

Bipolar Network News

Bipolar Network Update

Robert M. Post, M.D.

The five major academic sites of the Stanley Foundation Bipolar Network (SFBN), located in Los Angeles, Dallas, Cincinnati, Bethesda, and Utrecht, Netherlands, have begun entering patients into the SFBN naturalistic follow-up study, as baseline to the first of several double-blind randomized clinical trials to be implemented by the Network.

This first clinical trial is designed to assess the relative effectiveness of three newer antidepressants in patients with bipolar depression. The effectiveness of these three antidepressants will be studied with patients who have experienced an episode breakthrough while taking at least one mood stabilizer. The serotonin-selective reuptake inhibitor (SSRI) sertraline (brand-name Zoloft®), will be randomized and compared with bupropion (brand-name Wellbutrin®). Bupropion has a highly atypical mechanism of action, one which appears to involve increased neurochemical dopamine in areas of the brain thought to be crucial in the control of pleasure and psychomotor activity. If patients respond successfully to either one of these two antidepressants, they will be offered the option of continuing treatment for a 12-month period in order to assess the ability of these medications to prevent recurrent depressions without intensifying mania.

If patients do not respond successfully to the first antidepressant offered in the randomization, they will be eligible for a re-randomization with either a switch to the opposite medication or to venlafaxine (brand name Effexor®), a serotonin-nonspecific reuptake inhibitor (SNRI). Venlafaxine has potent effects on the reuptake of the neurochemicals serotonin and norepinephrine and is reported to be highly effective in unipolar patients with a history of difficult-to-treat depressions non-responsive to other conventional antidepressants.

For the double-blind study, the patients and clinicians at each of the academic centers will assess in detail the therapeutic outcome of the medication treatment, using both standardized mood rating scales and prospective daily life-chart ratings to record even minor mood changes. Since the randomization involves comparison of two medications widely used in clinical practice, this clinical trial represents the state-of-the-art in psychiatric treatment. The clinical trial conveys no risks to patients beyond those risks already encountered in regular clinical practice.

In light of these considerations, we will be conducting a parallel study in non-academic clinical practice settings of the same randomized medication comparisons, but with less detailed and less intensive outcome measures on an open rather than double-blind basis. With this parallel study we hope to gather systematic data on a large number of patients, ultimately to provide guidance to patients and clinicians on which drugs have the best short- and long-term overall effectiveness in bipolar illness.

"We intend to compare three new antidepressants which have different mechanisms of action for their acute and long term efficacy in bipolar"

For further information about possible participation in the double-blind studies at the participating academic centers, please call the 800 number listed on page 4 of this issue. If patients and their physicians would like to participate in the open part of the randomization, they should also call the 800 number for further information, or write the Stanley Foundation Bipolar Network, 6001 Montrose Road, Suite 809, Rockville, Maryland 20852.

See page 4 for SFBN contact phone number...

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The Life Chart as a Guide to Therapeutics: Differential Response Among Mood Stabilizing Anticonvulsants

Gabriele S. Leverich, M.S.W.

The NIMH Life Chart Method (The LCM) has been adopted by the Stanley Foundation Bipolar Network as an effective way of monitoring the long-term course of bipolar illness by tracking depressive and manic episode severity and frequency, including hospitalizations, by charting medications on a daily basis, and by recording important life events. These daily life chart entries build an ongoing and permanent graphic representation of each patient's course of illness and provide crucial clinical information needed when making the next treatment decision. Additionally, charting one's own course of illness, much as one would monitor and chart glucose levels in diabetes, promotes active and knowledgeable participation in the control and regulation of one's own illness.

Much can be learned not only from charting current mood, life events, and treatment response but also from constructing a life chart of the past, or retrospective, course of illness. The number of previous episodes, changes in the cycling pattern, prior responses to medications as well as partial response or loss of response to a medication are all important factors in the choice of the next treatment step. Regular review of one's own life chart with the treating physician can be a valuable addition to clinical visits and make a significant impact on the acute and long-term management of the illness.

As part of our ongoing life chart discussions in the BNN, we would like to present a case history that demonstrates important clinical aspects in the psychopharmacology of bipolar illness and illustrates the utility of a systematic approach to treatment decisions based on life chart review.

The patient whose life chart is included came to the NIMH in 1985 after a lengthy prior course of illness with an onset of milder episodes of hypomania and depression in her late teens and early twenties. After an increase in episode se-

verity, requiring ECT, antidepressant medications, and short periods of a neuroleptic for a hospitalized mania in 1981, **lithium** was ultimately started early in 1982 as indicated on the life chart on page 3.

Despite therapeutic levels of lithium the patient continued to cycle within the mild to moderate range of depressive and hypomanic episodes thus falling into the group of 40-50% of patients who are not good lithium responders. There is increasing recognition (Vestergaard, 1992; Gelenberg, 1989) that only 40-60% of patients respond adequately to lithium rather than the earlier assumed 80% of patients. A subgroup of non-responders include patients who experience dysphoric, or "unhappy" mania, and/or rapid cycling.

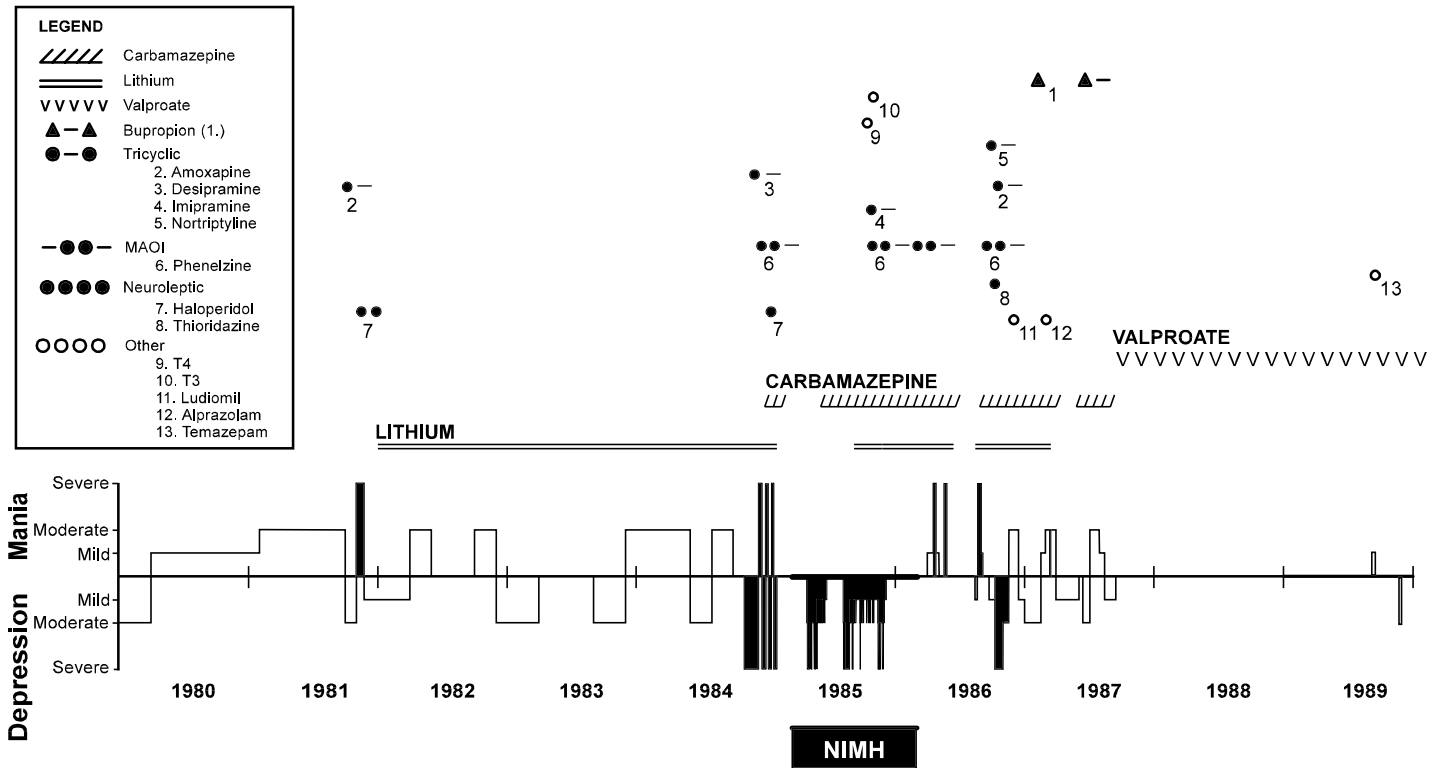
Increasingly severe manic and depressive episodes and hospitalizations despite continued lithium treatment brought the patient to NIMH in 1985. A brief trial with the anticonvulsant carbamazepine (**Tegretol**®), initiated during a hospitalization just prior to NIMH, was resumed at NIMH, first alone and then in combination with lithium. The **lithium/carbamazepine** combination prevented further manic episodes for this patient but the recurrent severe depressions required additional treatment with phenelzine (Nardi¹®) and other augmenting drugs. Despite concurrent treatment with two mood stabilizers in the springtime of 1986 severe manias and dysfunctional depressions broke through requiring further hospitalizations and adjunctive medications.

When another anticonvulsant, namely valproate or divalproex-sodium (**Depakote**®),

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PROPHYLACTIC RESPONSE TO VALPROATE IN A NONRESPONDER TO LITHIUM / CARBAMAZEPINE



After an extremely difficult course of illness with inadequate response to lithium alone and in combination with carbamazepine and a variety of antidepressant adjuncts, the patient showed a dramatic and sustained response to valproate.

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was instituted in the fall of 1987, the patient responded not only acutely with a complete remission of her manias and depressions, but has continued to remain essentially well for the last seven years.

The emergence in the last two decades of a series of anticonvulsant compounds such as carbamazepine and valproate for the treatment of bipolar disorder has brought new hope for the lithium non-responsive or lithium refractory patient. The efficacy of carbamazepine and valproate as mood stabilizers has been demonstrated in research studies and clinical practice settings and will be further investigated in the Stanley Foundation Bipolar Network together with other newer anticonvulsants thought to be potentially useful in bipolar disorder. Both carbamazepine and valproate have shown to be ef-

fective agents for the treatment of bipolar disorder, and as illustrated in the life chart, **non-response to one anticonvulsant does not predict non-response to the other** thus offering multiple treatment options to the patient struggling with an unstable mood disorder.

The patient whose life chart has been presented in this article has resumed a full and productive life. She gave us permission to use her life chart and case history as a message of encouragement and hope: even when there is non-response or refractoriness to some of the available mood stabilizing medications for many years, a series of alternative compounds are now available. Life-charting of the past and present course of bipolar illness will significantly assist in making informed treatment decisions.

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AROUND THE NETWORK

The coordinating director of the SFBN is Keith G. Kramlinger, M.D., of the Mayo Clinic. Dr. Kramlinger was trained at the Mayo Medical School and was a psychiatric resident at the Mayo Graduate School of Medicine, both located in Rochester, MN. He completed a two-year fellowship at the NIMH, during which time he documented the clinical efficacy, chemical effects, side-effects, and interactions of the anticonvulsant carbamazepine and the mood stabilizer lithium and their combined therapeutic use. Dr. Kramlinger found that many patients who inadequately responded to carbamazepine therapy alone, on a double-blind basis, responded well to the addition of lithium, with minimal additional side effects. Although this combination caused thyroid suppression, it did not interfere with the degree of symptom response. Moreover, lithium stimulated bone marrow growth factors necessary for the development and proliferation of white blood cells (termed the "colony stimulating factor") and this lithium effect was able to overcome carbamazepine's mild white blood cell suppression. Dr. Kramlinger also reported the first well-documented observations of patients with otherwise classical bipolar affective illness who demonstrated mood cycle fluctuations faster than once every 24 hours (termed "ultra-ultra rapid" or "ultradian" cycling). Previously it had been thought that the fastest a patient with bipolar illness could cycle in mood was 48 hours, i.e., one day of heightened mood and one day of depressed mood. Dr. Kramlinger showed that many patients with ultradian

cycling require combination therapy with several mood stabilizers, such as lithium, carbamazepine, or valproate (although we have now observed patients who respond to nimodipine as well. [BNN Vol. 1 Is. 1]).

Dr Kramlinger returned to the Mayo Clinic in 1987. He took a one-year fellowship in the laboratory of the world renowned biochemist Urban Ungerstedt in Stockholm, Sweden, in order to acquire expertise in the use of *in vivo* dialysis.

The Network looks to Dr. Kramlinger to bring his experience and skills to assist in the implementation and coordination of this complex multi-center undertaking in order to rapidly advance the clinical and biological knowledge base for better understanding and treatment of bipolar illness.



Keith G. Kramlinger, M.D.
Mayo Clinic, Rochester, MN

Are you connected to the Internet?

See this issue of the Consumer Corner for the Stanley Foundation HomePage address!

For further information about the Stanley Foundation Bipolar Network or if you have specific questions about potential participation call the Stanley Foundation Bipolar Network (SFBN) at:

1-800-518-SFBN(7326)

Breakthroughs in Brain Imaging of the Recurrent Affective Disorders

Researchers at the NIMH's Biological Psychiatry Branch and elsewhere, have made remarkable strides over the past several years in discerning the neurochemical and neuroanatomical substrates for depression. Dr. Terence A. Ketter has found that bipolar I patients tend to show relative functional hyperactivity in their temporal lobes while unipolar depressed patients tend to show hypofunction in the frontal cortex compared with normal volunteer controls. Bipolar II depressive subjects are more heterogeneous and show degrees of both abnormalities.

These different cerebral topographies imaged with positron emission tomography (PET) scan have been preliminarily linked to clinical response to different drug treatments. Dr. Ketter has found that patients with the pattern of temporal lobe hyperactivity tend to respond to the anticonvulsant carbamazepine, while those with the pattern of frontal hypoactivity tend to respond to the calcium channel blocker nimodipine (See BNN Vol. 1 Is. 1). In each instance patients who respond on the drug have a relative normalization of their glucose utilization (metabolic activity as measured by the PET scan) in the areas that were aberrant. In contrast, non-responders to these agents show lack of improvement or further exacerbation of the initial defect. In the future it is hoped that these data can be strengthened and extrapolated so patients can be rapidly matched to drugs to which they are most likely to respond.

A variety of other studies using diverse methodologies implicate limbic system dysfunction in the affective disorders as well. This system consists of structures in the medial part of the temporal lobes of the brain, long thought to be involved in normal and pathological emotion regulation. *The limbic system includes structures such as the amygdala, hippocampus, septum, and anterior cingulate gyrus with connections to the insula, and orbital frontal cortex.* There is some evidence of hypometabolism and decreased blood flow in these structures at rest, but in depression the main evidence of their hypofunction occurs when these

structures are activated with specific neuropsychological tasks or with a pharmacological probe, such as the local anesthetic procaine (Novocaine®).

Using psychological activation strategies, Dr. Mark S. George has observed that affectively ill patients not only show deficits in recognizing the type of facial emotions displayed in pictures of facial expressions, but also fail to activate the appropriate anterior temporal area normally involved in this function in healthy volunteers. Similarly, when they do a Stroop test (which involves minor degrees of cognitive conflict, e.g., reading the word "blue" when it is printed in red letters) depressed patients also fail to activate the middle part of the cingulate gyrus (George et.al., *Human Brain Mapping*, 1:194-209, 1994).

Dr. George and colleagues also found that depressed patients have difficulty in accessing normal emotions of happiness and sadness when they think about past experiences in their lives and look at emotion-appropriate pictures of faces. When normal volunteers become transiently sad they activate various parts of the limbic system and frontal cortex (George et al., *Am J Psych*, 152:341-351, 1995).

Remarkably, healthy women use seven times more of the anterior limbic system and the left anterior part of their brains when they are getting into the mood of a past sad event, compared to a happy one, or compared to men experiencing similar degrees of self-rated sadness or happiness. Affectively ill patients show not only psychological difficulties in accessing these mood states, as might be expected, but also show alterations in limbic activity and frontal blood flow as well.

Finally, Dr. Ketter's work with procaine shows remarkable deficits in the ability of affectively ill patients to activate the limbic system. Procaine, a limbic-selective probe when administered intravenously, increases activity in the amygdala, insula, orbital frontal cortex, and anterior cingulate gyrus. This limbic activation studied in 32 healthy volunteers, has been associated with different patterns of mood response ranging from euphoria

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Schizophrenia-Bipolar Symposium

Reviewed by Robert M. Post, M.D.

At the 1995 International Schizophrenia Conference Stanley Foundation Satellite Symposium: "The Schizophrenia-Bipolar Interface: Current Research and Future Directions" organized by Dr. E. Fuller Torrey, there was a rich exchange of important new scientific data, insights, and areas of future exploration. The purpose of this symposium was to bring together researchers to explore the commonalities and differences in these two major mental illnesses.

Two polar arguments were presented. Dr. Irving Gottesman maintained that the two illnesses are separate, breed true, and are polygenic (i.e., more than one gene is expressed in the development of these disorders). Dr. Tim J. Crow argued that schizophrenia and bipolar disorder are not separate diseases, but are on a continuum with no clear "cut points" in the diagnostic boundaries in patients or their offspring. Yet, Dr. Crow feels that a single gene underlies the development of these illnesses (which this observer, at least, considers an unlikely proposition, ed.)

Other researchers have found that physical and environmental factors may be involved in the development of schizophrenia. Dr. John L. Waddington presented evidence that there were minor physical abnormalities associated with the illness, suggestive of developmental abnormalities. He also presented evidence that illnesses tended to cluster in various parts of Ireland, suggesting involvement of environmental factors. Dr. Robin M. Murray suggested that males were overly represented in early onset neurodevelopmental schizophrenia associated with physical anomalies while females were preponderant in those with later onsets in adulthood associated with life events; this latter type of illness conveyed a much more positive prognosis.

Dr. E. Fuller Torrey presented new and exciting data on seasonality of birth in patients with schizophrenia and bipolar disorder, finding a clear-cut winter seasonality for schizophrenia and somewhat overlapping spring seasonality for schizoaffective illness and bipolar disorder. These data further fuel the argument of an infectious agent

potentially being involved. Using these calculations, Dr. Torrey felt that perhaps only 10% of schizophrenia and 30% of bipolar illness was genetic. Dr. Bob Yolken furthered the notion that a viral infection could be associated with these neuropsychiatric disorders. He considered the potential of retroviruses to mimic neurotransmitter function and to induce super antigens. In the DNA from lymphocytes of bipolar monozygotic twins discordant for the illness, he found an E-cadherin gene insert overly represented in the ill twins.

This exciting finding possibly suggests that a viral infection could be associated with a neuro-developmental abnormality, as cadherin is a gene critical in CNS development. Dr. Yolken also presented evidence of an AA71 virus inserting a triple repeat sequence into the ill twins, again suggesting the possibility of a viral etiology of the bipolar syndromes and potential explanation for the phenomenon of genetic anticipation with earlier onsets of illness in each generation.

Dr. Robert Post reviewed treatment commonalities between bipolar illness and schizophrenia with the general view that lithium and the anticonvulsants are sequentially less effective as one moves from treating pure bipolar illness to schizoaffective illness to schizophrenia. The atypical neuroleptics play an important role in the treatment-refractory rapid cycling bipolar patients and are increasingly recognized and used for their treatment of negative-symptom schizophrenia. The calcium channel blockers may represent one area of clear-cut differences in the two syndromes with many patients showing positive responses in the anxiety and affective disorders, but exacerbation of schizophrenia as reported by Dr. David Pickar. In both syndromes there is evidence that early intervention and sustained long-term prophylactic treatment may yield a beneficial outcome on not only recurrence, but on the course of illness. There is substantial evidence indicating that repeated relapses can make psychopharmacological response more difficult in both affective disorders and schizophrenia. Some of these changes may be driven by illness-related alterations in gene expression.

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*Brain Imaging:**Continued from Page 5...*

to dysphoria and panic (Ketter et.al., *Arch Gen Psych*, 1996). These data are convergent with the view that abnormalities in limbic system function could mediate both the euphoric and dysphoric components of bipolar affective illness.

The data obtained in baseline resting PET scans and neuropsychological and pharmacological activations are consistent with the view that there are both frontal cortical and temporal-limbic dysfunctions in patients with affective disorders and might be linked to differential pharmacological response.

In a future BNN issue, Dr. George will review his exciting findings from the BPB in collaboration with researchers of the National Institute of Neurological Disorders and Stroke (NINDS) indicating that repeated transcranial magnetic stimulation (rTMS) of the brain may be able not only to exert positive therapeutic effects in patients with parkinsonism, but may have antidepressant properties as well.

Since rTMS is capable of providing electrical stimulation of the brain without producing seizures or the need for anesthesia, it could ultimately provide an alternative to electroconvulsive therapy if initial findings are confirmed in an on-going double-blind clinical trial. It would also raise the possibility that the alterations in cerebral glucose metabolism and blood flow observed on PET scans or functional Magnetic Resonance Imaging (f-MRI) could not only be used for diagnostic and therapeutic purposes in targeting patients to the most appropriate drug treatments, but also that these excesses and deficits in function could be ameliorated with rTMS.

What is the Stanley Foundation Bipolar Network?

The Stanley Foundation Bipolar Network is 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 managing this illness.

*Symposium Summary:**Continued from Page 6...*

At a different part of the meeting, Dr. Joe Coyle presented a new concept about the potential pathophysiology of schizophrenia. PCP, a glutamate antagonist, mimics positive and negative aspects of schizophrenia. However, it is puzzling how glutamate antagonism could be associated with a long-term neuro-degenerative process when this has typically been associated with glutamate-agonism or excess. Dr. Coyle linked the two concepts by suggesting that N-acetyl-aspartyl glutamate (NAG), a chemical within the brain, acts as a natural glutamate antagonist and has been found to be elevated in patients with schizophrenia. NAG is converted by the enzyme naladase to glutamate and N-acetyl-aspartate. Naladase has been found to be deficient in patients with schizophrenia. This deficiency leads to an increase of NAG which blocks activation of inhibitory GABA interneurons. This in turn causes glutamate cells to increase their firing which further leads to excitotoxicity and programmed cell death (apoptosis) in neighboring brain cells. The loss of cells in the limbic and frontal cortical areas of the brain may explain some of the structural changes and neuronal cell loss that are reported in schizophrenia.

Consumer Corner*

*Note that while NAMI publications typically refer to afflicted individuals as consumers rather than patients, the Stanley Foundation Bipolar Network will continue to use the terms interchangeably. The SFBN will focus on "patients" in an effort to continue to medicalize and destigmatize bipolar illness.

We want to thank all of our BNN readers for writing in with their comments and questions. Overall, our readers have found the BNN to be "interesting," "a vital source of information," and "the research much appreciated."

Other readers have written asking to use information in the BNN in their newsletters and to give it to other interested people. Please feel free to copy and distribute the BNN to others. It is our goal to share information, research news, and treatment findings, and we appreciate your help.

The following is a comment submitted by one of our readers:

I have not met one "consumer" who liked being labeled "consumer." Some accept it because they think they can't change it (probably true). Some don't like being called "patient," but one who goes to a doctor is a "patient." I am a "survivor," (for 11 years anyhow). Webster's definition of

"consumer" is one that consumes, specifically one that utilizes economic goods.

B. Green

BNN is Available on the Internet

The BNN is a free publication, available by mail and now via the Internet and World Wide Web! The SFBN e-mail address is:

stanley@sparky.nimh.nih.gov.

If you have access to the World Wide Web, the Stanley Foundation Bipolar Network Homepage address is: <http://165.112.218.13>. The SFBN Homepage is available between 4 p.m.- 6 a.m. daily. Past and current issues of the BNN can be accessed easily, as can other information pertaining to bipolar illness.

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