug. Studies in early onset patients would thus appear indicated.

(4) Forty-eight patients have been studied on **topiramate**, the most effective of the newly approved add-on anticonvulsants. Topiramate has unique mechanisms of action that may be important to its spectrum of therapeutic and side effects. It is a direct blocker of glutamate AMPA/kainate receptors, and thus has the ability to decrease glutamatergic tone selectively through this receptor system, while at the same time enhancing GABA_A mechanisms through an indirect (nonreceptor mediated) mechanism. In addition, it blocks influx of sodium through the sodium channel and thus may decrease glutamate release. Its actions as a carbonic anhydrase inhibitor may be associated with the side effects of renal stones in 1% of individuals and paresthesias in a larger group.

Preliminary evidence suggests topiramate may have positive effects on manic mood in bipolar patients. A significant degree of dose-related weight loss was also evident, which appeared to occur both as a function of decreased appetite or craving, and perhaps altered metabolism as well; the weight loss (which averaged about 10 pounds) was sustained during treatment with this agent. The side effect of weight loss contrasts with many other of the commonly used psychotropic agents such as lithium, valproate, many antidepressants, and atypical neuroleptics. Much further work is needed to better delineate the potential role of this agent with its helpful side effect profile in bipolar illness.

Thus, each of the drugs (noted above) approved for other indications (one atypical neuroleptic for schizophre-

(Continued on page 11)

Bipolar Network News

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The BNN is published 4 times a year by the Stanley Foundation Bipolar Network, an international group of investigators who, together with patients with bipolar disorder who participate in research studies, investigate the long-term course and treatment of bipolar disorder. The goal of the Network is to improve the understanding of bipolar illness and develop better strategies for treatment.

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

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Meeting Highlights

“The Neurobiology of Psychiatry”

Association for Research in Nervous and Mental Disease
December 4-5, 1998, New York City, New York



78th Annual Conference
December 4-5, 1998

The Association for Research in Nervous and Mental Disease (ARNMD), in conjunction with the New York Academy of Medicine, held its 78th Annual Conference from December 4th-5th, 1998, on the topic, “The Neurobiology of Psychiatry.” Leading researchers from around the United States and Canada presented exciting and groundbreaking work on this important topic. Among the presenters were the following:

Dr. Joseph LeDoux, PhD, “Emotion, Memory, and the Brain.” Dr. LeDoux began the meeting with an exciting presentation on dissecting the role of the amygdala and related circuits in conditioned fear, and how this information may lead to new targets of therapeutics in psychiatry.

Dr. Bruce McEwen, PhD, “Stress, Sex, and Hippocampus: From Serendipity to Velerance.” Dr. McEwen reviewed his work on the effects of sex hormones on morphology and function of the hippocampus, indicating that structural changes may occur in this crucial structure (for cognition) in a variety of stress-related animal models, and in humans with Cushing’s disease, recurrent depression, post-traumatic stress disorder, schizophrenia, normal aging, and dementia.

Dr. Steven Hyman, MD, (Director, National Institute of Mental Health) “Molecular Neurobiology and Genetics.” Dr. Hyman presented his view of the potential for molecular neurobiology and genetics of psychiatric disorders in the next century, outlining the technical revolution that has occurred in our

ability to identify alterations in gene expression with gene chips and rapidly relate these to specific alterations in the brain. Dr. Hyman indicated that a major focus of the NIMH will be on these kinds of new molecular approaches to psychiatry.

Dr. Solomon Snyder, MD, “Novel Neural Messengers.” Dr. Snyder reviewed the novel class of neuronal messengers that turn out to be gases—nitric oxide and most surprisingly, carbon monoxide. Neurotoxicity of glutamate and other insults can be largely blocked by blocking the enzyme that synthesizes nitric oxide—nitric oxide synthase (NOS). Moreover, NOS inhibitors block stroke damage in animals even when the drugs are given after tying off the middle cerebral artery. These drugs are thus important targets for clinical therapeutics in a variety of degenerative disorders and more subtle alterations involving toxicity, i.e., perhaps in the psychiatric illnesses as well.

Dr. Huda Akil, PhD, “Molecular, Anatomical and Functional Studies of Stress: Implications for Understanding Mood Disorders.” Dr. Akil presented elegant data indicating that the meaning or significance of the stressor to an animal can be associated with very different changes in its neurobiology. These studies are revealing much information about the neuroendocrine and neurochemical dysregulation of depression and post-traumatic stress disorder at the level of environmentally-induced changes in gene expression.

Dr. Eric Nestler, MD, PhD, “Molecular Basis of Addictive States.” Dr. Nestler spoke on the molecular basis of

addictive states, indicating a new understanding of how many of the drugs of abuse also induce long-lasting alterations in neurochemistry at the level of gene expression and how some of this new understanding may be translated into therapeutic approaches in the future.

Dr. Philip Seeman, MD, PhD, “Dopamine Receptors, Antipsychotic Drugs and Psychosis.” Dr. Seeman reviewed the relationship of dopamine receptor blockade to the antipsychotic effects of the major neuroleptic drugs.

Dr. Patricia Goldman-Rakic, PhD, “Salmon Lecture: The Dopamine D₁ Receptor in Cortical Structure and Cognitive Function.” Dr. Goldman-Rakic’s lecture indicated an important role for dopamine D₁ receptors in prefrontal cortical structures and cognitive function. Her integrative work is a paradigm for examining the biochemistry and physiology of a brain area that has been closely linked to pathology in both affective disorders and schizophrenia.

Dr. Sue Swedo, MD, “The Neural Basis of Psychiatric Disorders: OCD and Autoimmunity.” Dr. Swedo presented her new data on how childhood obsessive-compulsive disorder (OCD) can be associated with an infectious autoimmune illness, in the same way Sydenham’s chorea or rheumatic fever can occur with postgroup A Streptococcal (strep) infections. She terms these illnesses “Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections,” or PANDAS, in which patients often present with obsessive-compulsive disorder, tic disorders, prepubertal onset and episodic course,

(Continued on page 10)

Life Chart Highlight

Lithium and valproate combination therapy in a 9 year-old with bipolar disorder

Nora K. McNamara, MD, Robert L. Findling, MD,
Tricia E. Robben, Kwang-Hie Park, MD, Joseph R. Calabrese, MD

It is an extraordinary opportunity to be involved with the Stanley Early Intervention Initiative. As part of our work at Case Western Reserve University/University Hospitals of Cleveland, we have begun enrolling youngsters with bipolar disorder in a 2-year study that will compare the efficacy and safety of lithium carbonate to divalproex sodium (Depakote[®], or valproate for rest of article). This trial is one of only a few randomized clinical trials in pediatric bipolar disorder (see BNN Vol. 4, Iss. 2, for an update on the comparison of lithium (Eskalith[®], Lithobid[®]) carbamazepine (Tegretol[®]), and valproate in early onset mania by Dr. Kowatch of the Dallas Center). The project is also unique in that this study is more than just a few weeks long. In the first phase of the study, youngsters (ages 5 to 17) with bipolar disorder (type I or II) are stabilized on lithium and valproate combination therapy. After mood stabilization, they are transitioned into the second phase of the study, during which only 1 of the mood stabilizers (lithium or valproate) is continued.

Having begun this study, we have seen several consistent patterns in our patients with pediatric bipolar illness. First, we have observed that most of our patients have been extremely symptomatic for years with their mood disorder adversely affecting their development, peer relations, functioning at school, and functioning within their family. In addition, families often report that the children have received treatment from numerous other professionals prior to coming to the Stanley Center. Generally, parents also note that their children with

bipolar disorder have previously received many inaccurate diagnoses and ineffective treatments. By the time we have seen the child/adolescent, families often express concern that “nothing would ever help.”

In this report, we tell the story of one patient and his family to illustrate how accurate diagnosis and appropriate treatment can change the course of a child's life. This child's name and identifying characteristics have been changed to protect his right to confidentiality.

Case Report: Mood History

Richie is a 9 year-old boy who was evaluated in September 1998 at the Case Western Reserve Stanley Center. Prior to our seeing him, Richie's mother estimated that her son had been seen by at least 10 specialists and treated with numerous psychotropic medications in a variety of combinations.

Richie's mother provided additional history. Richie was born at term. He was very colicky until he was a toddler, at which time he was noted to be moody and prone to extensive and frequent temper tantrums. He reached all of his developmental milestones early, and despite his failure to outgrow his moodiness and his tantrums, was considered to be very bright and verbal. Richie had been extremely hyperactive since toddlerhood, and was diagnosed in kindergarten as having attention-deficit hyperactivity disorder (ADHD) (see Figure 1).

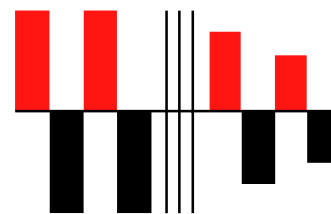
While Richie was in kindergarten, he was referred for art therapy. His symptoms did not improve, and he began to exhibit periods of very aggressive behavior that would last for days. Periods of

extreme irritability, low self-esteem, and social isolation soon became pervasive (Figure 1). He was then referred to a psychiatrist who prescribed methylphenidate (Ritalin[®]) which, in Richie's words, did “nothing.” He was then prescribed dextroamphetamine (Dexedrine[®]) with the same result. During this time, he engaged in some sexual play with older female children, and began smearing feces on the bedroom wall on a regular basis.

Initial Medication Trials

Richie's mother then took him to a second psychiatrist. Over the next two years, Richie would have trials of sertraline (Zoloft[®]), carbamazepine (Tegretol[®]), and one brief trial of valproic acid (valproate). Despite these interventions, his symptoms continued to get worse. He began to have recurrent thoughts of hurting himself, and made frequent suicidal gestures when overwhelmed. His mood symptoms became more distinct, with depressed periods lasting up to a month and manic episodes lasting 7 to 10 days (see Figure 2). He would have 8 to 10 mood switches per year. He also had many mixed episodes. His clinical deterioration continued despite aggressive case management, school interventions, respite care, and a day treatment program. Prior to coming to the Case Western Reserve Stanley Center, Richie's last psychiatrist told his mother that if Richie did not improve on carbamazepine and sertraline, he would never get any better and would be a chronic mental patient.

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Clinical effectiveness of lithium and valproate combination therapy in a nine year-old child with bipolar disorder

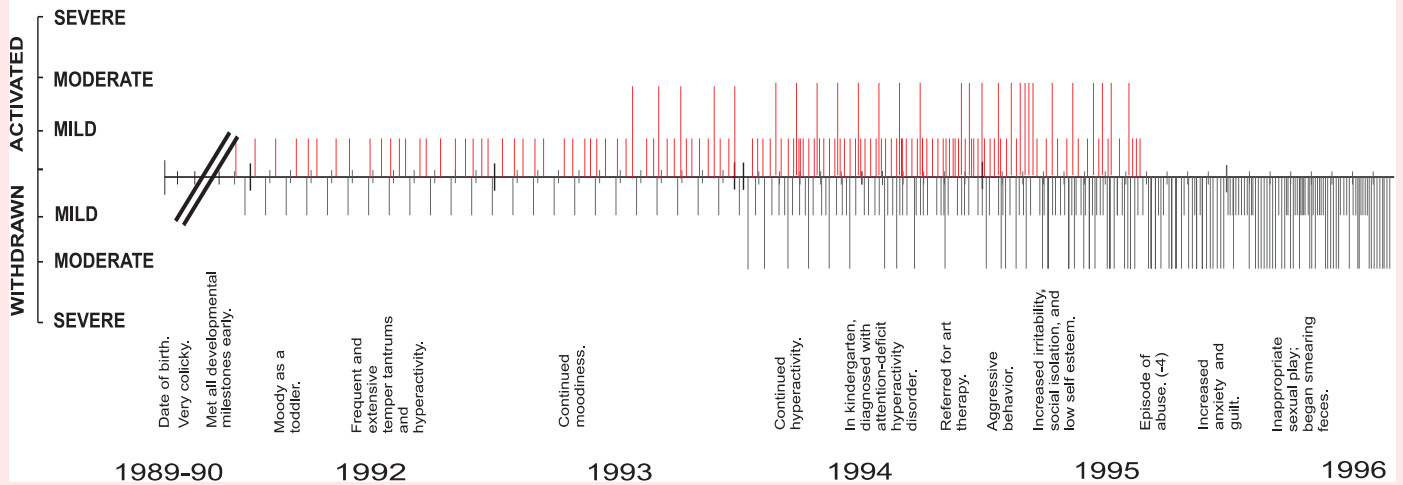


Figure 1: Richie's life chart showing moodiness, hyperactivity, inattention, aggressiveness, and inappropriate behavior prior to medication treatment.

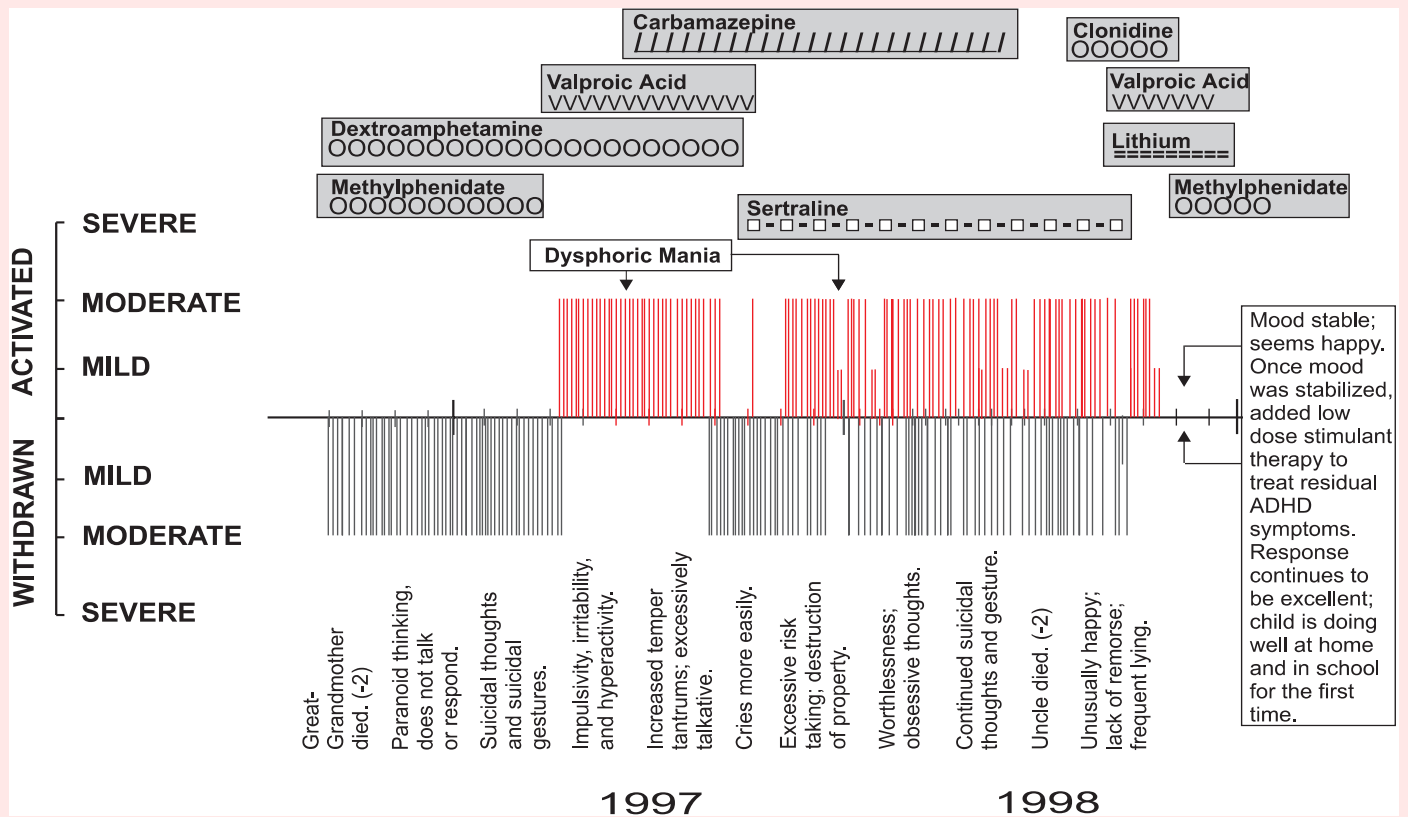


Figure 2: After several failed medication trials, Richie's treatment with lithium and valproate (1998) as part of an E.I.I. study, together with methylphenidate, stabilized his mood for the first time.

Life Chart Highlight

(Continued from page 4)

Study Entry

After a diagnosis of bipolar disorder was established, Richie was enrolled in our study. Richie's medications were tapered and then discontinued. He continued to meet diagnostic criteria for bipolar disorder type I, most recent episode manic. He began combination lithium and valproate treatment as per study protocol (Figure 2). Within 4 weeks, Richie's mood was stable. Richie's mother reported that for the first time, Richie seemed happy. Despite Richie's stable mood, he was still having difficulties at school and in social situations due to continued impulsivity, hyperactivity, and inability to concentrate. Because these were residual symptoms of ADHD, Richie was offered a therapeutic trial of adjunctive methylphenidate. Initially, Richie and his mother were both reluctant to try a stimulant again due to his

poor response in the past. We informed him and his mother that it was our experience that few patients derive robust benefit from treatment with stimulants before mood stabilization, and that almost every one of our patients with bipolar disorder and ADHD have benefited from stimulant treatment after mood stabilization. With this information, Richie and his mother agreed to a methylphenidate trial. It was subsequently found that 10 mg doses of methylphenidate were very helpful (Figure 2).

Exactly 8 weeks had passed since we had first seen Richie. His mother was ecstatic. She told the Center staff that she had never been so happy with her son before. For the first time in his life, Richie was doing well at home and at school.

Richie had some trouble accepting the need for medication. We worked with his mother on the importance of medication compliance. We also provided developmental guidance for his mother regarding the impact of a psychiatric illness on his view of himself. Richie's mother developed increased confidence in her parenting skills.

At present, Richie is doing well and is back on his normal developmental track. His mother states that he is like any other boy now. She feels that his improvement is nothing short of a miracle. Our greatest hope is that through the information learned through all of the activities of the Stanley Foundation Early Intervention Initiative (E.I.I.), more children like Richie will one day be able to get the assessment and treatment they deserve. ■

Publication Update:

Olanzapine in Treatment-Resistant Bipolar Disorder

Susan L. McElroy, Mark Frye, Kirk Denicoff, Lori Altshuler, Willem Nolen, Ralph Kupka, Trisha Suppes, Paul E. Keck, Jr., Gabriele S. Leverich, Geri F. Kmetz, Robert M. Post

Journal of Affective Disorders 49: 119–122, 1998

Introduction: Substantial clinical data suggest that the atypical antipsychotic clozapine may be effective in the acute and prophylactic treatment of some patients with bipolar disorder, including some patients inadequately responsive to treatment with mood stabilizers, electroconvulsive therapy (ECT), and conventional antipsychotics. The new atypical antipsychotic olanzapine has a pharmacologic and electrophysiologic profile similar to that of clozapine. To investigate the efficacy, tolerability, and safety of olanzapine in bipolar disorder, we reviewed the response of patients with bipolar disorder who received treatment with olanzapine at our centers for persistent affective symptoms inadequately responsive to standard psychotropic agents.

Methods: Patients with bipolar I disorder who were participating in the Stanley Foundation Bipolar Network naturalistic follow-up study and who received treatment with olanzapine for at least 1 week were included in the study. Patients were excluded if olanzapine was begun when they were euthymic or within 2 weeks before or after any other major changes in their medication regimens. Response to olanzapine was rated with the Clinical Global Impression Scale modified for bipolar disorder at two points in time: response of affective state at time of olanzapine initiation was assessed after 1 month of treatment with olanzapine; and overall response of illness was assessed at the patient's last evaluation while receiving olanzapine.

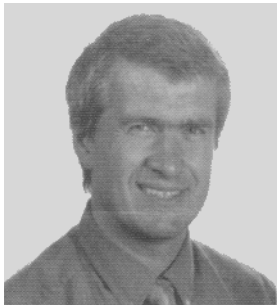
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Around the Network

The Munich/Freiburg Site in Germany

Heinz Grunze, MD, Jörg Walden, MD, PhD
Sandra Schlösser, MA

Professor Heinz Grunze at the University of Munich and Professor Jörg Walden at the University of Freiburg in Germany have entered the Network as an affiliated Site via their funding as a freestanding European Stanley Center. They are an ideal group to join the Network from a number of perspectives. They are extremely experienced in the psychopharmacology (both clinical and basic) of the routine and novel mood stabilizers and have examined the unique mechanisms of action of nimodipine and related calcium channel blockers on calcium dependent models of seizures as well as their clinical efficacy in bipolar illness. Additionally, they are studying the newer anticonvulsants and have conducted trials of the GABA-active agents gabapentin (Neurontin®) and gabapril (Tiagabine®).



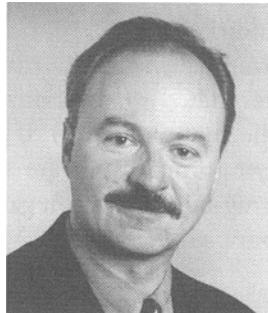
Prof. Heinz Grunze

Dr. Grunze received his medical degree in 1986 after studying in Aachen, Germany, as well as in England at Oxford and London. After a research fellowship in psychiatry at the Max Planck Institute in Germany he was a research fellow from 1993 to 1995 in the Department of Psychiatry at Harvard Medical School in Cambridge, Massachusetts. His major research interests include neuroendocrinological changes in depression and schizophrenia, electrophysiological investigations of the effects of

antiepileptic drugs in vitro as well as clinical studies of the neurobiology of schizophrenia and bipolar disorder. One of the clinical studies was done in collaboration with Professor Walden, looking at prophylactic efficacy of nimodipine (Nimotop®), carbamazepine, (Tegretol®) and lithium.

Dr. Walden studied medicine and psychology at universities in Germany as well as in England. He received his M.D. degree in 1984, his doctoral degree in physiology in 1989, and his doctoral degree in psychology in 1994. He completed residencies at the universities of Essen and Freiburg, with a specialty in psychiatry in 1994, and received his professorship in psychiatry at the University of Freiburg in 1995. He and Dr. Grunze have won several awards for their research and clinical work and both shared a Stanley Foundation research award for studies on the clinical efficacy of calcium agonists in psychiatry.

Sandra Schlösser, who had previously been working with both doctors as a research assistant, joined them as a master's degree psychologist in their longitudinal studies in bipolar disorder following their appointment as a free standing European Stanley Center in 1998. In her role as coordinator of the Stanley Foundation studies in the affective disorders at the Ludwig-Maximilians-University of Munich, Ms. Schlösser recently spent



Prof. Jörg Walden

2 weeks at the Bethesda Site to be trained in Network methodology. She received certification as a highly reliable rater on all Network assessment tools, including the life chart method, and will be instrumental in implementing some of our Network protocols at the Munich/Freiburg Site in Germany. She has taken the lead in a collaborative effort to translate all Network forms into German and is in the process of submitting the AD-1 Network protocol for a blind randomized comparison of sertraline (Zoloft®) and venlafaxine (Effexor®) (bupropion is not yet available in Germany). They are also interested in participating in the double-blind evaluation of omega-3 fatty acids, a Network protocol about to be launched.



Sandra Schlösser

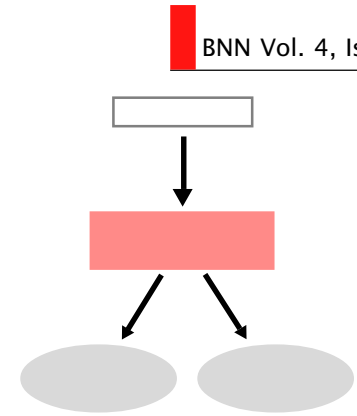
We very much look forward to this and other European Stanley Centers filling an increasingly important role in the acquisition of new patients for more rapid completion of Network protocols. In this fashion, critical information from a large number of patients can be collected on the relative acute and long-term efficacy of medications so that a better clinical knowledge base can be created for more effective treatment of bipolar disorder. ■



GERMANY

Network News Briefs

The Bipolar Network Protocol Flow Chart



As illustrated in the flow chart on page 9, the 8 randomized clinical trials currently available in the Network are designed to answer a number of clinically important questions. If patients are starting lithium prophylaxis they will be offered the opportunity to be randomized to augmentation with levothyroxine sodium (T_4) to see if this will improve outcome over lithium alone. If they enter a depressive episode they are eligible for the double-blind antidepressant trial-1 (AD-1) comparing bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®) (see p. 1). Partial but inadequate responders to any antidepressant are offered a randomized comparison of triiodothyronine (T_3) augmentation versus the psychomotor stimulant methylphenidate (Ritalin®) in AD-2 (bottom left, p. 9).

Those failing to respond to AD-2 are offered a randomized comparison (AD-3) of the putative mood stabilizer lamotrigine (Lamictal®) versus the monoamine oxidase inhibitor tranylcypromine (Parnate®), which has an excellent record of response in bipolar depression (Himmelhoch et al., 1991; *Am J Psychiatry* 148: 910-916). Those depressed patients (as well as those in a manic episode or those who are cycling) who fail to respond adequately will be offered the blind, randomized evaluation of augmentation with omega-3 fatty acids (6 grams) compared to placebo for 4 months, with all patients offered an additional 8 months of open treatment with omega-3 fatty acids if so desired (bottom right, p. 9).

If patients require a major tranquilizer, we will compare the atypical neuroleptics olanzapine (Zyprexa®) and quetiapine (Seroquel®) for efficacy and side effects. If cycling patients require the addition of a new putative mood stabilizer, gabapentin (Neurontin®) will be compared to topiramate (Topamax®) (bottom right, p. 9). If patients are not symptomatic but are struggling with drug-induced weight gain, we will compare sibutramine (Meridia®) with

topiramate (top left, p. 9). Sibutramine is a recently approved dietary aid that blocks the re-uptake of all three major neurotransmitter amines (serotonin, norepinephrine, and dopamine). Its efficacy and tolerability in bipolar patients has not previously been studied. ■

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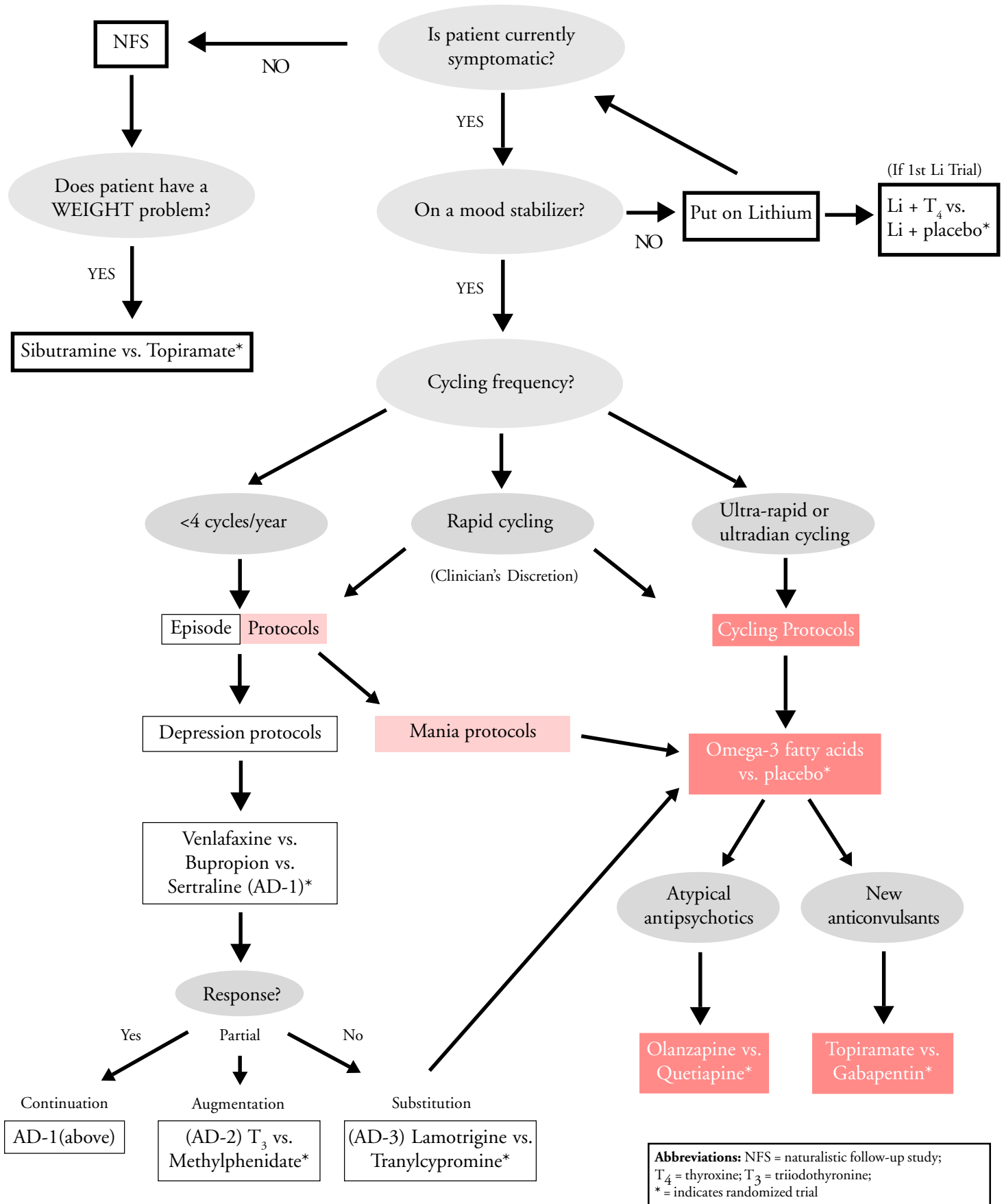
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Bipolar Network Protocol Flow Chart



Meeting Highlight: ARNMD

(Continued from page 3)

temporal association of symptom exacerbation to strep infections, and associated neurological abnormalities. Promising new data on therapeutics suggests that both antibiotic treatment and immunoglobulin treatment may be helpful in patients with PANDAS.

Dr. Robert Post, MD, “Bipolar Disorder/Kindling and Pharmacologic Implications.” Dr. Post presented new data from the Stanley Network on how early life experiences impact the unfolding of bipolar disorder, including data that show that patients with physical abuse have a higher incidence of worsening mania, and patients with sexual abuse have increased suicidality. These severe early stressors (physical/sexual abuse) were associated with an earlier onset of bipolar illness and a higher incidence of ultra-rapid and ultra ultra-rapid (ultradian) cycling. Preclinical data in a rodent model of maternal separation suggest that some of these effects may be associated with stress-induced alterations in neurotrophic factor gene expression and subsequent long-term changes in the regulation of endocrine and stress-reactive behavior.

Dr. Carol Tamminga, MD, “Neurobiology of Schizophrenia.” Dr. Tamminga reviewed new evidence of glutamate involvement in schizophrenia, using glutamate blockers (such as the anaesthetic ketamine) as probes of this illness. This work and the work of others in this area has led to possible therapeutic approaches to psychosis by facilitating a glycine modulatory site of the glutamate receptor.

Dr. William Bunney, MD, “Neuropathological Abnormalities in Schizophrenia.” Dr Bunney reported that in the dorsolateral prefrontal cortex of schizophrenic patients, 3 neuronal markers of the neural subplate show significant alterations in their anatomy. He suggested that schizophrenia may be associated with several factors related to faulty neuronal migration.

Dr. Jack Gorman, MD, “Neurobiology of Anxiety Disorders.” Dr. Gorman presented exciting new data on the neurobiology of the anxiety disorders, indicating important roles for serotonergic transmission and the possible involvement of corticotropin-releasing hormone (CRH) in stress sensitivity and fear conditioning. CRH receptor antagonists will be available for clinical studies in the near future and all are anticipating their potential therapeutic application in a variety of syndromes.

Dr. Steve Goldman, MD, PhD, “Neural Progenitor Cells of the Adult Human Brain: Their Identification, Isolation and Use.” Dr. Goldman reported on the culturing of neuroprogenitor cells from the subependymal zone of the ventricular lining. These cells are pluri-potent and can develop into either neurons or glia, and hold promise for the ultimate ability to repair brain dysfunction.

Thus a tremendous body of knowledge was reviewed in the two days of the ARNMD meeting, leaving one with the impression of considerable progress in understanding some of the neural pathways to the major psychiatric illnesses and many avenues of exploration for new approaches to therapeutics. ■

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Publication Update: Olanzapine

(Continued from page 6)

Results: Fourteen consecutive patients with bipolar I disorder treated with olanzapine and meeting the inclusion criteria were identified. Eight (57%) patients were evaluated prospectively and six (43%) were evaluated retrospectively. Thirteen patients had received prior treatment with an antipsychotic other than olanzapine. Olanzapine was added to pre-existing psychotropic regimens in all but one patient. Olanzapine was begun in all patients at 5–10 mg/day, usually given all at one dose at night. Olanzapine doses were subsequently increased by 5–10 mg/day every 7–14 days according to patient response and side effects to a maximum dose of 30 mg/day. At their last evaluation, 8 (57%) of the 14 patients were rated as much (n=6) or very much (N=2) improved, after a mean \pm S.D. (range) of 117.4 ± 46.8 (57–217) days of treatment with a mean \pm S.D. (range) olanzapine dose of 15.2 ± 6.7 (7.5–30) mg/day. Olanzapine was generally well tolerated; one patient discontinued the drug due to bad dreams. No patients developed extrapyramidal symptoms or required concomitant anti-parkinsonian agents.

Conclusion: These preliminary observations are limited by several methodologic shortcomings: (1) data were obtained nonblindly and without a randomized control group; (2) in all but one patient, olanzapine was added to ongoing psychotropic regimens; and (3) formal rating scales for extrapyramidal side effects were not used. However, even when these limitations are considered, the response observed in 57% of patients with treatment-refractory bipolar disorder is promising. ■

NIMH Recruitment

Repeated Transcranial Magnetic Stimulation (rTMS) and Patients with Depression

The NIMH Site continues to need volunteers (18 years or older) with a diagnosis of unipolar or bipolar depression who wish to participate in studies evaluating the comparative efficacy of high (20 Hz) and low (1 Hz) rTMS vs. sham rTMS (all patients will receive both active forms of rTMS [20HZ and 1 Hz] during the study). We continue to observe differential effects on mood and brain activity with low versus high frequencies of rTMS, and are attempting to ascertain which patients respond best to which frequencies. A new study at a higher intensity of stimulation (110% of motor threshold as compared to the current study set at 100%) will test 3 weeks of 1 Hz vs. 20 Hz rTMS vs. sham over the left frontal cortex in the future. Each patient will have an opportunity for another 3 weeks of continued rTMS if they respond, or they can cross over to the other frequency should they fail to respond in the first phase. If you are interested in the rTMS study, please call Nadine Khoury or Dr. Andy Speer at (301) 402-2294.

Six-Week Comparison of Lamotrigine, Gabapentin and Placebo

The NIMH Site also continues to recruit bipolar patients with affective disorders who have not been treated with gabapentin or lamotrigine so that we can continue to examine the efficacy of these agents compared with placebo, and establish potential clinical and biological predictors and correlates of response. Currently, the data suggest that lamotrigine monotherapy is more effective than that of gabapentin or placebo. However, many of the add-on trials in bipolar illness with gabapentin show it to be effective, and the overall clinical utility of this agent remains to be further delineated. If you are interested in pharmacological intervention with lamotrigine and gabapentin, please call Dr. Robert Dunn at (301) 402-2293 or Gabriele Leverich, MSW, at (301) 496-7180.

Survey: Early Symptoms Preceding A Diagnosis Of Childhood Affective Illness

Parents whose children ages 4–16 have been diagnosed with (1) **bipolar disorder**, (2) **unipolar depression**, or (3) **no psychiatric diagnosis** (children doing well in school, social, and family environments) are encouraged to participate in a retrospective survey to better define the earliest symptoms of these affective illnesses (1 and 2) compared with non-ill controls (3). This survey, which would be mailed to you, will take approximately an hour or more to complete—depending on your child's age and symptoms experienced—and will provide the Network with very important preliminary data about the early presentation of childhood affective disorders, which can then be further validated and pursued in more detail in prospective studies.

We thank all those who have already contributed to this study, the results of which will be reported. However, it now appears that we will need a substantially larger number of parents who have children with major depression in order to draw more definitive conclusions about what early behaviors are most typical of childhood onset bipolar versus unipolar illness. We hope you can contribute to this effort. Please contact Emily Fergus at the following address or phone number to participate: 5430 Grosvenor Lane, Suite 200, Bethesda, Maryland 20814 (phone: (301) 496-6827; fax: (301) 402-0052; e-mail: emily.fergus@nih.gov).

Clinical Trials Update

(Continued from page 2)

nia and three anticonvulsants for epilepsy) preliminarily explored in open Network trials appears to have promising utility in different aspects of bipolar disorder. We are very pleased that a range of options beyond lithium, valproate, and carbamazepine are now being studied, potentially allowing for better differential targeting of symptoms and side effects in bipolar illness.

Omega-3 Fatty Acids

The double-blind, randomized evaluation of omega-3 fatty acids (6 grams) versus placebo will be a leading protocol effort for 1999. The initial phase of the trial is 4 months of adjunctive double-blind treatment with either omega-3 fatty acids or placebo. Nonresponders will be offered an open 8-month extension of the trial so that all patients will have the opportunity to be on active drug treatment for at least 8 months. ■

Visit the Stanley
Foundation
Bipolar Network
World Wide Web Site
at:

www.bipolarnetwork.org

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Bipolar Network News

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In This Issue:

1998: The Year in Review
Treating Childhood Bipolar Disorder
ARNMD Meeting Highlights
Affiliated Site in Germany
