

Bipolar Network News

Clinical Trials Update

Nineteen ninety-seven brings the Bipolar Network to a new stage in which multiple clinical trials are being conducted in a blind fashion at academic sites (at Level I), and parallel studies are being offered in a randomized but open fashion for patients who are treated in clinical practice settings (at Level II). In this latter instance, minimal physician time is required and only a brief global outcome assessment is utilized to assess the relative effectiveness of the medications that are being evaluated. Patients, who are very much active collaborators, provide more detailed Network outcome measures about the course of their illness and their response to treatment.

The Bipolar Network materials are designed in such a way that a detailed tracking of the longitudinal course of the illness is as much a clinical device for optimizing treatment response as it is a systematic research tool. In this fashion, we hope to recruit relatively large numbers of patients into randomized, but open, clinical trials to gain information, as rapidly as possible, about what might be optimal strategies at each clinical choice-point. Physicians and patients do not currently have a systematic database at these choice-points upon which to make judgments about the relative efficacy of one or more clinical interventions in a given situation.

Thus, at level III, a randomized clinical trial is available for bipolar patients suffering depression breaking through concurrent mood stabilizer medication (antidepressant trial #1, i.e., 1-AD). Patients may be randomized to start on one of three different treatments with novel mechanisms of action: bupropion (Wellbutrin®) with its predominant dopaminergic mechanisms, sertraline (Zoloft®) as a representative of the serotonin-selective reuptake inhibitors (SSRI), and venlafaxine (Effexor®) as an SNRI (serotonin-norepinephrine reuptake

inhibitor). Non-responders will be crossed over to the other agents. Responders to any of the three drugs will be offered one year continuation therapy in order to document long-term effectiveness in preventing further depressive episodes without engendering additional manias.

A second protocol (2-AD) for treatment of patients with incomplete responses to antidepressants during bipolar depression involves a randomization between the psychomotor stimulant methylphenidate (Ritalin®) versus thyroid augmentation with T₃ (Cytomel).

If patients are inadequate responders to either protocol 1 or 2, or are not eligible for them, they may enroll in a third antidepressant protocol (3-AD), the first of its kind, comparing a traditional antidepressant of the monoamine oxidase inhibitor (MAOI) category (tranylcypromine [Parnate®]) with a putative new mood stabilizer anticonvulsant with preliminary evidence of good antidepressant properties (lamotrigine [Lamictal®]). Since many antidepressants that are effective in bipolar depression also increase the risk of switches into mania or increases in cycle frequency, the direct comparison of an antidepressant with a potential mood stabilizer will be of critical importance in ultimately informing patients and physicians about optimal choices of first- and second-line strategies for bipolar depression.

A series of anti-manic (AM) and anti-cycling (AC) protocols involve the study of the drugs (#4) gabapentin (Neurontin®) and (#5) lamotrigine (Lamictal®), two recently ap-

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proved anticonvulsants for “add-on” therapy in refractory epilepsy, with some preliminary evidence of their ability to stabilize mood. Patients can enter industry-supported acute drug trial comparisons of these drugs with placebo and then participate in follow-up studies in the Network, or they can directly enter a randomized comparison of lamotrigine versus gabapentin on an open basis in Level III of the Network.

Clinical trials of the new atypical neuroleptic olanzapine (Zyprexa® #6-AC) will also be available at Level III in the Network in order to ascertain whether this agent, which is biochemically most similar to clozapine (Clozaril®), but does not produce agranulocytosis (decreased white blood cell count) and thus does not require frequent blood monitoring, is able to help some treatment-refractory patients with rapid cycling and dysphoric manic presentations of bipolar illness. The “atypicality” of this drug involves typical effects of a major tranquilizer in treating psychosis, but without the liability of causing acute extrapyramidal motor side effects (such as parkinsonian rigidity) or, presumably, the risk of longer-term tardive dyskinesia. This “atypical” profile is thought to relate to the ability of drugs to block D1 and D4 dopamine receptors in brain areas important for regulation of emotional and cognitive functioning (such as the amygdala, thalamus, and prefrontal

cortex, as well as nucleus accumbens), without major effects on the caudate nucleus and other elements of the extrapyramidal motor system.

We hope that physicians and patients will join this clinical trial in clinical trial in clinical practice (Level III) aspect of the Stanley Foundation Bipolar Network so that a partially controlled, systematic, new knowledge base can be acquired as quickly as possible in a larger number of patients to help identify the best options in the clinical treatment of patients with bipolar illness.

Life Chart Highlight

Acute Response to Carbamazepine in a Lithium Non-Responder: Long-Term Follow Up

This patient whose life chart is shown on the next page is a 58-year-old mother of several children whose illness started at age 17 with a brief manic episode, several years of remission, and a recurrence of her illness with a severe depression and treatment with ECT at age 25. Another moderate depression with multiple suicide attempts occurred at age 27. Several years of relatively stable mood were ended by a severe depression followed by a hospitalized mania and two more profound depressions in the next year. A subsequent episode-free period of three years was disrupted by a severe depression and a manic episode (not shown in this life chart graph).

This seemed to mark the onset of illness acceleration and the patient experienced multiple hospitalizations for acute manias that proved unresponsive to the institution of lithium and adjunctive medications in 1974. In 1978, at age 39, she was referred to NIMH for further evaluation and study participation. During another manic episode, carbamazepine (Tegretol®) was started blindly and resulted in dramatic amelioration of her manic symptoms. To confirm that this response was due to the medication rather than a spontaneous remission, placebo was substituted under double-blind conditions. When the patient showed a recrudescence of her mania, double-blind carbamazepine was again restarted with good results.

Since there had been an ongoing discussion as to whether the patient had been compliant with her lithium regime in the past, she was discharged to outpatient status on lithium with very close monitoring and therapeutic blood levels of .7meq/l and higher. Despite this, a third manic episode occurred which again rapidly re-responded to the blind institution of carbamazepine, thus demonstrating unequivocally her carbamazepine responsiveness. Following the appearance of moderate depressions on carbamazepine, lithium augmentation was started with good result.

The patient did well for the next two years with only a brief moderate depression for which an antidepressant was added. When she discontinued carbamazepine and lithium in 1981, a full-blown manic episode occurred, further confirming her need for prophylactic medications

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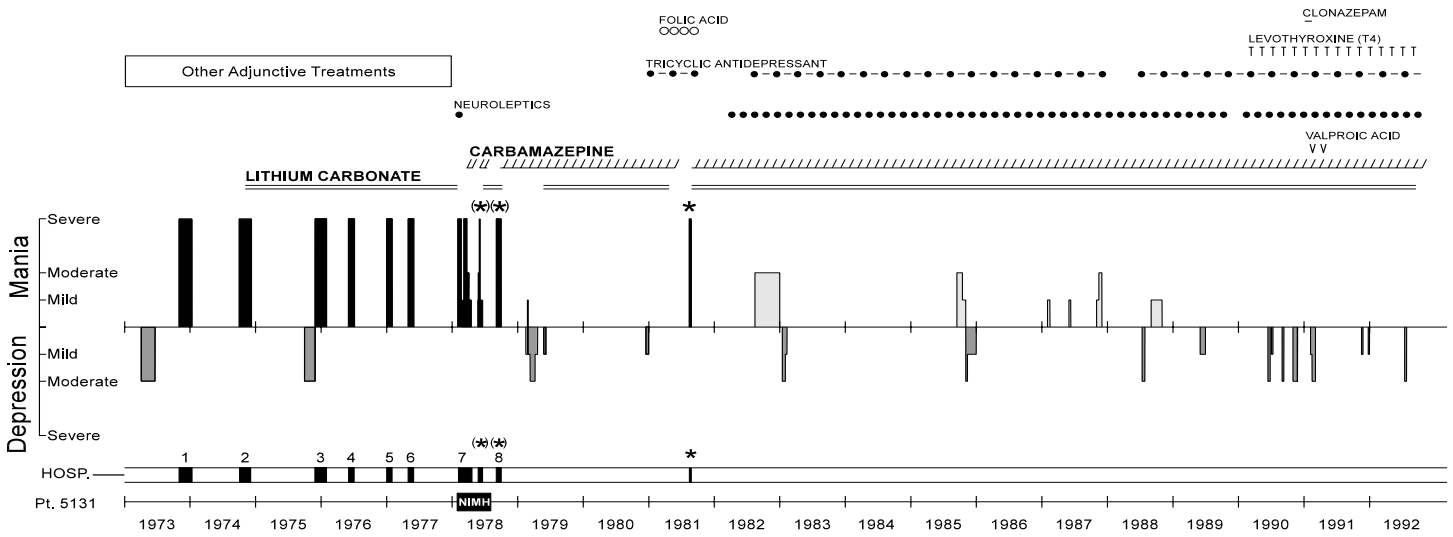
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CONFIRMED ACUTE AND PROPHYLACTIC RESPONSE TO CARBAMAZEPINE
IN A LITHIUM NONRESPONDER**



*Relapses Observed
During Carbamazepine
Withdrawal; () = on Blind Basis

1973 | 1978 | 1979 | 1992

8 Hospitalizations for 9 Manias in 5 years | **0 Hospitalizations for Mania in 14 Years on Carbamazepine/Lithium Combination (with adjuncts)**

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to sustain her remission. The patient was rapidly restarted on the lithium/carbamazepine combination with good response, and she experienced no further hospitalizations over the next 16 years. Because of some ongoing mood lability breaking through this combination therapy, a tricyclic antidepressant and low dose neuroleptics were used adjunctively to augment the good response to the mood stabilizers.

A variety of studies, summarized by Vestergaard and many others, indicate that lithium is now often a less than adequate treatment for mood stabilization. This patient showed multiple manic relapses despite lithium treatment prior to NIMH, and despite close monitoring of her lithium in our outpatient clinic and excellent compliance, she again relapsed but rapidly restabilized on carbamazepine. These data are convergent with a number of controlled or partially controlled studies of carbamazepine prophylaxis which indicate an approximate 61% marked or excellent response. This closely approximates the 62% rate in a much larger group of uncontrolled studies reviewed elsewhere (Post et al. 1996, The place of anticonvulsant therapy in bipolar illness, *Psychopharmacology* 128, 115-129).

Lithium and carbamazepine share some mechanisms of action, such as the ability to decrease the second messenger adenylate cyclase, and some of the associated G-protein responses, as well as increasing substance P levels in the striatum and decreasing GABA_B receptors in the frontal cortex of animals with chronic but not acute administration. However, there are a multitude of differences as well, and it is unclear whether the shared mechanisms of carbamazepine and lithium could account for their important effects in affective illness or whether the differential properties of these compounds add together to make a more robust response than either agent alone, as suggested by the life chart shown in this article.

Since carbamazepine is an anticonvulsant, we originally thought that its ability to dampen activity in the limbic areas of the brain may be important in its action. However, when we evaluated limbic hyperactivity through an assessment interview of psychosensory symptoms (commonly described in epilepsy), we found that the patients with the highest percentage of answers that endorsed psychosensory symptoms, were better responders to lithium. However, more recently, Ketter and associates

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Meeting Update

Review of the American College of Neuropsychopharmacology (ACNP) Meeting December 9-13, 1996: Bad News/Good News

The ACNP continues to be one of the premier fora for interchange among clinicians and basic scientists interested in advancing the field of treatment of the major neuropsychiatric disorders. Only a very few of the multiple exciting new findings in the field presented at the ACNP can be alluded to here.

Politics of Bipolar Illness Research

Before mentioning these several highlights, however, it is important to note that, for the second consecutive year, clinical, pharmacological, and neurobiological approaches to bipolar illness have been grossly neglected in comparison with other major psychoses such as schizophrenia. Sixteen major panels or symposia were related to the better understanding or treatment of schizophrenia, with an average of five speakers and one discussant per 3 ½ hour symposium. In marked contrast, only one, and if one stretched it a bit, two symposia were directly pertinent to bipolar illness or its pharmacotherapeutics.

This general state of affairs is not entirely unexpected. NIMH-sponsored meetings on bipolar illness were specifically convened in 1989 and 1994 to address the reasons for the relative neglect of the study of bipolar illness and its therapeutics compared with the other major psychiatric illnesses. No notable increases in funding for bipolar illness have occurred, and the decade of neglect and lack of adequate funding of studies in bipolar illness is now being reflected in the dearth of representation of bipolar illness in the ACNP program over the past several years.

[Editor's Note: We suggest that bipolar illness should be specifically targeted for increased funding, with some sort of adjustment given in the priority scores or a specific amount set aside. This would help insure that some modicum of studies can be NIMH-funded in this area despite continued arguments about optimum methodology and research designs that will likely continue for some time to come, as outlined in our December 1996 BNN issue. This would appear an ideal area for input from advocacy groups, since this strategy has proven very effective in reallocating funds in other branches of medicine toward specific targeted illnesses, such as breast cancer or AIDS.]

Despite the gloomy bipolar illness research portfolio of the extramural NIMH program, there are still many reasons for optimism. Individual small investigator grants sponsored by the Stanley Foundation and NARSAD are increasingly funding novel research in bipolar illness with some considerable success. The Stanley Foundation is also supporting a variety of sites participating in the Bipolar Network, as well as a separate Centers program. Moreover, for the first time in several decades, drug companies are beginning to fund clinical trials in bipolar illness whereas, previously, major pharmaceutical company interest had focused predominately on schizophrenia, depression, anxiety, and obsessive-compulsive disorder, while bipolar depressed patients have generally been excluded from antidepressant clinical trials. Now, in addition to the industry-sponsored trials with divalproate sodium (Depakote®) that led to its approval by the FDA two years ago, there are studies in bipolar illness of the potential mood-stabilizing anticonvulsants lamotrigine (Lamictal®) and gabapentin (Neurontin®), as well as the atypical neuroleptic olanzapine (Zyprexa®). In addition to the clinical trials by our group and those of Mark George in South Carolina, a variety of other investigative groups within and outside of the Stanley family are exploring the potential clinical efficacy of repeated transcranial magnetic stimulation (rTMS) of the brain. Preliminary studies provide some hope that a subgroup of otherwise drug-nonresponsive patients with unipolar and bipolar depression may respond to this modality, as reviewed in more detail in *BNN* 1(3), 1995 and *BNN* 2(3), 1996.

Selected Highlights from the ACNP

An interesting symposium was conducted on the potential relevance of oxytocin and vasopressin as brain peptides that might be involved in social affiliative behaviors as well as aggression. This work has been highlighted by Tom Insel with the findings of increased oxytocin receptors in the brains of social voles (small rodents), compared to a closely related strain of non-social voles.

Findings of Eric Hollander at Mt. Sinai raise the question of whether autistic children, with their major cognitive and social/emotional defects, have a higher incidence of births involving a pitressin drip, which could affect the development of these peptide systems. This group has also found

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preliminary positive effects of oxytocin-related compounds on autism, and a variety of agonists and antagonists are being developed that will ultimately lead to better clinical research tools and, potentially, new therapeutic approaches.

Steve Paul, the former Scientific Director of the Intramural Program of the NIMH, and now one of the chief medical officers of the Eli Lilly Corporation, gave a talk about new drug development from the extremely optimistic perspective that virtually any neurotransmitter receptor system can now be systematically targeted for new drug development. He indicated that there is a high likelihood of finding an orally active drug for any receptor system within a year or less, because of the new technical innovations available to industry and the automation of procedures that allow the screening of hundreds of thousands of compounds in the matter of only a few days.

Sol Snyder of Johns Hopkins presented exciting new work on the role that immunophilins may play not only in immunosuppression, but also in trophic effects in neuronal development, learning, memory, and neuronal re-growth after injury. In one set of preclinical studies, animals given these new compounds after injuries showed selective regrowth and functional activity of the damaged neurons. These, and a variety of other approaches directly or indirectly involving neurotrophic factors, also promise to yield a new generation of compounds that may be important for the neurodegenerative disorders as well as recovery and repair in the more traditional psychiatric disorders .

Chris Ross emphasized some of the implications of the clinical findings in molecular genetic neurobiology of Huntington's chorea for other psychiatric illnesses, including bipolar illness. He emphasized that the gene locus first located on the short arm of chromosome 4 has now been identified as a protein called "huntingtin", and that there appear to be associated proteins that might be involved in the degeneration of the caudate nucleus. This loss of neurons in the caudate accounts for the progressive onset of motor dyscontrol (i.e., the chorea), the inexorable progressive dementia, and premature death. He noted the high incidence of affective and bipolar affective presentations in patients with Huntington's chorea which often occur earlier than the motor or cognitive deficits. **[Editor's Note: These data, again, emphasize the potential role of the caudate nucleus or the dorsal striatum in the neurobiology of bipolar illness, even though this area of brain is often relatively neglected**

in favor of the more ventral aspects of the striatum, i.e., the nucleus accumbens, which is involved in the modulation of motor activity and reward behaviors in animals and other hedonic and anhedonic symptoms that are often part and parcel of the depressive disorders.]

The data also emphasize that it is the number of triple repeat expansions that occurred during germ line replications that account for the onset and severity of the illness. In general, all of us who have less than 36 trinucleotide repeats in our sequence coding for the huntingtin protein are free from the risk of Huntington's chorea. If one has just a few trinucleotide repeats greater than 40, the onset of Huntington's chorea is likely to be very late in life, in contrast to larger numbers of triple repeats over 60 or 70 which herald both an earlier onset and more severe form of the illness. This ability for expansion of trinucleotide repeat segments accounts for the phenomenon of genetic

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Life Chart Highlight (continued from page 3)

have reported that depressed patients who have global hypermetabolism, particularly in the temporal lobes, tend to be responsive to carbamazepine and that non-responders overwhelmingly belong to the depressed group which has the more typical pattern of initial hypometabolism at baseline. This latter group of patients appears to be more responsive to the calcium channel blocker nimodipine (Nimotop®), or, in unipolar patients, venlafaxine (Effexor®) or bupropion (Wellbutrin®). Further work is needed to ascertain whether this potential differential responsiveness among carbamazepine and other psychotropic agents continues to hold up in a clinically robust fashion.

This life chart is an example of the vast majority of bipolar patients who can show amelioration of their illness either on lithium or other mood stabilizers and augmentation regimens. Moreover, non-response to lithium does not predict non-responsivity to other agents such as carbamazepine or valproate. The approval by the FDA of two new anticonvulsants, lamotrigine (Lamictal®) and gabapentin (Neurontin®) with effects on excitatory and inhibitory neurotransmitter systems, respectively, has led to the evaluation of these agents which may further increase treatment options for patients with a mood disorder. The Stanley Foundation Bipolar Network should help to rapidly expand this work.

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anticipation in which each successive generation has an earlier onset of the illness than their parents had.

[Editor's Note: It is noteworthy that several investigative groups now document a possible cohort or anticipation effect in bipolar illness wherein the onset of illness may occur as much as ten years earlier in the offspring of parents who have the illness. While a variety of potential explanations for this phenomenon remain to be explored, one possibility for which there is preliminary evidence from at least one laboratory, suggests that it could be the same type of genetic anticipation mechanism found in Huntington's chorea that accounts for the phenomenon in bipolar illness. If this were the case, then more aggressive attempts at early intervention and pharmacoprophylaxis would obviously be in order.]

Some cautionary notes are also derived from Professor Ross' talk in that it took more than a decade from the identification of the gene locus on chromosome 4 to discover the protein defect. Now that the protein defect has been identified, elucidating how the defective huntingtin protein might relate to the pathophysiology of the illness appears several more years distant. Moreover, how this would ultimately lead to a treatment intervention may be an additional decade away as well. All of these long time frames are in relation to an illness (Huntington's chorea) that has a single genetic locus, almost complete penetrance, and is a dominant mutation. This is unlikely to be the case for bipolar illness, ultimately making the linkage of these types of genetic analyses to the therapeutics of bipolar illness substantially more distant than even that for Huntington's chorea. Somehow, one needs to balance the current excitement about molecular genetics and the paternal transmission of bipolar illness that has been linked to a locus on chromosome 18, as previously discussed in other issues (*BNN* 1[1], 1995; *BNN* 2[1], 1996; *BNN* 2[2], 1996; *BNN* 2[3], 1996) with the view that much practical clinical psychopharmacotherapy still needs to be elucidated with the current treatments available. Studies are needed to determine how to maximally use combination therapies, as well as to continue to develop a variety of new therapeutic approaches without the early assistance of the molecular genetics revolution. As noted before in this issue, there are currently a panoply of treatment-related targets and many new drugs to specifically explore for their utility and optimum usage in the long-term treatment of bipolar illness.

Patricia Goldman-Rakic delivered another one of her wonderful integrative talks at the ACNP reporting the existence of neurons in the prefrontal cortex that are responsible for holding memories on line, and that the memory fields of neurons in the prefrontal cortex can be established. This is done with intracellular recording from primates. They are trained to stare at a point, observe a brief target (a stimulus present at a given location in clock time relative to the focus point; i.e., 3 o'clock would be directly to the right of center), and then respond to indicate where the target had been in order to get a food reward. Goldman-Rakic and her colleagues have observed that different neurons in the precentral gyrus fire differentially as a function of location or direction of the stimulus; i.e., some fire at 3 o'clock but other neurons are specifically tuned to targets localized at 6 o'clock, etc. Another whole set of neurons fire selectively during the interval between the disappearance of the stimulus from the screen and the emission of the response by the animal. These neurons are thought to be the ones that hold the memory of target location on line. Finally, a third set of neurons fire in association with the completion of the accurate directional response.

This prefrontal cortical system involved with holding memories on line may be a paradigm for other types of memory in addition to that related to location in space, much of which may be pertinent to deficits occurring in schizophrenia and affective illness. Interestingly, these illnesses are associated with prefrontal cortical deficits in blood flow or glucose utilization on brain imaging scans. It is of interest that the Goldman-Rakic group has found that dopamine D1 receptors are located along the dendrites of the main pyramidal outflow neurons of the prefrontal cortex, while D4 receptors are located on GABA interneurons, and that disruption of these dopaminergic systems leads to faulty memory processing. Some areas of the prefrontal cortex are selectively vulnerable to stress while others are not, leading to the possibility that dysfunctional prefrontal cortical function could be affected both by genetic and developmental vulnerabilities, and also by life events and psychosocial stresses pertinent to the precipitation of schizophrenic and affective episodes.

The interaction of these dopamine receptors impinging on prefrontal cortical glutamatergic pyramidal neurons via a GABAergic interneuron may also set the stage for understanding therapeutics with the atypical neuroleptics

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Clinical Research Update

Characteristics of Patients Who Have Been Good Lithium Responders: Preliminary Feedback from the Stanley Foundation Lithium Study

Gabriele S. Leverich and Nancy Palmer

We want to thank many of the readers of the BNN and other newsletters of patient advocacy groups (NAMI, NDMDA, DRADA) for responding in such a positive fashion to our request to participate in a naturalistic questionnaire study. This study seeks to look at the demographic and course of illness characteristics of patients who remain well on lithium for an extended period of time (at least five years) versus those who have not been sustained lithium responders. Thus far, 66 lithium-well patients have completed the study and filled out the *Questionnaire on Bipolar Illness*. We thought that a brief overview of the preliminary data might be of interest to many who participated.

The group of the 66 lithium responders has a mean age of 51 years with an average illness onset at age 22. Interestingly, although there is a 50-50 representation of males and females in the general bipolar population, almost 70% of the lithium responsive patients in this study are female. Fifty-two percent (52%) are married (for an average number of 24 years) and are highly educated with more than half with four or more years of college. They rate themselves as highly compliant and 84% checked that they never or rarely missed taking their medication as opposed to frequently or often missing them. They report a comparatively low, but still substantial, rate of alcohol abuse (22%) and drug abuse (18%) and describe a high rate of social support for their bipolar illness (79%) and a highly supportive environment in general (84%).

Eighty percent (80%) of the lithium responsive group are Bipolar I patients (i.e. they have been hospitalized for mania) and 62% of them are non-rapid cyclers (less than four episodes per year). However, one-quarter of all lithium responsive patients in this group reported that they were ultra-rapid cyclers (episodes shorter than a week) or ultradian cyclers (distinct and dramatic mood shifts within a 24 hour period), i.e., types of illness generally considered less responsive to lithium. Only 38% of all patients in this group describe a family history of bipolar illness in first degree relatives which is of some interest since the literature strongly suggests that a positive family history is a particularly good marker of lithium response.

While more definite interpretation awaits ongoing collection and analysis of the data from a comparison group of similarly recruited patients who have not done well on lithium and also completed the same *Questionnaire on Bipolar Illness*, even an initial look re-emphasizes the importance of medication compliance, the avoidance of some of the perils of alcohol and substance abuse, and the potential benefits of a supportive environment.

We continue to recruit for additional patients who have done well on lithium for at least five years and who would like to fill out the Questionnaire on Bipolar Illness. We would also like to hear from people who have not done well on lithium despite giving it a good trial (therapeutic blood levels for at least six months or longer), and who would be willing also to complete the questionnaire. This will help us to further characterize features that may distinguish excellent responders from non-responders to lithium. To participate please call (301) 496-6827 or 1-800-518-7326; e-mail: stanley@sparky.nimh.nih.gov; or write to: The Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200 Bethesda, MD 20814.

Again, we want to thank all of you who have helped us with this study and we appreciate your efforts and ongoing collaboration with us.

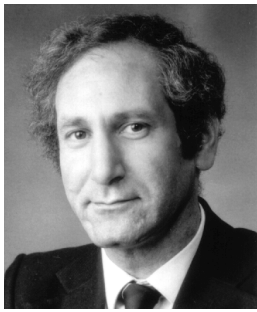
ACNP Highlights (continued from page 5)

such as clozapine and olanzapine, which are potent blockers of D4 receptors. Clozapine is also reported to be highly effective in dysphoric mania and rapid cycling bipolar patients not responsive to conventional medications. It is of considerable interest that olanzapine (Zyprexa®) is the atypical neuroleptic most closely related to clozapine, and there is much hope that it will fill a similar therapeutic spectrum to clozapine in the refractory bipolar disorders. **[Editor's Note: The little-used antidepressant trimipramine (Surmontil®) also has effects on D2 and D4 dopamine receptors and its potential role as a mood stabilizer remains to be better studied.]**

Around the Network

Robert M. Post, M.D., Chief, Biological Psychiatry Branch, NIMH and Head, Stanley Foundation Bipolar Network

Dr. Post was born into a family in which the principles of hard work and academic achievement were imparted by his father and mother, respectively. He grew up in New Haven, Connecticut and attended Yale University from which he was graduated with a B.A. in psychology. He obtained his M.D. degree at the University of Pennsylvania School of Medicine in Philadelphia, and took a medical internship at the Einstein-Bronx Municipal Hospital in New York prior to one year of psychiatric residency at Massachusetts General Hospital. In 1970, he arrived at the National Institute of



Robert M. Post, M.D.

Mental Health (NIMH) for a clinical associateship under the tutelage of Fred Goodwin and Biff Bunney. After becoming Unit and then Section Chief in the Psychobiology Section of the Biological Psychiatry Branch (BPB), Dr. Post became Chief of the BPB when Biff (Bunney) left to become Chairman of the Department of Psychiatry at USC-Irvine.

Dr. Post has been particularly interested in the longitudinal course of the recurrent affective disorders and in uncovering the neurobiological mechanisms involved in illness progression and regression with appropriate treatment. He has used the model of kindling as one reflective of neuronal learning and memory that might provide clues as to how repeated stimulation of the brain may come to produce increasing effects over time. In the case of kindling, repeated stimulation of the amygdala for one second eventually produces full-blown seizures and, with sufficient number of stimulations, the seizures begin to occur spontaneously. Dr. Post thinks similar learning and memory mechanisms may take place with repeated stressors and episodes of affective illness, which may also leave behind memory traces increasing vulnerability to recurrence in the affective disorders.

These observations fit in with the literature since the time of Kraepelin, who described that initial episodes of affective illness are often associated with stressful life events and psycho-social precipitants, but that with sufficient numbers of episodes, they may, as in the kindled seizure

paradigm, begin to occur spontaneously. It is important to note that Dr. Post does not believe that seizures underlie the affective disorders — only that the kindled seizure model is a useful one for conceptualizing mechanisms that might underlie long-term memory traces pertinent to affective illness. These may occur in very different areas of brain from those involved in seizure generation. Use of this model has led to reconceptualization of cyclic episodes of illness as related to the balance between pathological and adaptive neurochemical processes acting at the level of gene expression.

The kindling work also led to the first double-blind clinical trials of carbamazepine (a potent drug for inhibiting limbic over-excitability) for patients with bipolar illness. Positive findings have now been replicated in 18 other studies of acute mania and in numerous studies of carbamazepine in long-term prophylaxis. Recently, in collaboration with Dr. Susan Weiss, Dr. Post has focused on mechanisms for blocking kindled seizures and has begun to utilize a process called quenching. This involves relatively longer stimulation of the amygdala with very low frequencies (1 cycle/sec for 15 min) as opposed to the parameters that induce kindled seizures (60-100 cycles/sec for 1 second). Quenching stimulation, if given after kindling, will completely inhibit the development of seizures and suppress fully developed kindled seizures if it is given once daily for a period of a week.

These preclinical findings in relationship to amygdala excitability for seizure induction and suppression may be pertinent to the affective disorders in that dysregulation of the amygdala has long been linked to disorders of emotional function (even if not related to full-blown seizures). Moreover, the new technique of repeated transcranial magnetic stimulation (rTMS) of the brain, which was developed in collaboration with Drs. Mark George, Eric Wassermann, and Mark Hallett, and more recently, Tim Kimbrell, John Little, and Una McCann of the BPB, may be able to utilize moderate frequencies (20 cycles/sec) for potential antidepressant effects and low frequencies (1 cycle/sec) for the treatment of post-traumatic stress disorder. The hope is that the correct parameters of rTMS will ultimately be found to optimize treatment for a variety of neuropsychiatric conditions. Towards this end, Dr.

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Post, in collaboration with Drs. Eric Wassermann and Mark George, developed an informal consortium to exchange information and most rapidly find the best stimulation patterns for optimal therapeutics.

In a similar fashion, Dr. Post and his colleagues have recognized the need for a consortium of investigators to further advance clinical trials of new approaches to the lithium-refractory bipolar patient. The field is greatly indebted to Ted and Vada Stanley and to Dr. E. Fuller Torrey, Administrator of the Stanley Foundation, for enabling the formation of such a treatment outcome network. The Stanleys were present at a meeting in Chicago at which both Dr. Post and Dr. Susan McElroy spoke about recent advances in treatment approaches to bipolar illness, and noted the relative dearth of systematic studies to guide clinicians to the optimal therapeutic regimens. As opposed to the clinical trials literature in other medical specialties, in which complex regimens are compared with one another in order to ascertain the most effective approach, clinicians and patients who are dealing with bipolar illness currently have to rely on a sequential clinical trial algorithm in individual patients in order to establish the best approach for that individual.

While this approach is most often ultimately successful, it frequently requires months or years to achieve a full remission. It is the hope that the randomized clinical trials of the Stanley Foundation Bipolar Network will help accelerate this process with systematic comparisons of the efficacy of different approaches at each of the choice points now confronted by clinicians and patients, so that the relative benefits and liabilities of a given approach, and the potential clinical and biological markers of which patients might respond best to which treatments, can be more rapidly derived.

The field is much indebted to Dr. Post for his creative energy. He has advanced the knowledge and study of affective illnesses, and his longitudinal perspective of the recurrent and variegated course of bipolar illness has generated and facilitated many innovations in the investigation and treatment of this devastating illness. As Head of the Stanley Foundation Bipolar Network, together with all of the principal investigators at the different Network sites described in each of the previous issues of the *BNN*, he has created, for the first time, an alliance of clinicians, researchers, advocacy groups, and patients for better understanding bipolar illness, for identifying predictors of

treatment response, and for the development of treatment approaches.

A recipient of many distinguished awards, and a prolific writer on the time course and mechanisms of biochemical and behavioral changes in the affective illnesses, the Network is indeed fortunate to have Dr. Post's expertise, knowledge, leadership, and his dedication to the alleviation of the suffering brought on by these illnesses.

Consumer Corner

To the Newly Diagnosed and Others in Need of Help in Managing Their Illness

Jim Whitted, UCLA Site, SFBN

In 1979 I was diagnosed with bipolar disorder. I had a good job, a good family life, and what I thought was a good doctor who prescribed an antidepressant and gave my wife and me what we thought was a good plan for her to intercede if she thought the illness was getting out of control. Two years later I shot up into a medication-induced mania (the plan failed), and my poor judgment and erratic actions caused me to lose my job. I got a new doctor, began taking lithium along with an antidepressant, and my moodswings calmed down. However, the shame and consternation arising from my manic actions and losing my job had thrown me into a tail spin. I made no efforts to prepare for the rest of my life. I was either making futile efforts to regain my job or wallowing in a depression that the medications couldn't handle. My wife thought that this was the way I was going to be for the rest of my life (and I guess that I did also) and, in 1983, we agreed to divorce. This happened mainly because we had insufficient knowledge of the true consequences of the illness and how to handle them, and no one to turn to for help (even today most psychiatrists don't fully appreciate this aspect of recovery).

The situation is better now (in 1997). However, someone who is newly diagnosed almost surely doesn't know what steps to take to properly manage their illness. Therefore, I offer these suggestions.

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- Find a doctor who specializes in your illness. Proper medication management is paramount. It may take a while to find the right doctor and the right medication for you, but persistence pays off.
- Interact with others who have your illness. Only then will you be with people traveling the same road as you, many of whom will be further along that road and can give you good, practical advice. This can be done in self-help support groups like NDMDA (Depressive and Manic-Depressive Association) for patients or NAMI (National Alliance for the Mentally Ill) for families, or in more formal groups led by a mental health professional (but beware of ineffective groups that just satisfy a clinic's protocol). If one group doesn't suit your needs (after several meetings), search for others. Again, persistence pays off.
- Search for additional mental health care. A doctor who sees you once a month to monitor your medication is not enough, especially at first. You need a psychologist or therapist well versed in your illness to educate you about your illness, give you feedback on your symptoms, help you to deal with adjunct issues, help you manage your illness, and supply psychotherapy when appropriate.
- Become educated in your illness—the more you know about the illness, the better you will be able to manage it. Read books and attend lectures. Take an active role in your treatment. *[Editor's Note: Consider systematically charting the course of your illness on the LCM].*
- Establish a close support group and include them in the previous steps. Mental illness is not something that can be managed well alone. You need understanding people who can help you get to the doctor's office when you are too sick to believe that you are sick or too depressed to care about being helped. Overcome your resistance to accepting help.
- Reduce the stress in your life. For those of us with a mood disorder, this is especially paramount.
- If your illness has taken away your primary goals in life (as happened to me), find others. I have found that having proper life goals has been vitally important in the management of my illness.
- Medication and therapy can only do so much. Diet, exercise, and an active and healthy lifestyle are also important. Act like you aren't ill, and one day you will be acting no more.
- Trust. Don't stop taking your medications because of the bad side effects. It may take your doctor a while to get you stabilized on the right drugs. Believe the knowledgeable people around you when they tell you that your symptoms are worse. Take the advice of those who have gone before you. *[Editors Note: Be sure to talk with your doctor about the side effects you are experiencing. In most cases they can be dealt with by dose reduction or alternative medication.]*
- Proper management of the illness is the goal. You will have to accept whatever "recovery" your illness and treatment will allow for the time being. New medications and treatments are coming.
- Have faith. Mental illness can be successfully managed, even if in your present state of mind you cannot possibly imagine how.

You will make little progress until you finally decide to get serious about managing your illness. It took many years and the help of a lot of good people for me to get a handle on my disorder. Things got worse before they got better, and they don't always go smoothly now. However, I am leading a happy and productive life with a bright outlook for the future. I can well remember when this wasn't the case.

The Stanley Foundation Bipolar Network/Early Intervention Initiative (EII) is looking for families with a mood disorder on both sides (with at least one parent bipolar) to fill out a questionnaire about their children and the ethics of early intervention. This information will not only help us identify the symptoms and behaviors associated with bipolar disorder in children and adolescents, but will also help us design early intervention protocols for this population.

If you are interested in filling out the questionnaire, please call (301) 469-6827 or (800) 518-7326; e-mail us at: stanley@sparky.nimh.nih.gov; or write to: The Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814.

Survey of Experience with Naltrexone (Revia®) in Bipolar Illness

Recently, the drug naltrexone (Revia®), based on two positive placebo-controlled studies in the literature, has been approved in conjunction with psychotherapy management for the reduction of craving in alcoholic patients. However, there is little systematic data on the effects of naltrexone in patients with bipolar illness who also have concomitant alcoholism. We would be most interested in hearing from patients and physicians who have clinical experience with naltrexone in bipolar illness. We will form an initial registry to keep track of the open anecdotal data and then will make further decisions about whether to engage in a formal clinical trial depending on the initial information submitted. All information will be kept confidential and will only be used for research purposes without your name or initials connected to it.

Thus, if you or someone you know with a mood disorder has been given a clinical trial of naltrexone, we would appreciate hearing how well the drug worked in reducing the craving for alcohol and whether or not it affected mood in either a positive or negative way.

Please check one: **Self-Report** **Clinician's Report**

Diagnosis (please circle one): **SA** **BPI** **BPII** **BP NOS** **UP** **Don't know**
Schizo/affective Bipolar I Bipolar II Bipolar Not Otherwise Specified Unipolar

Revia® (Naltrexone)

Duration of total trial ___weeks **Maintenance dose** ___mg/day **Still on Drug?** ___Yes ___No

Please rate how you felt on Revia® compared with just before starting the drug (check one box in each row).

	A Markedly Decreased	B Moderately Decreased	C Slightly Decreased	D No Change	E Slightly Increased	F Moderately-Markedly Increased
Alcohol Craving						
Alcohol Intake						

	A Markedly Improved	B Moderately Improved	C Slightly Improved	D No Change	E Slightly Worse	F Moderately-Markedly Worse
Depressed Mood						
Manic Mood						

Side Effects* (please list and check severity) (*if none, please write NONE in the column below)	MILD 1	MODERATE 2	SEVERE 3
1.			
2.			

Please list name(s) and dosage(s) (if known) of other medications you (or patient) are taking:

Drug Name	Dosage/Day
1.	
2.	
3.	

Drug Name	Dosage/Day
1.	
2.	
3.	

Please write in your (or patient's initials ___ ____, City _____, and State ____, and return this form to: The Stanley Foundation Bipolar Network, Attn: Revia® Survey, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814. If it is acceptable to you that we contact you about this information, please include your name, address, and telephone number. **Again, this information will be kept strictly confidential.** Thank you for your assistance with this survey.

Name: _____

Address: _____

Phone Number: () _____

Today's Date: ____ (month)/ ____ (day)/ ____ (year)

Bipolar Network News

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