

CLINICAL TRIALS UPDATE

**E.I.I. Consortium Meeting
Current E.I.I. Studies
High Risk-Early Treatment Study**

The first formal meeting of the Stanley Foundation Early Intervention Initiative (E.I.I.) Consortium was held March 18, 1998, in Bethesda, Maryland, and was attended by investigators and grantees from a variety of Stanley-supported sites and Centers interested in the diagnosis and treatment of early-onset bipolar illness. The representatives from their respective sites were: Dr. Kiki Chang from the Stanford Center, headed by Dr. Terence Ketter; Dr. Mark Frye from Dr. Lori Altshuler’s site at UCLA; Dr. Robert Kowatch from the Dallas Center, headed by Dr. John Rush; Dr. John Zajecka and colleagues Patti Meaden, Helen Jeffriess, and Earlene Strayhorn from the Chicago Center, co-chaired by Dr. Jan Fawcett; Drs. Susan McElroy and Cesar Soutoulo from the Network site in Cincinnati; Dr. Robert Findling from the Cleveland Center, headed by Dr. Joseph Calabrese; Dr. Marcia Slattery from the Mayo Clinic; Dr. Robert Post, Dr. Andy Speer, and Gabriele Leverich from the Bethesda site and Center; and Dr. Willem Nolen from the Network site in Utrecht, Netherlands.

At the meeting, the consistent use of a core group of common rating instruments across the various Stanley Centers, Network Sites, and affiliated academic programs was reaffirmed, including: 1) the Kiddie-Schedule of Affective Disorders and Schizophrenia (K-SADS) for overall diagnostic purposes; 2) the retrospective and prospective Kiddie-Life Chart Method (K-LCM) for mapping the evolution of affective symptoms and their response to treatment; 3) the Young Mania Rating scale; 4) the Inventory of Depressive Symptoms (IDS) (because of the availability of a self-rated as well as a clinician-rated depression scale); and 5) the revised Clinical Global Impressions scale for Bipolar Illness (the CGI-BP) for assessing the global magnitude of clinical improvement on any given treatment regimen.

Ongoing Child and Adolescent Studies

Dr. Robert Kowatch reviewed the results of the first randomized comparison of 3 different mood stabilizers in childhood- and adolescent-onset bipolar illness. In his 6-week randomized open trial, he found a 56% response rate to divalproex sodium (Depakote®), a 29% response rate to carbamazepine (Tegretol®), and, surprisingly, only a 17% response rate to lithium. Even in the responsive patients, he found that in the continuation phases of treatment

over the next 6 months, almost all patients required combination therapy in order to achieve adequate mood stabilization, and the majority of patients also required stimulant augmentation of the mood stabilizers for treatment of their comorbid attention deficit hyperactivity disorder (ADHD) symptoms. He noted that if patients were not mood-stabilized first, then the stimulants could escalate the mood and behavioral fluctuations. He also found better responsivity in patients with more discrete episodes in contrast to the patients with more extreme mood lability and ultra-rapid cycling.

Dr. Robert Findling has been conducting a double-blind study of methylphenidate (Ritalin®) vs. placebo in children and adolescents, with the option of being on a mood stabilizer as well. Twelve of 13 of these children completed this study successfully. Dr. Findling reviewed some of the preliminary results of his study showing a high prevalence of comorbidities in children and adolescents thus far, including: 40/49 (81%) with ADHD; 20/50 (40%) with conduct disorder; 40/50 (80%) with oppositional-defiant disorder; and almost none with formal anxiety disorders. He also plans a study of valproate vs. placebo in children treated with paroxetine (Paxil®).

Dr. Findling’s group has compiled retrospective LCM data on 50 children. He reported that these children averaged 4.5 mood cycles per year, and the number of cycles experienced increased with age. Many of these children are very irritable and are chronically hypomanic. Beginning in July, Dr. Findling will start a new study—an extension of the adult studies of Dr. Calabrese—directly comparing lithium and valproate for four months.

Dr. Willem Nolen reported that in contrast to the U.S., in the Netherlands there is very little treatment of ADHD with the psychomotor stimulants amphetamine (Dexadrine®, Adderal®), Ritalin, or pemoline (Cylert®). He also observed a very low incidence of early-onset bipolar illness with rapid and ultra-rapid

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cycling patterns, and raised the question of whether these two phenomena were related. That is, was the use of psychomotor stimulants in bipolar patients with comorbid ADHD in the U.S. actually exacerbating the underlying mood disorder and accelerating mood cycling? Most investigators in the U.S. now believe childhood bipolar illness should be treated with a mood stabilizer first, and then a stimulant can be safely added. However, the threshold for reaching a formal diagnosis of bipolar illness in children, even with extreme mood fluctuations and major associated dysfunction, appears to be artificially set much too high.

Bipolar Network News

Editors-in-Chief:

Robert M. Post, M.D.

Gabriele S. Leverich, M.S.W.

Production & Design:

Chris Gavin

The *BNN* is published four times a year by the Stanley Foundation Bipolar Network, an international group of individuals with bipolar disorder together with their mental health care providers who participate in research studies investigating the long-term course of bipolar disorder. The goal of the Network is to improve the understanding of bipolar disorder and develop better treatment strategies to manage this illness.

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

Bipolar Network News

c/o Stanley Foundation Bipolar Network

5430 Grosvenor Lane

Suite 200

Bethesda, MD 20814

Telephone: (800) 518-SFBN (7326)

Fax: (301) 571-0768

Internet address:

stanley@sparky.nimh.nih.gov

High Risk-Early Treatment Study

The Bethesda Center is coordinating the first randomized High Risk-Early Treatment Study (HR-TS) in an attempt to prevent the onset of full-blown illness in children at very high risk for affective disorders. Children with a high genetic loading for affective illness—that is, with affective illness in both parental lineages (with at least one bipolar)—will be eligible for the study. The onset of first significant symptoms that could be indicative of a future affective disorder (even before a diagnostic threshold is reached) will allow the patients to be entered into this medication trial. The trial will be a comparison of valproate versus careful monitoring with a placebo pill. If symptoms do not improve in either the valproate or placebo arm of the study, patients will be offered an additional intervention with either lithium or gabapentin (Neurontin®). Lithium is clearly the best-studied intervention for adult affective illness, with a modicum of data indicating its efficacy in children. There is only preliminary evidence of the efficacy of gabapentin in adults, but its excellent safety record with few side effects, and clinical case studies suggesting efficacy in children, would appear to justify its early use in comparison to lithium in this trial.

The main outcome measures of the HR-TS will be to assess whether valproate is able to prevent the development of full-blown illness and whether it decreases the need for adjunctive treatment with lithium or gabapentin. Another outcome measure will be whether valproate decreases the need for stimulant augmentation in order to treat the potential associated ADHD that accompanies affective illness in a high proportion of children with early onset bipolar illness. The HR-TS will also provide the first evidence of comparative efficacy of lithium versus gabapentin (either as monotherapy or as an adjunct to valproate) in childhood onset bipolar illness.

The unique perspective of this study is that only children at very high risk for bipolar illness (by virtue of the potential of genetic vulnerability passing through both sides of the family [bi-lineal]) would be treated this early. The high benefit-to-risk ratio makes a strong case for attempting early intervention. In most children with early symptoms in the general population, it is very unlikely that these symptoms will progress to more full-

blown affective episodes of such severity and duration that they meet full criteria for mania or depression, and, therefore, intervention with medication might not be warranted. In contrast, in this study, a high percentage of children are expected to ultimately experience more major affective dysfunction because of the genetic vulnerability potentially conveyed from both sides of the family, therefore justifying more aggressive early intervention in order to attempt to prevent the illness.

This protocol is only in its early stages of design and has not yet been submitted for approval by the appropriate institutional review boards and other review panels. Therefore, it is not likely to be available for active patient recruitment and randomization to treatment for approximately one year. However, we are very interested in acquiring a list of names of families with affective illness on both sides who might be interested in seeing whether early intervention with medication would assist in their children's early symptoms. Please write or phone (see box below) if you might be interested in enrolling your children after receiving more detailed information about the study outlined here. ■

Future E.I.I. Protocol Interest

Children whose parents both have affective illness (at least one bipolar) are being sought as potential candidates to enter a clinical trial to determine if treatment instituted at first symptoms can prevent the development of full-blown illness. Valproate (Depakote®) will be compared to placebo with careful monitoring. Those showing no improvement will be offered open treatment with either lithium or gabapentin (Neurontin®).

Protocol enrollment will not be possible for 6 months to 1 year, but for more information or to request to be on the registry of families with affective illness on both sides, please call Emily Fergus at (301) 496-6827, or write to: E.I.I., c/o Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814.

LETTERS TO THE EDITOR

A reader responds to the note in BNN
Vol. 4, Issue 1, March 1998:
"Caution for patients starting lamotrigine:
go slowly"



The BNN welcomes all letters from our readers, and will print responses to those we feel would be of interest to the Network.

Dear Editor:

Since a family member has had to deal with bipolar depression for over 25 years, I have more than a passing interest in the subject. So in your most recent issue of your newsletter, I took particular note of the grey box on page 8 titled: "Caution for patients starting lamotrigine: go slowly."

This is not a medication with which I have any knowledge. However, I could not ignore the statements, "5–10% incidence of a rash", and "1 in 500 instances the rash can proceed to a very severe, life-threatening form where the skin starts to slough off." Obviously this medication must be deemed to be worth the risk.

But I wonder. I wonder at the increase of incidence of bipolar depression here in Canada (this is not attributed simply to better diagnosis of the illness). And I wonder at research being so unidirectional.

I have seen the marked improvement when my relative stays away from nicotine, caffeine, alcohol, and even sugar. Yet when any word of this type of "treatment" reaches the media, accepted wisdom says there is no proof. And it's so blatantly dismissed as a "health-food" fad that I wonder if we will ever see serious research in that area.

We would undoubtedly hear that to limit diet and life-style is to infringe on the free will of the patient. It appears it's so much easier to prescribe a medication that can cause one to lose skin and face possible death.

This is truly a case of the inmates running the asylum.

- BNN reader

The BNN replies:

Thank you for your letter to the *BNN*. You raise a series of important issues for discussion.

First, you wonder whether the increased incidence of bipolar depression in Canada (and elsewhere) is not simply attributable to better diagnosis of the illness. There seems to be a generational or "cohort" effect across most countries in the world, i.e., in every generation since World War I the incidence of the illness has increased and the age of onset of the illness has decreased. The reason for this effect occurring in both unipolar and bipolar illness is, however, not well understood.

You comment about the unidirectionality of research, and that you have seen marked improvement when your relative stays away from nicotine, caffeine, alcohol, and even sugar. We only wish that this were the case for the vast majority of patients with unipolar and bipolar illness who have typically tried these and a large variety of other dietary and psychosocial manipulations in an attempt to prevent what can be a devastating illness. Clearly, trying things that are not only safe but also healthful, such as avoiding nicotine and alcohol and increasing exercise, etc., can be tried even without much evidence of efficacy because of their apparent safety.

However, one needs to be reminded that the health food/amino acid L-tryptophan was widely used for its effects on mood and sleep, and yet was found about a decade ago to be contaminated with a substance that caused a serious and life-threatening immunologic illness called eosinophilia-myalgia syndrome for which there is no adequate treatment. Moreover, when one's budget, in health-related dollars in particular, is being spread so thin, it seems that one would want to have some systematic evidence of efficacy of a given treatment before one spent considerable amounts of money on what later

could turn out to be just a health-food fad without demonstrated efficacy.

As cited in previous issues of the *BNN* (Vol. 3, Iss. 4, 1997; Vol. 4, Iss. 1, 1998), there have been new data from controlled studies of the potential benefits of some dietary supplements that are available in health food stores, such as omega-3 fatty acids and inositol. Dr. Stoll and colleagues recently presented a study at the 1997 ACNP meeting indicating that 9 grams of omega-3 fatty acids per day was much more effective than an olive oil control in a small but highly-controlled randomized, double-blind study of bipolar patients. Similarly, a number of well-controlled double-blind studies indicate the potential antidepressant and antianxiety effects of inositol (12 to 18 gms/day) in the studies of Belmaker and associates and others. The Stanley Foundation Bipolar Treatment Outcome Network will soon begin a study to assess the degree of long-term efficacy of the omega-3 fatty acids in a large number of patients. Both omega-3 fatty acids and inositol are quite expensive, and we as physicians and clinicians, as well as our patients, wish to know just how effective these agents might be in different kinds of symptoms and patients.

In this issue we report the possibility of maintaining sleep deprivation-induced mood improvement in depression with a sequential phase change in the time of returning to sleep (see "Meeting Highlights"). Thus, we are willing to report, support, and study both dietary and other psychosocial manipulations that might be helpful to our patients, but feel that they should know the risks and benefits involved as well as the potential likelihood for success.

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LIFE CHART HIGHLIGHT

Acute antimanic response to olanzapine in a patient with recurrent psychotic depression



The patient represented in this Life Chart (Figure 1) is a 26 year-old single white male with a history of recurrent psychotic depressions and full-blown manic episodes. The first manic episode occurred in 1992 at age 20; the second, in 1995, was associated with tapering of paroxetine during lithium treatment. Lithium had appeared to attenuate the severity of manic and depressive episodes, but even when lithium was combined with valproate and perphenazine (Trilafon®), the patient continued to have moderate episodes breaking through prophylaxis. The patient had a brief trial of adjunctive risperidone (Risperdal®) to lithium and valproate treatment, with only mixed success.

At the National Institute of Mental Health (NIMH), after suffering from a full-blown manic episode requiring seclusion, the patient had a good response to treatment with the atypical neuroleptic olanzapine (Zyprexa®) (Figure 2).

This rapid acute response to olanzapine in full-blown mania is similar to the response reported in the double-blind, placebo-controlled trial of olanzapine compared with placebo of Dr. Maricio Tohen at the 1997 ACNP Meeting (see “Meeting Highlights”, *BNN* Vol. 4, Issue 1). Thus as typified by this patient, olanzapine, which is approved for use in the treatment of acute schizophrenia, appears to have acute antimanic efficacy both in large controlled trials and in more open clinical observations when used as an adjunctive treatment. Dr. Susan McElroy (of the Stanley Network) et al. recently reported a good response in 8 of 14 patients (57%) to this agent (McElroy et al., 1998, *J Affect Disord* 49: 119–122). These responses were sustained in follow-up; whether olanzapine is useful in long-term prophylaxis remains to be determined. Olanzapine and other atypical neuroleptics (with the exception of clozapine) have reportedly exacerbated mania in several patients.

Table 1A outlines a series of atypical neuroleptics approved or about to be approved for the treatment of acute schizophrenia. Most U.S. psychiatrists would encourage the use of atypical neuroleptics in preference to the typical ones because of their unique side-effects profiles in comparison to the other agents.

The older major tranquilizers were called neuroleptics (or typical neuroleptics) because of their proclivity to produce side-effects similar to those experienced by patients with parkinsonism. Symptoms of Parkinson’s disease include motor slowing, tremor, and rigidity based on a deficiency of dopamine. The neuroleptics block dopamine receptors, resulting in a functional deficit of dopamine activity or a drug-induced mild parkinsonism in many instances. The older neuroleptics block dopamine receptors in the areas of brain involved with motor functioning (the striatum) as well as those that regulate mood (the mesolimbic system, including frontal cortex, amygdala, and nucleus accumbens).

The newer neuroleptics are considered “atypical” because they have weaker effects on the striatal systems involved in motor side-effects, while having equal or better antipsychotic efficacy. The classical atypical neuroleptic is clozapine (Clozaril®) which has an even higher response rate in bipolar and schizoaffective patients than in schizophrenia. However, clozapine’s use is complicated by the need for weekly blood monitoring, because in a small percentage of cases, white blood cell counts are significantly suppressed (agranulocytosis), a potentially fatal medical complication. In contrast to clozapine, neither olanzapine nor any of the other atypical neuroleptics have this liability.

Clozapine appears to have a positive motor side-effects profile and may be an effective treatment of tardive dyskinesia (an adverse effect of antipsychotics consisting of abnormal, involuntary, or irregular move-

Olanzapine (Zyprexa®) is an antipsychotic agent in the thienobenzodiazepine class. In controlled clinical trials, olanzapine was found to improve both positive and negative symptoms.

ments). It is likely that the risk of tardive dyskinesia will be considerably lower with the atypical neuroleptics compared with the typical agents. Because the atypicals do not cause the same degree of acute parkinsonian side effects or (hopefully) the longer-term risks of tardive dyskinesia, and bipolar patients are particularly prone to these side-effects, the atypical drugs should be increasingly utilized in preference to the older agents.

Olanzapine is generally well tolerated with a modicum of anticholinergic side effects (i.e., dry mouth, blurry vision, constipation, and a low to moderate incidence of weight gain [quite problematic in certain patients]). This patient experienced very few side-effects on olanzapine, but did slide into a mild to moderate depression characterized by increased sleep (hypersomnia of approximately 10 hours/night) and morning lethargy. Because of this and in light of prior inadequate response to other, more conventional mood stabilizers, the patient and his family agreed to further evaluation of his possible responsiveness to the putative anticonvulsant mood stabilizers lamotrigine and gabapentin in a randomized, double-blind comparison with placebo.

The possible antidepressant and mood stabilizing effects of olanzapine and other atypical neuroleptics (excluding clozapine) remain to be further evaluated in bipolar patients, as does their ability to prevent recurrent episodes of mania and depression. Nonetheless, the good response to olanzapine in approximately 50% of manic patients compared with only 25% on placebo (see “Meeting Highlights”, *BNN* Vol. 4, Issue 1) suggests that it is likely to occupy an important place in therapeutics when treating patients with refractory bipolar illness. ■

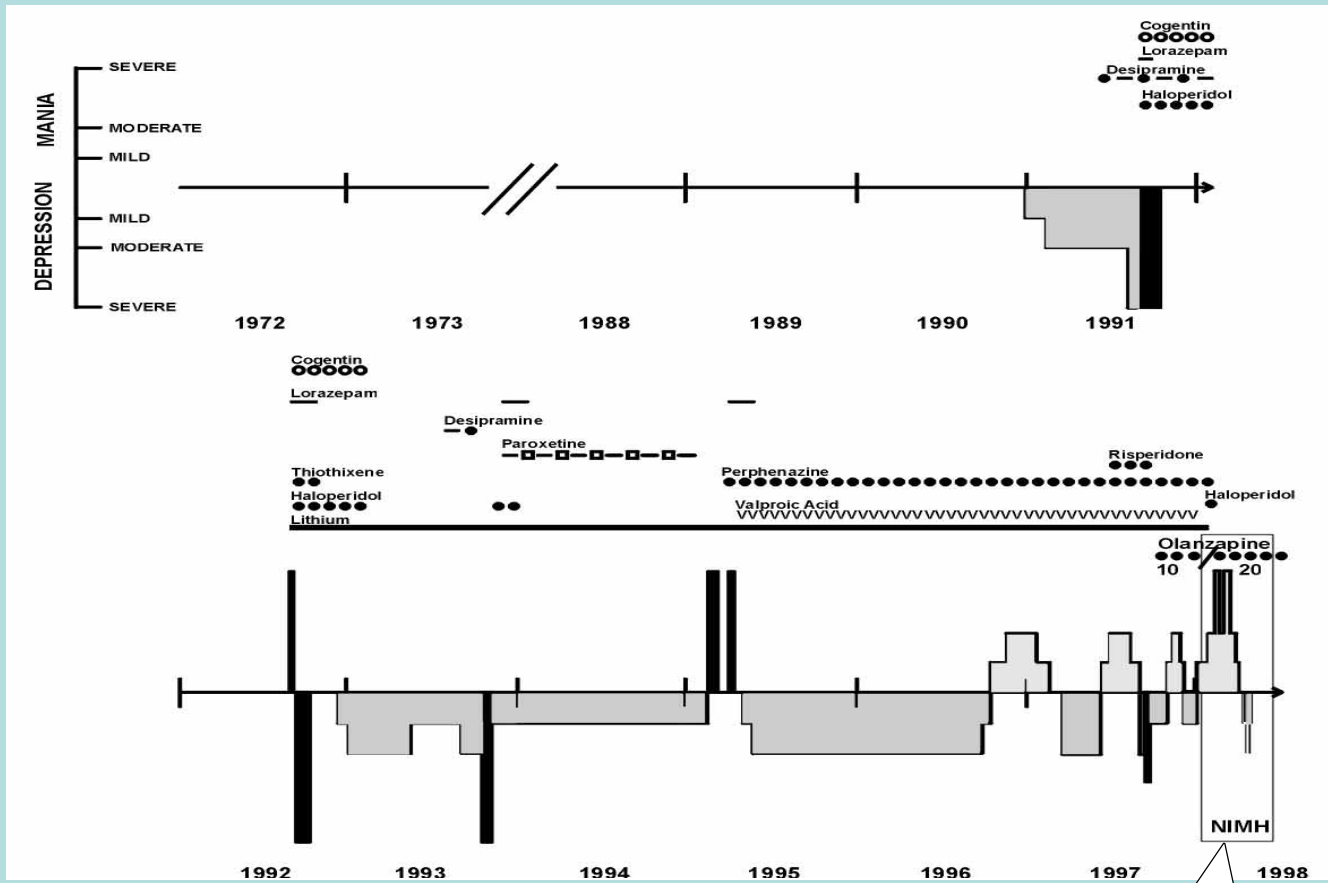


Figure 1: Lack of adequate response to lithium, valproate, and neuroleptics

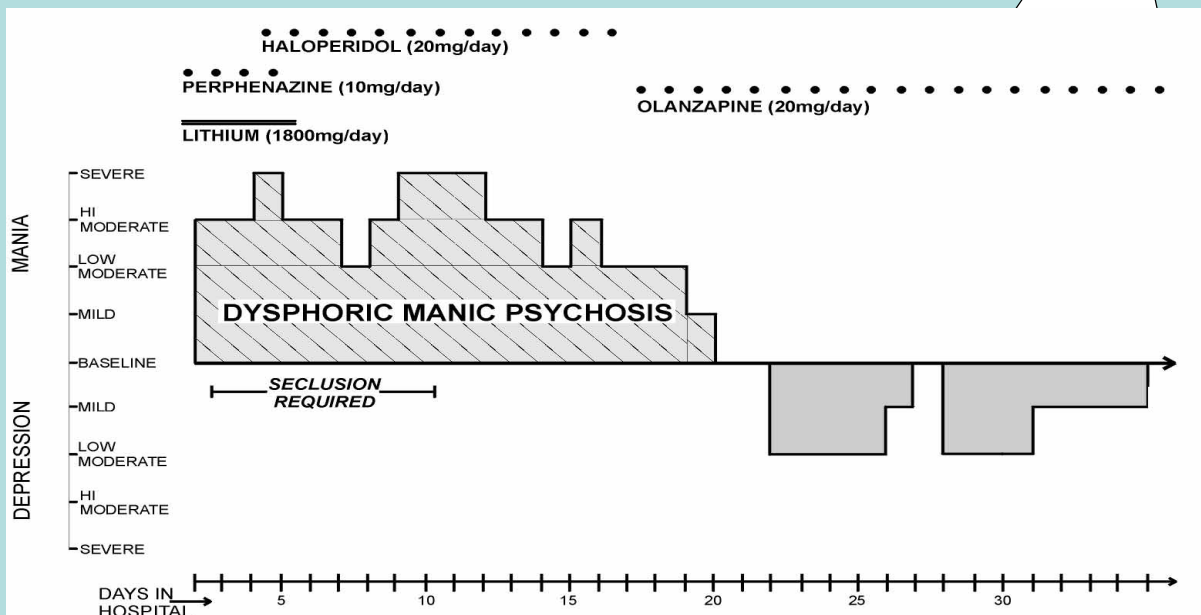


Figure 2: Possible antimanic response to olanzapine

Table 1A
New Atypical Neuroleptics

Drug (Database) (Trade Name) (Dose Range in mg)	Mechanism	Assets (+)	Liabilities (-)	Comment	Relative CPZ Equiv.
Risperidone (+) (Risperdal) (2 - 10)	↓ D ₁ (++) ↓ D ₂ (++++) ↓ 5HT ₂ , α ₁ , α ₂	+ Few EPS in low doses	- EPS in ↑ doses - ?Antimanic - Hypotension - ↑ Prolactin - Tachycardia - Sexual dysfunction	•Reports of exacerbation of mania with doses over 6–8 mg/day •Can ↑ OCD	1.5
Clozapine (+++) (Clozaril) (300 - 900)	↓ D ₁ (++) ↓ D ₂ (++) ↓ D ₄ , 5-HT ₂ ↓ α ₁ , α ₂ ↓ H ₁ , M ₁	+ No risk of tardive dyskinesia + Well studied and effective in dysphoric mania and rapid cycling	- Weekly blood monitoring - Sedation - Hypotension - Sialorrhea - Weight gain - Seizures	•Blood monitoring for agranulocytosis inconvenient and expensive •Do not exceed ↑ 50 mg every 2 days •Can ↑ OCD •5-HT block 10 times > D ₂ block	100
Trimipramine (±)?? (Surmontil) (50 - 300)	↓ D ₂ , D ₄ ↓ M ₁	+ Proven antidepressant	- Sedating - Unproven antipsychotic properties	•D ₂ , D ₄ blocker and antidepressant •?Mood stabilizer	
Olanzapine (+) (Zyprexa) (7.5 - 20)	↓ D ₁ (+++) ↓ D ₂ (+++) ↓ D ₃ , D ₄ , 5-HT ₂ ↓ α ₁ , α ₂ ↓ H ₁ , M ₁	+ No blood monitoring + Proven antimanic + Less EPS	- Sedation - Weight gain - Nausea/dyspepsia - Orthostatic hypotension	•Most similar biochemical profile to clozapine •Most widely used atypical	4
Quetiapine (Seroquel)	↓ D ₁ (+) ↓ D ₂ (++) ↓ α ₁ ↓ H ₁ , M ₁	+ No ↑ prolactin	- Somnolence - Alopecia - Constipation - Weight gain - Hypotension	•Limbic selective •Few anticholinergic side effects	100
Ziprasidone (Zeldox)	↓ D ₁ (+) ↓ D ₂ (++++) ↓ 5HT ₂ , α ₁ ,	+ No weight gain	- Somnolence - Dizziness - Nausea - Hypotension		50

Abbreviations: D₁, D₂, D₃, D₄ = Dopamine receptors; 5-HT = serotonin; α₁, α₂ = alpha receptors; H₁ = histamine receptors; M₁ = muscarinic receptors; EPS = extrapyramidal side effects; CLZ = clozapine; OCD = obsessive-compulsive disorder.

Key: (+) - (+++++) = strength of evidence

MEETING HIGHLIGHT

New Antiepileptic Drugs in Psychiatry

Schloss Elmau, Germany
March 27-29, 1998



This conference highlighted a number of new basic and clinical findings pertinent to the use of anticonvulsants in bipolar illness:

Third Generation Anticonvulsants

Dr. C. E. Elger emphasized that the older anticonvulsants were equally effective in patients with complex partial and generalized seizures and differed more from each other in their side-effects profiles than in their initial incidence of clinical response. The newer, third generation anticonvulsants helped to convert only an additional 5–10% of patients to the seizure-free state who had not been helped by the first and second generation drugs such as phenytoin, phenobarbital, valproate, and carbamazepine (Table 1). The new agents were all approved for their efficacy in adjunctive therapy, with 50% reductions in seizure frequency in patients with refractory epilepsy being accomplished in 20–40% of patients with gamma-vinyl-GABA (Vigabatrin®), lamotrigine (Lamictal®),

gabapentin (Neurontin®), felbamate (Felbatol®), topiramate (Topamax®) and tiagabine (Gabatril®) (Table 2).

Dr. Elger noted that what more clearly differentiates these newer third generation drugs from the earlier ones is their relatively benign side-effects profiles and easier use in combination therapy. Although the development of a severe, potentially life-threatening rash with lamotrigine has been a major concern, he emphasized that there has been very little problem with this unfavorable reaction as long as the dose is titrated extremely slowly.

Dr. Elger reported that with felbamate, the incidence of aplastic anemia was 1 in 4,000, and of hepatic failure, 1 in 2800. He indicated that tiagabine was effective in partial epilepsy, although it is difficult to titrate the dose and one has to go very slowly. Similarly, with topiramate, using typical anticonvulsant doses of 200–400 mg/day (with some patients taking as much as 1000 mg/day), he suggested a titration of 25 mg/week in order to avoid the high incidence of psychomotor slowing.

Dr. M. Trimble noted that a number of patients on vigabatrin were reporting retinal problems (decrements in the medial part of the visual fields) that are of unknown origin.

Lithium and Traditional Anticonvulsants

Dr. D. van Calker reported that chronic administration of lithium blocked the inositol transporter. Dr. van Calker cloned the inositol transporter and found that this blockade was highly specific and could be another potential mechanism of action of lithium in addition to the inhibition of inositol regeneration in the phosphoinositol second messenger cycle (because lithium blocks the enzyme inositol monophosphatase). How these results fit into the clinical picture remains to be determined, although they are of considerable interest in relation to the reported an-

Data on the new third generation antiepileptic drugs such as vigabatrin, lamotrigine, gabapentin, felbamate, tiagabine, and topiramate

tidepressant and anti-anxiety effects of inositol in very large doses (12–18 gm/day) (Benjamin et al., 1995, *Psychopharmacol Bull* 31: 167–175).

Dr. I. Ferrier described a number of characteristics of positive and negative lithium responders in their clinic. Positive lithium responders included: those patients without premorbid personality disorder or neuroticism, and those with good inter-episode functioning, high social support, a family history of bipolar illness, a predominant pattern of mania versus depression, less than 4 episodes prior to starting lithium prophylaxis, and less rapid cycling. Indicators of poor lithium responsiveness included: poor compliance; a pattern of mixed mania, rapid cycling, chronic depression, or severe mania; a family history negative for bipolar illness and negative for lithium responsiveness; and the pattern of illness characterized by depression, then mania, and then a well interval (D-M-I as opposed to M-D-I).

Dr. Ferrier reported that periventricular deep white matter abnormalities on Magnetic Resonance Imaging (MRI)—which have been reported to be increased in multiple series of bipolar patients compared with controls—were associated with older age, high blood pressure, vascular abnormalities, and cognitive impairment. He presented new data that these abnormalities were associated with winter births, findings that suggest that the season of increased viral infections (winter) could be influencing the appearance of white matter abnormalities. *Ed. Note:* This is of particular interest in relation to Dr. E. Fuller Torrey's findings of an excess of winter births not only in schizophrenic but also in bipolar patients (see "Around the Network", *BNN* Vol. 4, Issue 1). Could the white matter abnormalities be a possible mechanism for such an effect?

Dr. Ferrier also reported increased electroencephalogram (EEG) abnormalities as a

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Table 1
History of Approval of
Anticonvulsant Drugs
(from Elger et al., 1998)

First Generation:

1857	bromides
1912	phenobarbital
1940	phenytoin
1952	primidone
1958	ethosuximide

Second Generation:

1963	carbamazepine (Tegretol®) and benzodiazepines
1964	valproate (Depakote®)

Third Generation:

1992	γ-vinyl-GABA (Vigabatrin®)
1993	lamotrigine (Lamictal®)
1995	gabapentin (Neurontin®) and felbamate (Felbatol®)
1996	tiagabine (Gabatril®)

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function of lithium resistance, particularly a pattern of right temporal lobe slowing or theta activity. In this regard, he found that adjunctive therapy with lamotrigine (to lithium and valproate) resulted in a 3-year remission period in 3 of 7 rapid cycling bipolar I patients; interestingly, all 3 had the pattern of increased temporal slowing on EEG.

Dr. W. Greil reviewed his data on the prospective trial of 117 patients randomized to lithium and 117 patients randomized to carbamazepine. In his study, there were no suicide completions or attempts on lithium, whereas there were 5 attempts and 1 completion during treatment with carbamazepine. These data again indicate that lithium does have anti-suicide effects, as noted in previous issues of the *BNN*. These findings are also of considerable interest in relation to the similar outcome in regards to episode recurrence on both drugs. Lithium did appear to be more effective in those patients with classic mania, whereas carbamazepine appeared to outperform lithium in those patients with atypical presentations, and in particular, schizoaffective depression.

Lamotrigine and Gabapentin

Drs. H. Grunze and J. Walden reported that lamotrigine appeared to exert anticonvulsant effects in the hippocampal slice in a model sensitive to calcium flux. *Ed. Note:* Thus, in addition to its ability to decrease release of excitatory amino acids (presumably via a blockade of sodium influx presynaptically), lamotrigine also appears to have effects on calcium influx, possibly via the N-type voltage-dependent calcium channel.

Dr. J. Calabrese reported on the seven acute studies of lamotrigine in either depression or mania (in addition, 4 long-term trials are planned by GlaxoWellcome). As we have summarized in previous issues of the *BNN*, in his open prospective trial Dr. Calabrese observed an excellent response to adjunctive lamotrigine in 57% of rapid cycling bipolar patients. The overall response rate in that study was 54/75 (72%) response. Another study compared 200 mg of lamotrigine to 50 mg of lamotrigine to placebo for 7 weeks in bipolar I depressed patients with Hamilton Depression Rating Scale (HDRS) scores greater than 18. This study, to be first re-

ported at the 1998 American Psychiatric Association and Collegium Internationale Neuro Psychopharmacologicum (CINP) Meetings, apparently demonstrated significant effects for 200 mg/day versus 50 mg/day of lamotrigine, and both doses were more effective than placebo. *Ed. note:* These data are convergent with those of our own double-blind lamotrigine trial presented at the 1998 APA meeting by Dr. Mark Frye, in which we have seen a 52% response rate in the first 33 randomized subjects, as opposed to 27% response on gabapentin and 22% on placebo ($p < 0.02$).

Dr. Calabrese indicated that a long-term (52 week) study of lamotrigine prophylaxis for depression in bipolar patients has begun. This study, conducted in 55 sites and 25 countries, will compare 100 patients—each randomized to 50 mg of lamotrigine/day, 200 mg of lamotrigine/day, or 400 mg of lamotrigine/day—with 100 patients on lithium and 100 patients on placebo, making it one of the largest maintenance studies ever conducted in bipolar illness. *Ed. Note:* It is expected that by the end of 1999, lamotrigine will have been investigated by GlaxoWellcome in 11 controlled studies involving some 3,125 patients in 325 Centers. This impressive group of studies should not only help ascertain the appropriate role of lamotrigine in the treatment of bipolar illness, but should also “jump start” the field of therapeutics in bipolar illness, which has lagged behind too long in controlled studies of novel agents and, particularly, in studies of long-term prophylaxis.

Dr. M. Ebert reviewed his data on lamotrigine and gabapentin in amygdala-kindled animals demonstrating differential effects on different components of the seizure process. Lamotrigine was markedly effective in increasing afterdischarge threshold without decreasing seizure duration. In contrast, gabapentin had a small effect on increasing afterdischarge threshold, but a marked effect in decreasing seizure severity and a smaller effect in decreasing seizure and afterdischarge duration. *Ed. Note:* Thus, it would appear that lamotrigine decreases seizure susceptibility in this model whereas gabapentin decreases seizure spread. Whether these data suggest a potential rationale for the use of both drugs in combination in either epileptic patients or those with

refractory affective disorders remains to be further explored.

Dr. B. Amann reported on a single patient on gabapentin with evidence of increases in creatinine that returned to normal upon placebo substitution. *Ed. Note:* This is the first case report of any potential renal effects of this agent, which is wholly excreted through the kidney.

Dr. K. Kelly summarized the data on the mechanisms of action of gabapentin, which now appear to include effects on: 1) the L-amino acid transporter; 2) the α -2 γ subunit of the L-type calcium channel; and 3) other undescribed GABAergic effects.

Dr. X. Xie reported that lamotrigine blocked type-III sodium channels even more potently than type IIA. These type-III channels are ones that increase during treatment with kainic acid and their overall role in seizure and affective disorders remains to be demonstrated. However, because lamotrigine

Table 2
Efficacy and Tolerability of Third
Generation Anticonvulsants
in Epilepsy
(Elger et al, 1998)

Drug	% Improvement (50%) in seizures	% D/C rate
vigabatrin	41	20
lamotrigine	23	7
gabapentin	22	7
topiramate	41	14
tiagabine	21	15

D/C = discontinuation

tends to work in some patients who are non-responsive to carbamazepine and phenytoin (which block sodium type-II channels of batrachotoxin α -sodium benzoate-type), a novel action of lamotrigine on some other system (such as these type-III sodium channels) is obviously a mechanism to be further identified. Dr. Xie also reported that serotonergic effects of lamotrigine were not likely to be clinically relevant, since high doses (300 μ M) were required to either block 5-HT reuptake or the 5-HT₃ receptor.

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AROUND THE NETWORK

Robert A. Kowatch, M.D.
 Associate Professor of Psychiatry;
 Director, Pediatric Bipolar Program
 University of Texas Southwestern Medical Center
 Dallas, TX



Drs. Robert Kowatch and John Rush have recently received a Stanley Foundation Center grant from Dr. E. Fuller Torrey to extend their groundbreaking work in investigating the phenomenology, neurobiology, and treatment of early onset bipolar illness (Dr. Rush was previously highlighted in *BNN* Vol. 2, Issue 1).

Dr. Kowatch is an ideal investigator to take a leading role in this area, and has already been part of the informal alliance of investigators in the Early Intervention Initiative (E.I.I.) that developed a new core methodology to be uniformly used in many studies of childhood and adolescent bipolar illness. As noted in this issue (see “Clinical Trials Update”), Dr. Kowatch initiated the first randomized comparative trial of lithium, carbamazepine, and valproate in childhood onset bipolar illness, with initial results showing an advantage for valproate over lithium. He is interested in developing a variety of approaches to more successful intervention in childhood affective illness and has not only designed and conducted controlled clinical trials, but also has investigated neurobiological concomitants of the illness and potential markers of treatment response.

After receiving a B.A. degree from Northwestern University where he majored in biology and psychology, Dr. Kowatch received his medical degree from the Chicago Medical School. He interned in internal medicine at the Graduate Hospital of the University of Pennsylvania in Philadelphia from 1980-1981 and then completed his residency in psychiatry there in 1983. In 1985 he completed his fellowship training in child and adolescent psychiatry at Hahnemann University in Philadelphia. In December of 1986 he became the Psychiatric Director of Cumberland Hospital in New Kent, Virginia, and from 1987 through 1989 was the Director of the Sleep Disorders Center at the Medical College of Virginia. From 1989 to Au-

gust 1995, Dr. Kowatch served as the Associate Director of the Psychiatric Inpatient Unit at the Children’s Medical Center of Dallas. In 1995 he received the NIMH K07 Award for Child and Adolescent Clinical Mental Health, to continue through the year 2000.

Dr. Kowatch is the author of over 25 scientific articles and chapters on topics such as cocaine’s physiological effects; neurobiological aspects of depression in children and adults; and brain imaging and treatment of mood disorders in children and adolescents. He is also a coauthor of the recent article, “A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression”, the first positive controlled trial of an antidepressant in childhood depressive illness (Emslie et al., 1997, *Arch Gen Psychiatry* 54: 1031–1037).

Dr. Kowatch is now editing a book on childhood and adolescent bipolar illness, specifically written for parents of these children so that they can better assist in the understanding, assessment, and treatment of this most difficult childhood medical illness. As noted in this issue, this illness can have devastating effects on a child’s social and educational development, and on their ability to function effectively in the family unit. Children with bipolar illness can show marked disturbances in behavior, including obvious manic symptoms with grandiose delusions, poor judgment, conduct disorder, hypersexuality, and hyperactivity; these behaviors oscillate rapidly with periods of extreme withdrawal, depression, crying, suicidal thoughts and behavior. Even with clearly severe affective dysfunction, treatment has been partially immobilized by unnecessary controversy over whether these children meet the precise adult criteria for bipolar illness.

Dr. Kowatch, along with Dr. Findling at the Case Western Reserve Bipolar Network Center (see *BNN* Vol. 3, Issue 2, 1997) and

many others in the field, has helped move us beyond this controversy to a new era of empirical studies on clinical presentation and treatment of this severe disorder. His book on childhood bipolar illness should be an extremely valuable resource and an up-to-date summary of the state of knowledge in this field for parents and other caregivers of affectively disordered children.

The entire Stanley community—and patient community at large—appreciate Dr. Kowatch’s outstanding efforts to date, and look forward to his further important contributions in the future, which should help to make an impact on the early symptoms of affective illness and, possibly, prevent its potentially devastating consequences. ■

(Continued from page 8)

Maintaining Therapeutic Effects of Sleep Deprivation

Finally, Dr. M. Berger reported that there was a new mechanism for helping to sustain the clinical improvement in mood achieved after 1 night of total sleep deprivation. Typically 40–60% of patients with severe depression show acute improvement in mood (literally overnight) following 1 night of sleep deprivation, but almost invariably relapse on the day after a recovery night of sleep. Dr. Berger indicated that after a full night and day of sleep deprivation, if a patient went to sleep at 6 PM and then woke up at 1 AM after 7 hours of sleep, and the next day went to sleep at 7 PM and awoke at 2 AM, and then continued this pattern (advancing the hour of bedtime 1 hour each night while still getting 7 total hours of sleep), the sleep deprivation-induced improvement would be sustained. He indicated that this technique was now being widely used throughout many clinics and academic departments in Germany as a routine clinical treatment. ■

NETWORK NEWS BRIEFS

News from the various Network Sites and Centers



LOS ANGELES

Bipolar Support Groups

On June 3, 1997, the Los Angeles site of the SFBN began offering psycho-educational support groups to individuals with bipolar disorder. Open to participants in the study as well as individuals in the community who have bipolar disorder, the groups have received overwhelming response.

Since their inception, various groups have been offered, including general support and educational groups for adults with bipolar disorder, and vocational support groups for individuals considering re-entering the workforce or who need to learn more about their benefits. The vocational group has focused on such issues as the Americans with Disabilities Act, Social Security benefits, work-incentive programs, developing resumes, role-playing interviews, and issues of disclosure.

Currently a group for recently diagnosed individuals is nearing its completion. Topics that have been addressed include accepting the illness, compliance with medication, disclosure, and the impact on family and social relationships. We have had two guest speakers: Natalie Rasgon, MD, a psychiatrist and professor at UCLA's Department of Psychiatry, and Deborah Pitts, MBA, an occupational therapist and Director of Rehabilitation Services at the West Los Angeles Veterans Administration.

The groups are time- and space-limited, and run for 8 consecutive weeks. They are free of charge and the one requirement for enrollment is that individuals must be in treatment with a psychiatrist and compliant with medications. The groups are held on the UCLA campus and are facilitated by Liz Miller, a clinical social worker with the Los Angeles SFBN site.

Very shortly we will be adding another clinical social worker to our team, Sue Moss, who will assist in developing and facilitating

new support groups over the next year. We are pleased to be able to offer this service and look forward to continuing in the future. For more information on these support groups, please contact Liz Miller at (310) 794-9912.

- Liz Miller, MSW

BETHESDA

NIMH Study Participation Clinical Center, Bethesda, MD

rTMS

Depressed patients who wish to participate in a protocol to evaluate repeated transcranial magnetic stimulation (rTMS) of the brain should contact Dr. Andy Speer at (301) 402-2293.

Lamictal®/Neurontin®

Patients wishing to be screened for the Lamictal®/Neurontin® protocol (see *BNN* Vol. 3, Issue 4) should call (301) 496-6827.

PTSD

Patients with post-traumatic stress disorder interested in volunteering for a randomized clinical trial to evaluate the potential efficacy of repeated transcranial magnetic stimulation (rTMS) over the right frontal cortical area—with a month of either low frequency treatment or sham treatment and a crossover to the other phase—should contact Dr. Una McCann at 301-402-2947. ■

New support groups for bipolar disorder at the Los Angeles / UCLA Site; patient recruitment for 3 studies at the NIMH / Bethesda Site

THE STANLEY FOUNDATION

BIPOLAR NETWORK

Network Treatment Outcome Sites:

Los Angeles/UCLA

Los Angeles, CA
Lori Altshuler, MD
Mark Frye, MD
Principal Investigators

University of Cincinnati

Cincinnati, OH
Susan McElroy, MD
Paul Keck Jr., MD
Principal Investigators

NIMH / Bethesda

Bethesda, MD
Robert Post, MD
Kirk Denicoff, MD
Gabriele Leverich, MSW
Principal Investigators

Dallas/UTSWMC

Dallas, TX
John Rush, MD
Trisha Suppes, MD
Principal Investigators

Utrecht/HC Rümke

Utrecht, Netherlands
Willem Nolen, MD, PhD
Ralph Kupka, MD
Principal Investigators

New Bipolar Network Website!

Point your internet browser to the new Bipolar Network World Wide Web site in the coming month, at www.bipolarnetwork.org. Find the latest information on the Network, previous issues of the BNN, new email addresses, and much more.

(Continued from page 3)

This brings us to the case of lamotrigine (Lamictal®) that now has 2 double-blind, randomized studies supporting its efficacy in bipolar depression (Calabrese et al., and Frye et al., 1998 American Psychiatric Association Meeting) in treatment-refractory unipolar and bipolar patients. If one does not get either the common, benign rash (in 10% of patients) or very rare, severe rash (in about 1 in 500 patients), the drug appears otherwise to be very well tolerated, and, for many patients not responsive to a host of other agents, highly effective.

Thus, it is up to each individual, in consultation with his or her physician, to decide about the potential use of a series of proven or unproven agents in an attempt to better treat one's affective illness. In this case, it is fortunate that "the inmates help to run the asylum" and participate in their treatment decisions, just as patients do who have a range of other life-threatening illnesses in which considerable risk is often involved. Aspirin is a wonderful drug for pain and now has also been proven to help in the prevention of heart attack and stroke. At the same time, it kills individuals every year because of gastrointestinal bleeding, so almost no drug is without some risk.

We do know that the lifetime risk of suicide is between 10% and 20% for patients with unipolar and bipolar illness, respectively; and as such they deserve the most judicious care and attention and, potentially, the exploration of a range of treatments from health foods to those with potentially serious adverse medical consequences.

Again, we thank you for raising so many interesting issues for consideration and discussion. ■

Robert M. Post, M.D.
Gabriele S. Leverich, M.S.W.

Bipolar Network News

Stanley Foundation Bipolar Network
A Program of the NAMI Research Institute
5430 Grosvenor Lane
Suite 200
Bethesda, Maryland 20814

CHANGE SERVICE REQUESTED

In This Issue:

Clinical Trials Update: E.I.I. Consortium Meeting
Life Chart Update: Antimanic Response to Olanzapine
Meeting Highlights: New Antiepileptic Drugs
Around the Network: Dr. Robert Kowatch
