

Bipolar Network News

Welcome to the Network

Robert M. Post, M.D.

We wish to welcome physicians, researchers, patients and their families, and interested readers to the Stanley Foundation Bipolar Network and the first issue of the Bipolar Network News (BNN). The Network developed out of increasing recognition that bipolar illness was receiving inadequate research attention, and is made possible by the determination of the Theodore and Vada Stanley Foundation to address this need. The mission of the Network is to advance scientific understanding of the causes and treatments of bipolar illness, with the goal of establishing optimal long-term treatment strategies.

The Network creates an alliance of expert researchers and clinicians working in close association with the National Alliance for the Mentally Ill (NAMI) and the National Depressive and Manic-Depressive Association (NDMDA). There are currently researchers at five sites (four in the U.S. and one in Europe) participating in the Network. The goal is to utilize randomized clinical trials with large numbers of consumers in academic and clinical practice settings to assess the acute and long-term effectiveness of different treatments for bipolar illness.

While lithium carbonate is a wonder drug for many who suffer from bipolar illness, it is increasingly recognized that numerous people require augmentation of lithium with other agents or are inadequately responsive to or intolerant of this medication. The mood stabilizing anticonvulsants carbamazepine and valproate can play an important role as alternatives or adjuncts to lithium, but questions regarding dosage and optimal combination strategies remain to be answered. Further, there is a great deal of research to be done on the effectiveness of the various antidepressants in bipolar illness so that breakthrough depressive phases can be treated successfully with a minimum risk for switching into mania.

The first Network study will be a comparison of two antidepressants with different mechanisms of action: bupropion (Wellbutrin) and sertraline (Zoloft). These antidepressants will be assessed as adjuvant treatment to mood stabilizers for efficacy not only in acute depressive phases but in long-term prevention of depressive episodes as well.

The Network will function on a number of different levels of methodological rigor. In this "pyramidal" fashion, the top level will consist of relatively small, double-blind studies conducted at academic research centers using comprehensive rating measures and controlled randomization procedures. At the mid-level of the pyramid, much larger numbers of participants will be enrolled in open (not blind) randomized clinical trials. At the base of the pyramid, consumers in everyday treatment settings will participate in randomized, open clinical trials utilizing a minimum of structured rating materials. We hope that a large group of patients and physicians will participate in the Network, and look forward to establishing a truly collaborative effort.

"The mission of the Network is to advance scientific understanding of the causes and treatments of bipolar illness...."

This newsletter will serve as a vehicle for providing information on activity and progress in the Network, as a link between physicians and patient participants, and as a means of sharing research news and treatment findings. We hope that readers will participate in the Network and in the BNN by sharing experiences. We look forward to becoming a vibrant, collaborative network of patients, families and physicians dedicated to the goal of improved understanding and treatment of bipolar illness. Welcome, again, to this exciting and promising endeavor.

Life Charting: A Portable Psychiatric History *Gabriele S. Leverich, M.S.W.*

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A fundamental principle of the Stanley Foundation Bipolar Network is patient participation in the illness assessment and treatment decision process. Those who volunteer to become part of the Network will be invited to participate in the systematic charting and monitoring of their own retrospective (historical) and prospective (current and ongoing) course of illness utilizing the NIMH Life Chart Method (LCM).

Careful monitoring and record keeping are particularly important for people with bipolar illness. There can be great variability in frequency, duration, and severity of manic and depressive episodes, not only from person to person but also in the course of one person's illness over time. The life chart provides a means of recording and tracking episodes, medications, severity of mood (both manic and depressive), hospitalizations, and concurrence of significant life events. With daily entries, a graphic representation of the course of illness and response to treatment is built. It can be easily shared with treatment providers or family members and becomes a continuous and permanent record.

Crucial aspects of each person's course of illness emerge in the construction of a life chart. These may include: 1) prior responses to treatment, including partial responses and possible development of tolerance to some medications; 2) cycle acceleration independent of treatment or associated with some antidepressant medications; 3) periods of noncompliance or drug discontinuation that are associated with relapse; and 4) vulnerability to episode recurrence in the presence of psychosocial stressors. The life chart thus helps clarify responses to and choices of psychotherapies and drug treatments in various phases of the illness.

The life charting process can also help identify new and not yet studied aspects of the illness. A particularly poignant example of the value of

life charting is illustrated in the life chart on page 3. We are much indebted to Marina Geracoulis, whose experience directed us to a previously undescribed phenomenon now known as lithium discontinuation-induced refractoriness.

After the rapid onset of her illness with five severe, incapacitating depressions each lasting two to three months and followed by milder and briefer hypomanias, Ms. Geracoulis initiated long-term treatment, experiencing seven years of complete remission with renewed enjoyment of her life, family, and rewarding productivity. She considered lithium a "miracle drug." However, with the support of her physician she slowly tapered the dosage of her lithium thinking that ongoing treatment was no longer necessary. Unfortunately, she suffered a severe relapse 1½ years later (the relapse rate for people with bipolar disorder is 90% in the first 18

months after stopping medication [Suppes et al., 1991; *Arch. Gen. Psych* 48:1082-1088]). Despite restarting lithium immediately at the previously effective dose, and higher, she did not re-respond to lithium and remained treatment refractory to a variety of other medication combinations for the next five years.

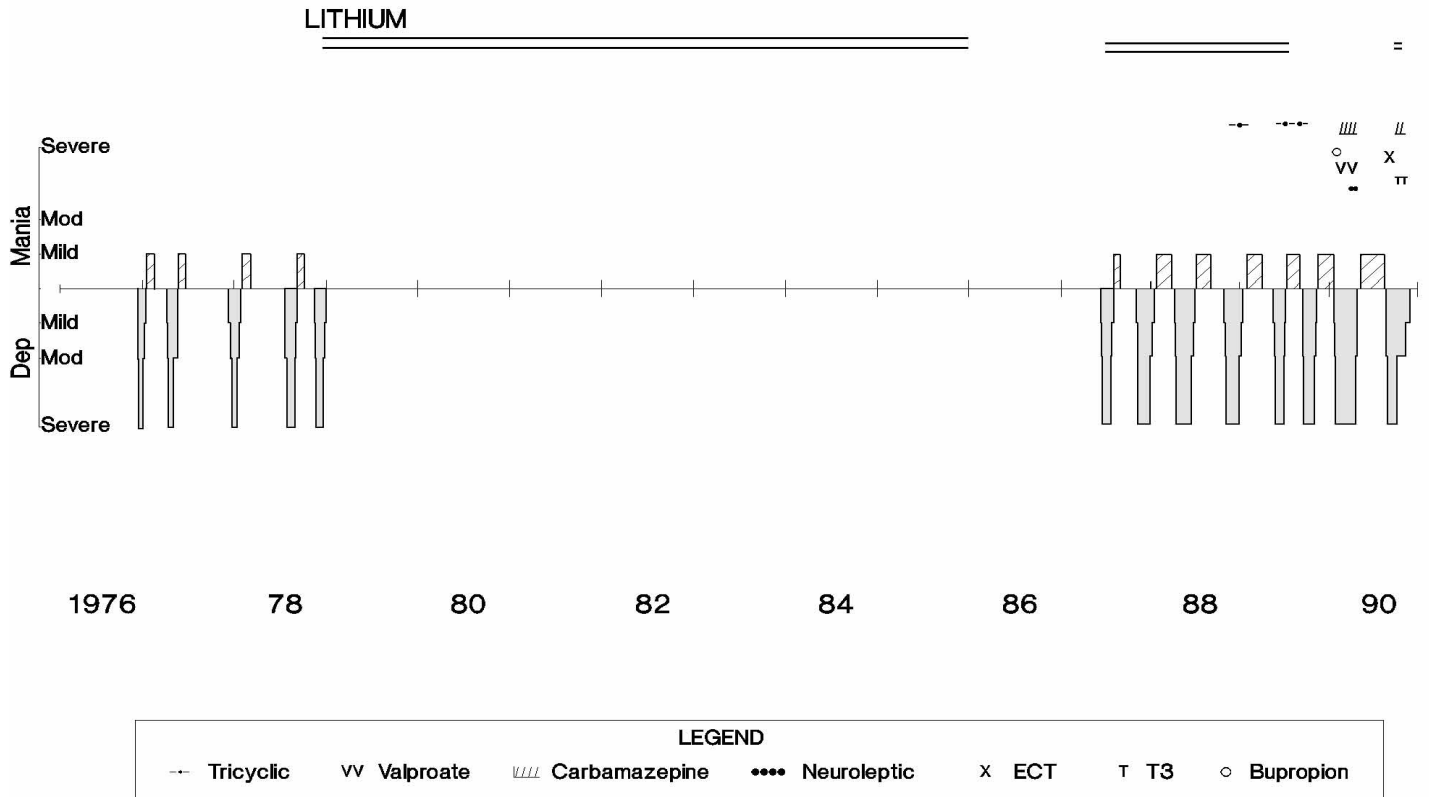
Ms. Geracoulis, who came to NIMH for a series of experimental drug trials, gave us permission to use her life chart as a teaching and research tool for patients and clinicians. She has also been active in telling other patients and members of advocacy groups not to discontinue effective long-term treatment of their illness without serious consideration with their physician of all the dangers, including discontinuation-induced refractoriness.

(Continued on page 4)

*"Careful
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LITHIUM DISCONTINUATION-INDUCED REFRACTORINESS

Pt. 5459



This life chart clarifies how graphic depiction of a course of illness and response to treatment can uncover a new phenomenon of considerable clinical importance. This life chart suggests that if this patient had continued her treatment with lithium, she would have stayed well. Discontinuing an effective medication can thus potentially add another liability to the already high risk of recurrence following the discontinuation of lithium, namely the possibility of failure to re-respond, as illustrated in this figure. Together these observations point to the importance of staying on long-term effective medications for bipolar illness even when there have been no problems for many many years!

Life Charting, cont. from page 2

In light of Ms. Geracoulis' experience, all NIMH life charts were re-reviewed and it was determined that a group (14%) of people who had become unresponsive to lithium shared this mode of lithium discontinuation-induced refractoriness. In other words, discontinuation of effective lithium therapy can result, for a small subgroup of patients, in recurrence of a pattern of cycling which may become unresponsive to subsequent re-initiation of lithium and/or other medications. We published our initial observations as a brief report (Post et al. 1992; *Am J Psych* 149:1727-1729) to alert physicians to the possibility of this phenomenon, which has since been observed by other clinicians.

We believe that the construction of a retrospective (historical) life chart and continued prospective (current and ongoing) charting of the illness are of value for everyone involved. The life chart represents a portable psychiatric history and enhances the partnership between patient, family and clinician.

Within the Stanley Foundation Bipolar Network, the LCM will be utilized as an important measure of outcome in the various research protocols. We will continue in this newsletter to publish information and findings derived from life charts as part of our effort to promote a collaborative and productive dialogue between patients, researchers and clinicians.

If you are interested in more information on life charting and its use in recurrent affective disorder, contact:

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Research Note**Current Findings**

A promising but not definitive marker for vulnerability to manic depressive illness has been found on chromosome 18. However, researchers reporting their findings at the 1994 meeting of the American College of Neuropsychopharmacology caution that it is likely to be many years before the biochemical defect coded by this area of chromosome 18 is identified, and note that the current state of knowledge is not sufficient to provide a diagnostic test.

AROUND THE NETWORK

In future issues of the Bipolar Network News we will spotlight activities of interest at the various research centers participating in the Network's clinical trials. To date, the principal investigators and field centers include:

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*An important goal of the Network is to encourage the exchange of information among clinicians concerning important issues in the diagnosis and treatment of bipolar disorder. The **Clinical Update** will provide a forum in which this exchange can take place. We will use this vehicle for reporting important research findings and articles of interest from the literature. The BNN invites clinicians to share clinical experiences, and research findings.*

Recognizing Lithium Failure

Although over half of those people with bipolar disorder who are on lithium therapy relapse while on the drug, this "failure" is often not recognized, and alternative or adjunctive therapies are often overlooked, according to Jonathan M. Himmelhoch, MD ("On the failure to recognize lithium failure," 1994; *Psych. Annals* 24:241-249).

Himmelhoch contends that part of the problem is the mistaken notion that lithium is solely an antimanic agent. In fact, it functions in the system in numerous ways, and has potent antidepressant effects both as a monotherapy and as an antidepressant augmenting agent. Himmelhoch notes that lithium's effects can be very subtle and may vary depending on the current affective state of the patient. Thus, strict adherence to traditionally accepted therapeutic serum levels may overlook the varying clinical effects of lithium and often results in levels that are too high or are subtly toxic. (The author notes numerous side effects such as weight gain, thirst, sluggishness, and decreased sex drive which are often tolerated unnecessarily as they might be alleviated by lowering the dose of lithium.) In other words, the wide range of mood states of the patient (manic, hypomanic, mixed, depressed, agitated, etc.) as well as the more subtle side effects must be recognized and the effects of pharmacological treatment monitored in light of these variations so that appropriate and optimal treatment decisions can be made.

Himmelhoch concludes by recommending that "...although lithium salts remain the principal agents for the management of manic-depressive illness, they cannot be used in a heavy-handed, mechanical fashion. Moreover, lithium therapy must often be supplemented by polypharmacological interventions consisting of permutations and combinations of antikingling agents, monoamine oxidase inhibitors, serotonin reuptake inhibitors, neuroleptics, benzodiazepines, and/or calcium channel blockers if optimal management of manic-depressive illness is to be achieved."

(Editor's note: Himmelhoch's arguments point to the usefulness of utilizing the life chart method for tracking an individual's illness over time. All the subtle or dramatic responses to lithium and other medications, as well as the entire range of dramatic and subtle side effects, are made visible for consideration and evaluation by consumer and physician, thus enhancing the likelihood of optimum treatment choices being made.)

Calcium Channel Blockers

An article by Pazzaglia et al. ("Preliminary controlled trial of nimodipine in ultra-rapid cycling affective dysregulation," 1993; *Psych Res* 49:257-272) reports the successful use of the calcium channel blocker nimodipine (Nimotop) in a small number of subjects at the NIMH with rapid and ultra-rapid cycling bipolar illness. In several instances, participants improved on active drug, relapsed on placebo, and improved again when the drug was reinstated. (A double-blind methodology was used.) In an extension of the original study, one-third of 26 otherwise refractory participants improved when treated with nimodipine alone or in combination with the mood stabilizing drug carbamazepine (Tegretol). The authors note that much work still needs to be done to more accurately define the population most likely to respond to nimodipine. Responders to nimodipine, which is very expensive, failed to respond to another calcium channel blocker verapamil (Calan), but were well maintained on the calcium channel blocker isradipine (DynaCirc).

Clinical Update

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 hope that this newsletter will serve as a vehicle for the exchange of information, ideas, and concerns among consumers and their families, and clinician investigators. To that end, we plan to use this section of the BNN to provide a format for sharing views on research, treatment, resources, experiences, ideas, and other areas of concern to readers. The Network's success depends very much on the interactions and collaboration of its participants, and we hope to reflect a sense of shared investment and effort. Anyone may write or fax the BNN at the address or fax number listed on page 2. Thanks to everyone involved and concerned.

Readers who would like information about local support groups, government programs, medications, or brochures on mental illness should call the **HELPLINE** of the National Alliance for the Mentally Ill at:

1-800-950-NAMI
(1-800-950-6264)

The **HELPLINE** is staffed by volunteers who are themselves consumers or family members of people suffering from severe mental illness.

Another resource is the National Depressive and Manic-Depressive Association, a national education and advocacy organization made up of patients, family members, and mental health professionals. You may reach NDMDA at:

1-800-82-NDMDA
(1-800-826-3632)

The BNN staff expresses its gratitude to Susan W. Post whose contribution of time, ideas, and editorial suggestions has resulted in the creation and evolution of this publication.

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