

Bipolar Network News

Clinical Trials Update

The principal investigators in the Stanley Foundation Bipolar Network (Network) met at the Cincinnati field center in June to accomplish a variety of tasks, including: 1) finalizing all aspects of the Network methodology; 2) updating the progress on the establishment of reliability and validity for all ratings utilized; 3) reviewing plans and drafts of 11 Stanley-supported manuscripts projected for 1996; 4) outlining a series of new protocols; and 5) meeting with Drs. Joseph Calabrese and Robert Findling of the Case Western Reserve University School of Medicine, who will be playing a lead role in the development of the Stanley Foundation Early Intervention Initiative (E.I.I.).

Over 200 patients have been entered into the naturalistic phase of the study, allowing a variety of methodological and descriptive papers to be initiated. A number of patients have been randomized into the study comparing the antidepressants bupropion (Wellbutrin®), sertraline (Zoloft®), and venlafaxine (Effexor®) for the treatment of bipolar depression breaking through ongoing mood stabilizer prophylaxis. New protocols will include: 1) a double-blind discontinuation phase at six months in patients who appear to have responded to these antidepressants on a long-term basis; 2) dovetailing with pharmaceutical industry-sponsored trials of gabapentin (Neurontin®) and olanzapine for refractory manic and cyclic patients; 3) a comparison of stimulant versus T3 augmentation for refractory bipolar depressed patients; and 4) a comparison of an intervention with a classical antidepressant treatment such as a monoamine oxidase inhibitor (MAOI) with a newly approved anticonvulsant, lamotrigine (Lamictal®). A variety of other protocols were discussed, including ways to maximize the systematic development of a treatment algorithm for bipolar patients who require complex multimodal treatment.

In relationship to the Early Intervention Initiative (E.I.I.), plans were formulated for a core packet of instruments specifically designed for the evaluation and follow-up of children and adolescents with bipolar illness as well as the initial design of a series of studies comparing lithium and valproate (Depakote®) in the acute and long-term treatment of these patients with early onset of illness.

At the annual NAMI meeting in Nashville, Dr. E. Fuller Torrey announced the funding of five new Stanley Centers in addition to the center at NIMH (which is also the home base for the Network) and a center in Pittsburgh under the direction of Dr. David Kupfer. The five new centers include:

Stanford University under the direction of Dr. Terence A. Ketter, which will focus on brain imaging as a potential predictor of clinical response to differential treatment; a Chicago center, under the direction of Drs. Jan Fawcett and John Zajecka, which will develop treatment algorithms, and further the study of the efficacy of repeated transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) in acute and long-term treatment; a Case Western Reserve center under the direction of Drs. Calabrese and Findling will develop the E.I.I.; a Baltimore center under the direction of Dr. Raymond DePaulo will further the work on genetics and brain imaging with Dr. Gottfried Paulson; and a McLean Hospital center in Boston, under the direction of Drs. Bruce Cohen, Mauricio Tohen, and Perry Renshaw will focus on single photon emission computed tomography (SPECT) imaging during manic, depressed, and well states.

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We are all fortunate to have the generosity and commitment of Ted and Vada Stanley of the Stanley Foundation and its Director, E. Fuller Torrey, who play a crucial role in supporting strong basic and clinical research in the illness.

LIFE CHART

Valproate Augmentation of Lithium in the Acute and Preventive Treatment of Recurrent Psychotic Bipolar Depressions

The NIMH Life Chart Method (The LCM) continues to be adopted in many academic, clinical, and pharmaceutical settings as an effective way of monitoring the long-term course of bipolar and unipolar illness. The tracking of depressive and manic episodes and their response to treatment, depicted on the life chart in the form of a graph, assists in clinical decision making, promotes better management of the illness for the individual patient, and facilitates the study of the details of clinical response in larger numbers of patients at various research and clinical practice settings.

We have chosen this patient's life chart as part of our ongoing clinical case presentations to illustrate the efficacy of a mood stabilizer, valproate (Depakote®), for this patient in the acute treatment of her severe and disabling psychotic depressions and their long-term prevention. Once a response to an episode has been achieved, the goal is to maintain this response in the face of the recurrent, episodic nature of this illness. For some patients loss of treatment response to the maintenance medication(s) can be a difficult and painful experience with sometimes devastating impact on their own and their families lives. This life chart helps demonstrate that even in the face of a prolonged phase of rapid cycling incapacitating illness a complete and long-term remission can be achieved through the use of newer treatment modalities such as the anticonvulsants, either alone or in this instance as augmentation of a formerly unsuccessful treatment regimen.

The life chart presented in this issue depicts the continuous cycling course of a patient with Bipolar I disorder. Her illness was previously responsive to ECT for her long, psychotic, postpartum depression in 1964 (not illustrated). When her illness re-occurred after 12 years in 1977 in the form of a severe manic episode and

two depressive episodes which were again acutely responsive to ECT (also not shown in this life chart), she became a good prophylactic responder to lithium and remained well for 5 years on the drug. However, 4 years after discontinuing lithium treatment her illness re-emerged unrelentingly in 1986 (see fig.) in the face of significant life stress. The episodes were now unresponsive to the reinstatement of lithium, adjunctive neuroleptics, and minor tranquilizers. It can only be speculated whether she might have remained well if she had stayed on her lithium prophylaxis, as discussed in the life chart in the first BNN issue (Vol.1, issue 1, 1995). One can also only speculate whether buspirone (Buspar®) may have contributed to the onset of three years of continuous cycling between moderate manias and severe depressions, a phenomenon that is more closely associated with typical tricyclics in approximately one fifth of bipolar patients.

A trial of carbamazepine (Tegretol®), alone and in combination with lithium, instituted during her NIMH hospitalization, was effective in reducing the amplitude of the manias but had no impact on the severe recurrent delusional depressions the patient was experiencing. When carbamazepine was discontinued and valproate (Depakote®) was added to the lithium, the patient started to get better. The remaining hypomanias and her profound depressions improved, and she soon experienced a complete and sustained remission for the first time in five years. Discharged on valproate, lithium, T₄ (Synthroid®) and a small dose of trifluoperazine (Stelazine®) which was discontinued shortly after discharge, the patient has continued to do well from mid-1990 until the present (1996). She slowly resumed work, first as a volunteer, then on a part-time basis, and has now returned to full-time employment in a rewarding position.

This patient's course of illness again illustrates that the illness can progress from episodes far apart (1964, 1977) to periods of continuous cycling, to which interruption of prophylactic treatment may have contributed. The patient had an excellent response for both mania and severe psychotic depressions to the combination of two mood stabilizers (valproate and lithium) when lithium with neuroleptics and with carbamazepine had not been

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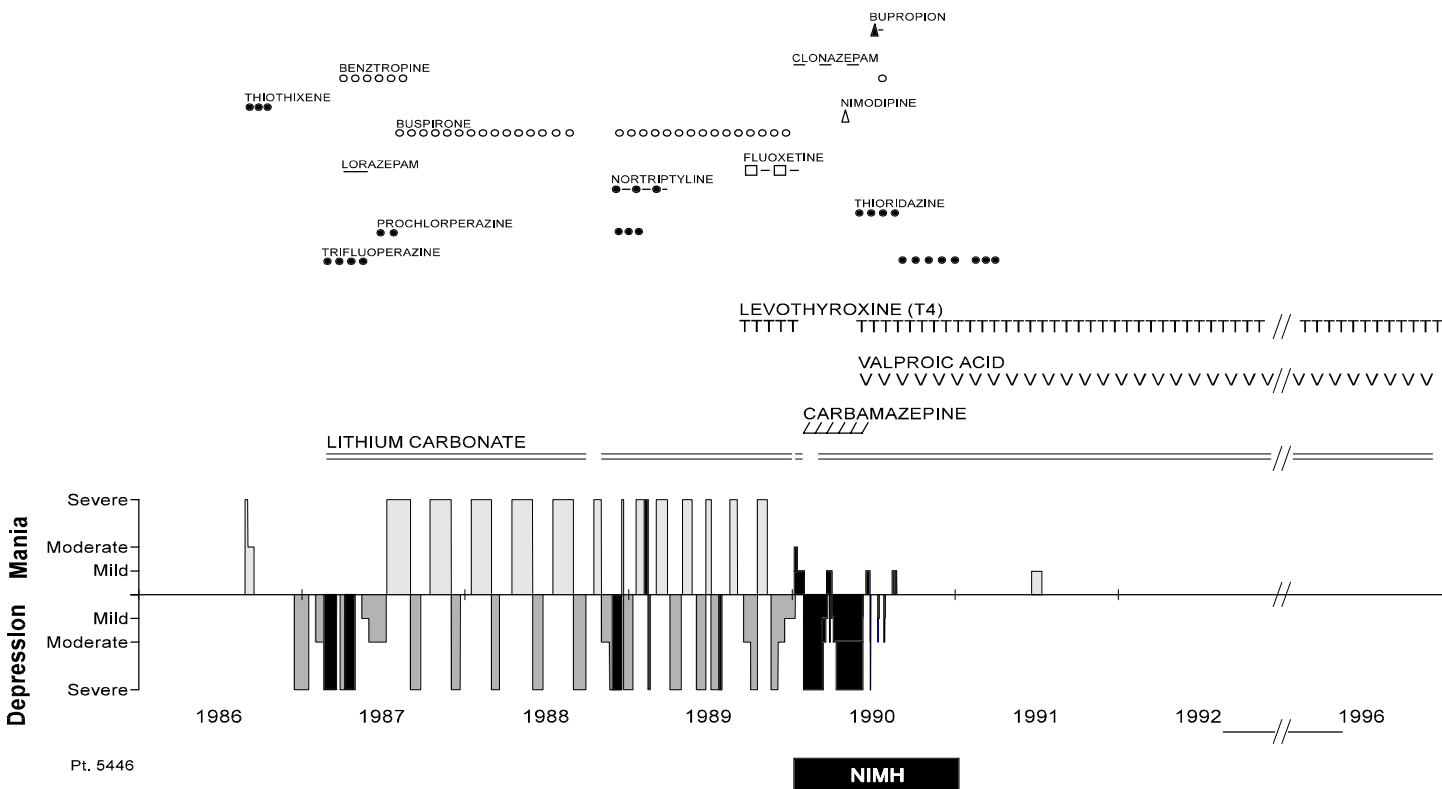
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VALPROATE AUGMENTATION OF LITHIUM-REFRACTORY BIPOLAR ILLNESS



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helpful. The approach of combination therapy with two mood stabilizers instead of antidepressants even for incapacitating depressive episodes in this bipolar patient, reduced and arrested the cycling. Susan McElroy and Paul Keck, both principal investigators at the Stanley Foundation Cincinnati site, and Jan Fawcett (Chicago) and Joseph Calabrese (Cleveland) have all described valproate's efficacy in the open treatment of rapidly cycling bipolar patients who were refractory to lithium and open carbamazepine. The literature review of 16 uncontrolled studies using valproate (McElroy et al, 1992) suggests that valproate may be an effective agent in the treatment of mania, especially dysphoric mania, rapid cycling, and in some psychotic disorders. The FDA has recently approved Depakote® for the treatment of acute mania (until now only lithium had received such approval), and some uncontrolled studies report its efficacy in the treatment of bipolar depression confirming our own findings at NIMH (see also BNN vol.1, issue 2) in a smaller subgroup of patients.

The arrival of two anticonvulsants in the last 15 years, carbamazepine (Tegretol®) and valproate (Depakote®), has significantly changed the current treatment approach to bipolar disorder, particularly for lithium refractory bipolar illness. The advent of two additional anticonvulsants, gabapentin (Neurontin®) and lamotrigine (Lamictal®) may further advance the effective management of this biphasic recurrent illness, although much continued work is required to further define the nature, completeness, and predictors of their possible response in bipolar patients. The complete remission illustrated here in the life chart helps reinforce the hopeful message that even a long phase of incapacitating illness does not preclude a complete response to different agents or their combination for the acute and long-term treatment of bipolar disorder.

Reference

McElroy, S. L., Keck, P. E. Jr., Pope, H. G., Hudson, J. I. (1992). Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. *J Clin Psychopharmacology* 12(Suppl. 1): 42S - 52S.

MEETING HIGHLIGHTS

Summary of the Conference on the Safety of rTMS

In a previous issue of the BNN (Vol. 1, issue 3), we reported on preliminary evidence of the efficacy of repeated transcranial magnetic stimulation (rTMS) in two of the six refractory depressed patients.

A second study by George et al in our laboratory comparing two weeks of active rTMS to sham rTMS was presented at the 1996 meeting of the American Psychiatric Association, and this study showed statistically significant improvement in the active rTMS phase compared with the sham rTMS phase. A study by Pascual-Leone et al (1996) reports successful antidepressant effects in 11 of 17 endogenously depressed patients with psychotic symptomatology following left prefrontal stimulation but not with right or vertex stimulation. Belmaker et al reported improvement in post-traumatic stress disorder (PTSD) symptomatology with single trains of TMS stimulation (i.e., at a very low frequency). In none of these studies, with the exception of one patient in Pascual-Leone's study, did any patient experience a seizure. In that study, the patient had been exposed to 10 Hz stimulation and showed an initial positive effect, but as response dissipated and the patient was treated with tricyclic antidepressants (Pascual-Leone et al, 1996) in combination, a seizure was induced. These observations suggest the possible seizure lowering effect with antidepressants that has been observed on a spontaneous basis in epidemiological studies. They further suggest caution in the use of rTMS in patients with seizure-lowering medications as well. However, it should be noted that the induction of a major motor seizure is the intentional treatment modality of electroconvulsive therapy (ECT). Thus, the possible induction of a seizure with rTMS as an unwanted side effect should not be considered as problematic in the treatment of a depressed patient as in that of a normal volunteer, in whom a seizure could not have a beneficial effect.

Nonetheless, the occurrence of seizures in four normal volunteers exposed to stimulation near parameters previously thought acceptable for safety does highlight the potential for adverse outcomes and the need for careful assessment of thresholds, other safety measures, and adequate informed consent. To date, major cognitive and memory side effects have not been reported in the normal volunteer patient studies, although side effects need to be systematically assessed with a variety of more subtle tests of impairment in learning and memory.

Susan Weiss presented animal data on the inhibition of amygdala kindled seizures with low frequency "quenching" electrical stimulation administered through the same electrode. Kindling is the gradual appearance of full-blown seizures to a previously subthreshold stimulation, i.e., of the amygdala with 60 Hz stimulation for 1 second each day. If this is followed by quenching (1 Hz for 15 minutes) the animal never kindles. This lower frequency stimulation may be anticonvulsant rather than proconvulsant.

CLINICAL RESEARCH UPDATE

Gene Watch: Progress Toward Identifying Neurobiological Vulnerability Markers

As noted in a previous issue of the BNN (Vol. 2, issue 2) there are now well confirmed findings of genetic vulnerability to bipolar illness. The Berrettini [Thomas Jefferson University] / Gershon [NIMH] group were the first to report a locus on chromosome 18 that was associated with risk for bipolar illness. This was confirmed by the Stine-DePaulo (Johns-Hopkins University) group who, in addition, found that only inheritance from the father was located on this chromosome. These findings were subsequently replicated by the Berrettini/Gershon group. Although not yet confirmed, the DePaulo group believes chromosome 18 is associated with inheritance of bipolar II illness. Additionally, several groups have replicated a chromosome 21 finding and Berrettini and colleagues believe this is associated with maternal inheritance. Berrettini, Gershon, and DePaulo won the prestigious Selo Prize in

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recognition of their ground-breaking work. Finally, a third replicated finding appears to be associated with the X chromosome, although the type of inheritance associated with the X chromosome has not yet been definitively identified.

Also noted in the BNN (Vol. 2, issue 2), Dr. John Kelsoe (University of California at San Diego) reported that the dopamine reuptake site, located on chromosome 5, may also be a vulnerability marker of bipolar illness and several other candidates have been identified as well, each of which requires additional replication and confirmation.

The field now has cleared the first hurdle - replicating genetic vulnerability findings in multiple laboratories. These data, taken in conjunction with the now well-replicated findings of the neurobiological abnormalities in depressive illness,¹ presently provide unequivocal evidence of the genetic and neurobiological basis of bipolar illness, putting it on the same footing as many other medical illnesses. As such, this should markedly reduce stigma and, in parallel, lead to the same degree of insurance and reimbursement coverage for bipolar illness compared to other chronic recurrent illnesses in medicine, such as rheumatoid arthritis, epilepsy, arteriosclerotic cardiovascular disease, cancer, or diabetes.

This is all the more the case in relationship to recent data on the degrees of disability and the economic burdens of the illness, both of which are equal or greater than many of the other chronic medical illnesses and disabilities as mentioned in the reviews of Greenberg et al (*Journal of Clinical Psychiatry* 54: 405-418, 1993) and Wyatt & Henter (*Social Psychiatry & Psychiatric Epidemiology* 30: 213-219, 1995).

¹ Some of the well-replicated neurobiological findings in depression include: decreased frontal blood flow and cerebral hypometabolism on PET scans, often correlated with the severity of depression and evidence of medio-temporal and limbic system dysfunction on PET and SPECT as well; evidence of peptide alterations including increases in CRH and TRH, as well as the well recognized findings of blunted TSH response to TRH, blunted ACTH response to CRE, and the associated hypercortisolemia; decreases in CSF somatostatin; evidence of increased physical size of pituitary and adrenal glands, as well as evidence of structural alterations on a variety of brain imaging techniques including an increased incidence of periventricular hyperintensities, as revealed by T₂ weighted MRIs, particularly in bipolar I individuals.

AROUND THE NETWORK



Ralph Kupka, M.D. (left) and Willem Anton Nolen, M.D., Ph.D. (right) head the Stanley Foundation Bipolar Network field center in Utrecht, the Netherlands. This field center was recruited into the Network for two reasons. First was Drs. Nolen's and Kupka's expertise in clinical trials methodology in the recurrent affective disorders, and the second was the availability of many drug treatments in Europe substantially earlier than in the U.S. such as the Reversible Inhibitors of Monoamine Oxidase type A (RIMAs).

Dr. Nolen is uniquely qualified to head the Utrecht field center. He conducted initial pioneering studies in patients with recurrent unipolar illness. These studies assessed the comparative efficacy of tricyclic antidepressants (TCAs) with different mechanisms of action in order to test the noradrenergic versus serotonergic subgroup hypotheses and to identify possible subgroups of patients with differential responsivity using crossover designs. Study of this topic and use of this methodology was a substantial advance over previous comparative trials which typically used antidepressants with relatively similar mechanisms of action. Dr. Nolen also conducted the first double-blind study with the classical monoamine oxidase inhibitor (MAOI) tranylcypromine (Parnate®) in refractory depression, and performed early work in bipolar illness comparing carbamazepine (Tegretol®) and lithium in refractory bipolar patients.

It is with much good fortune that, in 1993, Dr. Nolen changed jobs and moved to Utrecht where his major research interest returned to bipolar disorders, and he has now completed

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a major double-blind study comparing lithium and carbamazepine (Tegretol®) as well as a variety of other pharmacological trials. He has published more than 118 papers and has edited several books.

Dr. Nolen's methodological expertise is extremely valued in the Network and not only has he made crucial suggestions in the basic formulation of Network strategies, but is involved in the design of a variety of new clinical trials. For example, he will be taking a lead in the protocol comparing the effects of lamotrigine (Lamictal®) and MAOIs in refractory depression. Dr. Nolen will also play a key role in developing the Early Intervention Initiative for children and adolescents with early-onset bipolar illness to determine if the illness can be prevented from fully emerging or progressing.

In most of these endeavors, Dr. Nolen is joined by Ralph Kupka, M.D. who also brings extensive experience in the psychopharmacology of bipolar illness to the Network. Dr. Kupka is particularly interested in the differential presentations of the illness and how patterns and subtypes (such as those with rapid cycling) not only evolve over time, but also are associated with differential response to medications.

Drs. Nolen and Kupka are expanding their Network studies to a wide group of clinicians interested in participating in Network level-III studies (randomized but open) so that treatment outcome can be studied in a larger number of patients. The Network is indeed fortunate to have two such experienced and caring clinicians and expert methodologists in its founding group.

CONSUMER CORNER

Field Center News

by Debbie Miller, M.S.W.

In April 1996, the Stanley Foundation Bipolar Network's Los Angeles field center began a monthly series of evening lectures designed to meet the needs of Network participants and their families. The series which is open to all SFBN participants and their significant others and families, was launched with a lecture titled "Bipolar Disorder: An Overview," presented by Lori Altshuler, M.D., and Michael Gitlin, M.D., both of the UCLA Neuropsychiatric Institute. Drs. Altshuler and Gitlin provided a comprehensive overview of Bipolar Disorder, including the most up-to-date information on its course, symptomatology, and treatment. The lecture discussion was well-attended by SFBN participants, whose feedback on the evening was extremely positive.

The May lecture titled "Community Resources for People with Bipolar Disorder," was presented by guest lecturer Susan Dempsay, Executive Director of "Step Up on Second", a local social/vocational/education rehabilitation center for people with a history of mental illness. Ms. Dempsay's talk, which gave participants the opportunity to ask questions about community resources based on their individuals needs, was also very well received by attendees.

To choose topics for these monthly lectures, Network clinicians polled SFBN participants both informally and by questionnaire in order to gain a clearer understanding of their needs as individuals and as a group. The June lecture, presented by Dr. Jennifer Christian-Herman, focused on bipolar disorder and family relationships. Subsequent talks will center on such topics as returning to work following an episode, bipolar disorder and social/professional relationships, and topics specific to different age groups, life situations, and transitions. It is the hope of Network staff that SFBN participants will find the talks educational and helpful in numerous ways, and will use these lectures as a forum for sharing concerns with other

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participants, offering suggestions based upon individual experiences, and gaining a sense of community with other Network members.

For information on the SFBN Los Angeles field center lecture series, please call (310)-794-9912.

• Patient Recruitment •

- Patients with unipolar or bipolar depression are being sought as research participants in a trial of non-convulsant brain stimulation with rTMS and other protocols noted below:

The Biological Psychiatry Branch of the National Institute of Mental Health (NIMH) is looking for patients with unipolar or bipolar illness interested in participating in NIMH treatment protocols.

We currently have opportunities in both outpatient and inpatient studies examining the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. This involves electrical stimulation of the brain (induced by a magnet) without producing a seizure (see Vol. 1, issue 3, and "Meeting Highlights" this issue, for details).

We are also investigating the mood stabilizing effects of the anticonvulsants lamotrigine (Lamictal®) and gabapentin (Neurontin®).

We are seeking patients aged 18-75 without a history of seizures or current active alcohol or substance abuse.

If interested in the rTMS protocol, please call Dr. John Little at (301) 402-2293. If interested in the clinical trials studying the effects of anticonvulsants in the treatment of mania or depression, call Dr. Bob Dunn at (301) 402-2293 or call (301) 496-6827 for more information.

• Good Lithium • Responders Sought

-Recruitment of volunteers who have responded well to lithium for at least five years

We are seeking to identify characteristics of bipolar illness associated with a good response to lithium. If you have been taking lithium and have been well for 5 or more years, please call Nancy Palmer at: (301) 496-6827 or write for a questionnaire survey to: NIMH/BPB, 10/3N212, 10 Center Dr, MSC1272, Bethesda, MD 20892-1272.

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