Volume 2 Issue 4
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Bipolar Network News

Clinical Trials Update

Two-hundred twenty-six patients have been enrolled into the long-term prospective daily follow-up of mood and functioning in the naturalistic study component of the Stanley Bipolar Treatment Outcome Network. If patients become depressed during treatment with their mood stabilizer, they are offered randomization among three different antidepressants with different mechanisms of action—bupropion (Wellbutrin®) (with its dopaminergic effects), sertraline (Zoloft®) (with its serotonergic effects), and venlafaxine (Effexor®) (with its combined serotonergic and noradrenergic effects)—in the first antidepressant protocol (AD-1) of the Network. At each site, patients are stratified in the randomization according to whether they are rapid cyclers or not. If patients fail to respond to one of these antidepressant modalities, they can be re-randomized to the others. If they successfully respond, they are offered continuation evaluation for an additional year to confirm sustained antidepressant prophylaxis. Currently, 26 patients have been randomized in this first antidepressant protocol and 8 patients are in the continuation phase.

With this study, we are hoping to provide clinicians and patients with systematic evidence of which antidepressant might be most optimal in terms of efficacy without the liability of increasing vulnerability to subsequent manic episodes. The study is being organized such that some patients will be studied in a double-blind, highly controlled fashion with detailed ratings at academic centers in what we have called Level I. A much larger number of patients will be able to be entered into this randomized trial (and other future trials) and will be followed in an open fashion with only a minimum amount of paper work for physicians to complete (i.e., Level III).

Thus, information about the relative efficacy of the antidepressants in a large number of patients can be assessed so that differential responsivity according to sub-categories of the illness such as bipolar I versus bipolar II and rapid cycling versus non-rapid cycling can also be examined. Level III studies (i.e., patients and clinicians in clinical practice or mental health center settings) will become a very important component of the Stanley Bipolar Network so that much information can be gathered about this difficult illness. Physicians and patients wishing to participate in this open randomized antidepressant trial (and, if interested, in future Network studies) using a minimum of outcome measures, should write to the Stanley Foundation Central Office at 5430 Grosvenor Lane, Bethesda, Maryland 20814 or call 1-800-518-SFBN, Gabriele S. Leverich, L.C.S.W., at (301) 496-7180, or Tina Goldstein at 301-496-6827.

"One of the overarching ideas of the...Network at Levels I and III is to develop randomized trials at each of the choice points that a clinician and patient would face in the pharmacotherapy of bipolar illness."

One of the overarching ideas of the Stanley Foundation Bipolar Treatment Outcome Network at Levels I and III is to develop randomized trials at each of the choice points that a clinician and patient would face in the pharmacotherapy of bipolar illness.

Thus, Dr. Paul Keck is writing a protocol (AD-2) for a randomized comparison of stimulant vs. T_3 augmentation for patients who have failed to respond adequately to one of their antidepressants.

Another option to be systematized by Dr. Willem Nolen for use in the Network is a randomization between a classical monoamine oxidase inhibitor antidepressant (tranylcypromine [Parnate®]) and the novel putative mood stabilizer and antidepressant lamotrigine (Lamictal®). This randomized treatment option (i.e., AD-3) would compare the efficacy of the MAOI tranylcypromine which has the highest reported efficacy among antidepressants in bipolar depression against the addition of a novel mood stabilizer (potentially

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lamotrigine). There is increasing recognition that the combination of two or three mood stabilizers may be more helpful in some cycle-prone bipolar patients than the use of the more traditional antidepressant modalities for the treatment of breakthrough depressions, but this has not been previously systematically studied.

For patients with breakthrough episodes of hypomania and mania, as well as more persistent symptoms of rapid cycling despite initial mood stabilizer use, Drs. Denicoff and Frye at the Bethesda site are organizing a double-blind trial comparing the addition of gabapentin (Neurontin-4) or lamotrigine or placebo for six months with a crossover to the other phases (i.e., 4-5-Anti-cycling protocol). They will be organizing this study to also be used at Level III so that clinicians in private practice or mental health clinic settings will adopt only the active part of the randomization to compare the efficacy of lamotrigine with gabapentin as an add-on without a placebo phase.

Patients who fail to adequately respond to either arm of this regimen can then be placed on a systematic evaluation of the new atypical neuroleptic olanzapine (Zyprexia®) (protocol AC-6), which has a profile of effects most similar to that of the atypical drug clozapine (Clozaril®), which has been reported effective in rapid cycling and dysphoric mania by Network investigators McElroy, Keck, and Suppes. However, olanzapine does not appear to share the problematic side effects of clozapine, which induces a small but significant incidence of agranulocytosis (potentially fatal lowering of the white blood cell count) and thus requires weekly blood count monitoring. At some sites this treatment choice with an atypical agent will allow the comparison of olanzapine with risperidone (Risperdal®) (AC-3), which is being widely used as an augmenting agent, but Keck and McElroy as well as others have seen some problematic occurrences of manic induction in some patients.

Thus, the Network is well on its way toward a panel of systematic treatment choices, with a randomized comparison between agents that appear relatively equally effective at each of the choice points, although clinicians have their preferences which are often, however, based only on a relatively small personal experience and inadequate literature. In this way, through the randomized Network protocols in clinical practice, we hope to more rapidly build a body of systematic evidence to guide clinicians and patients toward their optimal choice of treatment agents. This database will also assist in the development of treatment algorithms which are increasingly being promulgated but are often based on one or two uncontrolled studies in small numbers of patients.

From the perspective of informed consent, it is important that patients realize that while they are engaging in a randomized clinical trial, they are following one of two treatment options often used in clinical practice but without any systematic comparative data about relative efficacy. Until such knowledge can be acquired, there is no reason to assume that either one of the drugs to be utilized would have a substantial advantage over the other. Thus, the patient must be willing to accept whichever of the two options is offered, with the understanding that at the current time both are thought to have an approximately equal chance of being effective. Since these designs of the first antidepressant (AD) and most anti-cycling (AC) protocols involve: a) comparison of two active treatments; b) do not include a placebo; and c) follow general clinical practice options, there are no additional risks or liabilities over those in the usual clinical practice in which a physician and patient together choose which of several approaches they "think" would be optimal, as opposed to this trial in which one of the two outcome options would be chosen on the basis of a randomized assignment. ■

LIFE CHART

Case Presentation:
The Role of Stress in the
Longitudinal Course of Bipolar Illness

The role of stressors or life events as precipitants of initial episodes of recurrent unipolar and bipolar affective illness has long been recognized. The field is rich with studies exploring the possible pathogenic role of certain events and the interaction of psychosocial and biologic factors in the evolution and progression of the illness. Prospective life charting helps illustrate the sequence of events and helps address the question of causality; that is, did the illness provoke the event or did the event precede and potentially contribute to the occurrence of the episode. The current life chart suggests how stressful life events in some patients at high risk could lead to the reemergence of episodes that had otherwise been successfully treated.

The patient shown here was admitted to the NIMH in 1984 after a 20-year history of bipolar disorder. Hospitalized at age 19 for a manic episode, with four more hospitalizations and a suicide attempt, she was started on lithium in 1973 (not shown here). After several years of good functioning, symptoms of anxiety and depression emerged, necessitating additional medications. After treatment with a tricyclic antidepressant the patient became manic, requiring another hospitalization in 1979. With a pattern of continuous rapid cycling (presented here in dotted lines indicating that precise timing and duration of these episodes is approximate), the patient was rehospitalized in 1983. At the NIMH, the patient showed a confirmed response to the addition of carbamazepine (Tegretol®) since she relapsed during blinded discontinuation and then re-responded to the reinstitution of the combination of lithium and carbamazepine. She did well upon discharge on the continuation of both medications and enjoyed being at home with her husband and small child, resuming all of her usual activities. However, a series of stressors appeared to be associated with the retriggering of her illness.

Initially, a move (1) to another city was accomplished without difficulty and the patient continued to function well on her lithium/carbamazepine combination therapy. The anticipated possibility of another move in September of 1985 because of her husband's potential job change was experienced as stressful, but did not affect the patient's mood and ability to function.

When a new job assignment for her husband became official in January 1986 with all the necessities of selling and buying a house, the patient began to feel the anticipation of renewed loss of home and friends more acutely, and by early March she was experiencing a mood swing into a dysphoric hypomania. She restabilized without a change in her medications, but she became significantly depressed once the second move (2) was accomplished. She felt suicidal, "psychologically battered", missing her social support system, and struggling to help her child adjust to a new environment. An increase in both carbamazepine (Tegretol®) and lithium brought a good response within a week and she remained stable and active for the remainder of the year.

In January 1987 she became depressed again when she heard of the likelihood of another job change and a projected third move (3) to another city. She responded to an increase in carbamazepine, but became depressed again in March when the move was scheduled for May with the concomitant losses of her familiar environment and friends. Both lithium and carbamazepine were increased again with a good response, although a mild euphoria occurred once the move was accomplished. She continued to experience her losses quite intensely and by early June (one month after the move) became depressed and remained so for several months. She felt more lonely and "vulnerable" to changes in her environment, more apprehensive about future responses to stressful life events, and expressed great concern over the reactivation of her illness.

The life chart presented here highlights the possibility that repeated stressors can not only be involved in the unfolding of the illness in its early phase, but also in the reactivation of the illness

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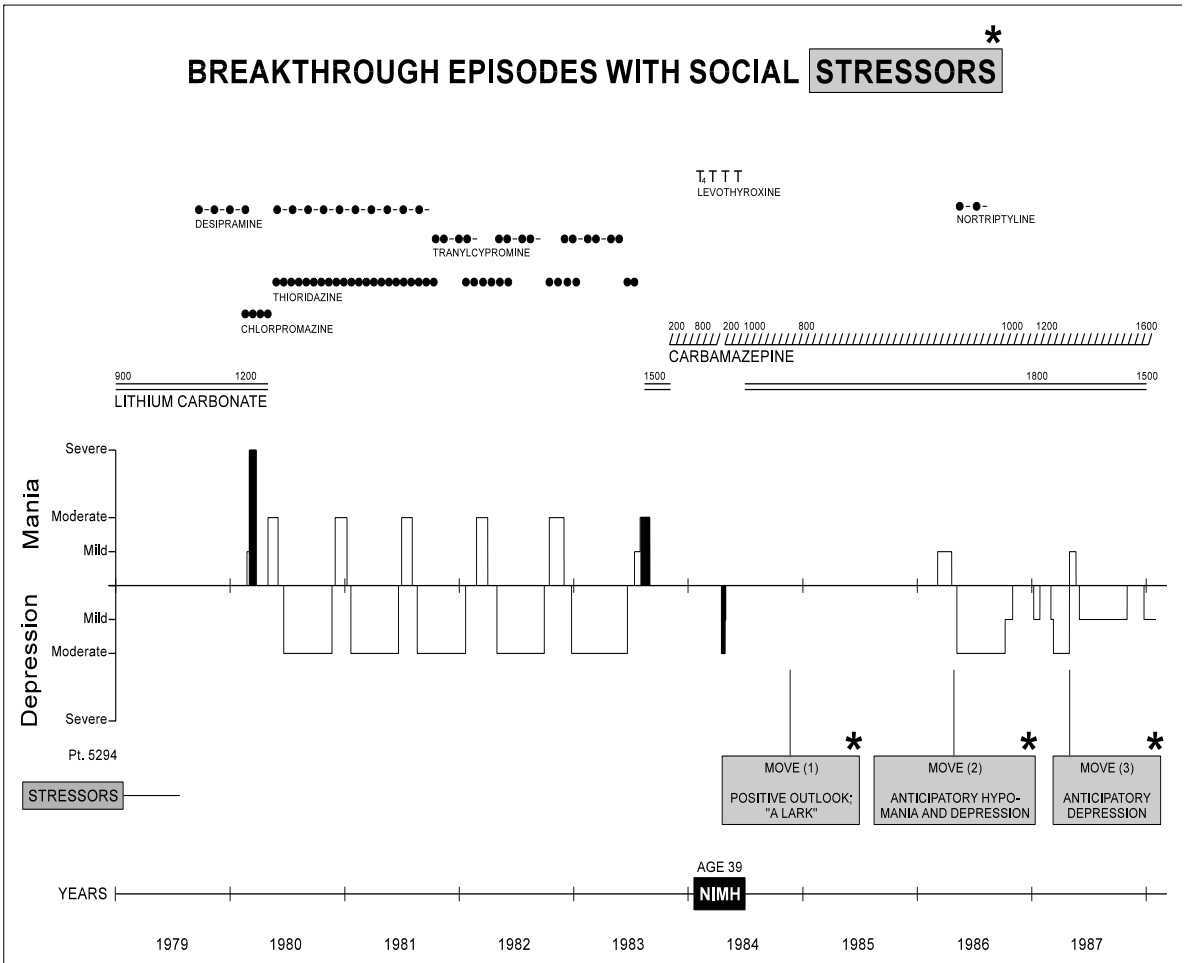

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with the occurrence of new episodes in an otherwise well-stabilized patient. We know from a meta-analysis of the pertinent literature (Post et al, 1992) that about 60% of first episodes of illness are precipitated by a recent psychosocial stressor. A preliminary view of the neurobiological mechanisms potentially involved in this phenomenon can be inferred. Acute stressors may be capable of leaving long-lasting biochemical alterations or memory-like residues that can serve as vulnerability factors in the precipitation of future episodes. New data from studies in animals indicate that stressors determine what genes (or transcription factors) in the body get expressed, which are then in turn able to initiate new sequences of gene transcription. Stressors furthermore can turn growth factors for nerves in the brain (neurotrophins) on and off. These neurotrophins are involved in synaptic and structural modifications as well as neuroprotection and programmed cell death.

What are the clinical implications of the long-lasting consequences of early stressors? Importantly, not all stress-induced changes in gene expression are pathological, and, as recent data by Drs. Meaney, Plotsky, and Sapolsky and associates indicate, mild stressors early in life may even be protective against neuronal loss and memory decline in adulthood. Moreover, the ability to cope with a stressor may lessen its negative consequences, as in the learned helplessness model. The need for opportunities to learn to cope with and manage stressful events points to the crucial role for social support and psychotherapeutic intervention to help acquire and instill a sense of mastery and control over an event to lessen its stressful impact and potential for pathological changes.

A second perspective has been uncovered by Dr. Mark Smith in our Branch, who found that antidepressant drugs, in addition to their

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many effects on neurotransmitters, induced changes in the neurotrophic factors BDNF (brain derived neurotropic factor) and NT3 (neurotropin-3), that were exactly opposite to those induced by stressors. These findings and the additional observations that chronic pretreatment with antidepressants blocks some of the effects of stress in decreasing brain-derived neurotrophic factor (BDNF) in the hippocampus and other important areas of the brain, raise the possibility that antidepressants could have multiple levels of beneficial effect when used in long-term prophylaxis of unipolar depression to:

1) lessen the negative impact of some stressful life events;

2) prevent the long-term cumulative impact of such stressful life events on brain structures;

3) reduce the chance of a stressor precipitating a new episode;

4) prevent the associated negative psychosocial, morbid, and potentially lethal effects of a depressive episode in the individual; and

5) possibly alter the long-term course of illness by preventing such depressions and thereby rendering the individual less vulnerable to subsequent relapses.

While all these propositions are hypothetical and remain to be directly tested, the fact that long-term prophylaxis in patients who have recovered from their unipolar depression markedly diminishes the rate of relapse has been unequivocally demonstrated with multiple antidepressants, and Dr. John Davis found that the likelihood of these positive results being due to chance are infinitesimally small ($p < 10^{-34}$). Thus, the hope would be that an early and sustained prophylactic treatment would not only prevent future depressions, but also help decrease vulnerability by lessening the impact of stressors and decreasing the number of depressive recurrences. ■

EARLY INTERVENTION INITIATIVE (E.I.I)

A number of investigators interested in the early presentation and treatment of bipolar illness in children and adolescents have developed a consortium under the general heading of the Early Intervention Initiative (E.I.I.) of Stanley Foundation-supported work. One of the key elements of the E.I.I. is the identification of a core set of rating instruments that would be able to acutely and longitudinally assess altered mood and behavior related to bipolar illness in some continuity with the adult scales. There is preliminary agreement on:

1) the use of the "kiddie" SCID in order to make the appropriate diagnostic assessment in parallel with the use of the SCID for adult diagnosis.

2) a kiddie life chart method (LCM-K) has been developed for daily prospective rating of childrens' behavior by parents which will have some measure of continuity with the adult LCM rating for degree of dysfunction driven by manic and depressive behaviors. However, in the LCM-K, degree of social or educational dysfunction is rated according to the severity of a variety of symptoms reflecting activation, such as impulsivity, hyperactivity, temper tantrums, aggression, etc., without having to meet specific diagnostic criteria for a manic syndrome. Similarly, withdrawn and depressive-like behaviors are rated for their degree of impairment in the child's usual roles, even in the absence of a depressive syndromatic diagnosis.

3) for acute ratings of children and adolescents, the Young Mania Rating Scale will be used as a core instrument (as it is in adults in the Stanley Foundation Bipolar Treatment Outcome Network).

4) the Inventory of Depressive Symptomatology (IDS) will be utilized for depression severity ratings because of both its continuity with the adult Network as well as the availability of a self- and observer-rated form with good scale reliability and validity characteristics.

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5) the Clinical Global Impression Scale as modified for bipolar illness (CGI-BP) (Spearing et al, 1997) will be used as a global assessment instrument for drug efficacy (as in adults).

In this fashion, it is hoped that many centers around the U.S. and internationally will adopt this core packet and begin to relate these common instruments to their own particular set of assessment tools, so that issues of cross-validation can ultimately be addressed. In the meantime, this core set of instruments should allow a partial common language in the longitudinal assessment of individuals that provides continuity into the adult domain.

A variety of clinical trials and treatment algorithms for the E.I.I. are proceeding at different sites, as discussed below. Additionally, we are particularly interested in assessing the degree of intervention desired by parents and children who are at very high risk for bipolar disorder. Thus, we seek families in which both parents have an affective illness (at least one bipolar) who would fill out a survey not only for the presentation of early symptoms in themselves and children, but also for their assessment of the ethical risk/benefit of intervention with different types of pharmacological and physiological treatment techniques in young children.

FAMILIES WITH AFFECTIVE ILLNESS ON BOTH THE MATERNAL AND PATERNAL SIDES WHO ARE INTERESTED IN PARTICIPATING IN SUCH A SURVEY SHOULD WRITE OR CALL 1-800-518-SFBN FOR FURTHER INFORMATION AND TO HAVE THE SURVEY MAILED.

A series of randomized clinical trials in the Stanley Foundation Bipolar Treatment Outcome Network and affiliated sites are being proposed to assess the efficacy of early intervention in patients with various levels of symptomatology and in different age groups. For example:

Dr. Robert Kowatch, in collaboration with Drs. Trisha Suppes and John Rush at Southwestern, will develop a treatment algorithm for children and adolescents with full-blown illness. They will also compare the efficacy of lithium, carbamazepine (Tegretol®), and valproate (Depakote®) in this age group.

Dr. Willem Nolen in Utrecht is planning a randomized comparison of valproate versus placebo in children and adolescents who have had one prior episode.

Finally, Drs. Findling and Calabrese at Case Western Reserve will be comparing valproate versus placebo, both with adjunctive family therapy, in the prophylaxis of adolescents aged 14 to 18 who have manifested early affective symptoms, in order to assess the efficacy of prophylaxis of valproate in this age group.

These data should both help establish the efficacy of valproate in child and adolescent mania, as suggested in the early open work of Kutcher et al, and should help in the assessment of clinical and biological predictors of response to lithium versus valproate and the development of alternative treatments for non-responders.

Thus, an emerging group of systematic controlled comparisons should help to better delineate the appropriate psychopharmacological choices and interventions for children at high risk for developing full-blown bipolar illness. At each of these sites, many other specialized scales will be used in conjunction with the core instruments, so that comparisons to these common scales across sites can be more readily achieved. The ultimate goal of the E.I.I. would be to discover and document ways to prevent the illness from developing at the outset, or at least lessen its impact with the earliest intervention possible. ■

BIPOLAR ILLNESS STUDY DESIGN

Alternative clinical trial designs for patients with bipolar illness: Attention Reviewers of NIMH Grants

One of the leading methodological experts in the field of bipolar illness, Dr. Alan J. Gelenberg, Professor and Head of the Department of Psychiatry, University of Arizona Health Science Center, and Editor, *Journal of Clinical Psychiatry*, was a special guest lecturer in the Biological Psychiatry Branch in September 1996. His presentation and the intensive discussion with other members of the NIMH community led to the conclusion that traditional designs for evaluation of the efficacy of drugs in long-term prophylaxis in bipolar illness continue to be: 1) highly debated; 2) unable to answer many of the questions posed; 3) extremely costly; 4) too narrowly focused on unrepresentative patients, i.e., those without a variety of comorbidities or rapid cycling; 5) logistically difficult because of recruitment and dropout rates; and 6) for many of the above reasons and others (especially the design issues), virtually unfunded by the extramural program of the NIMH.

For example, more than five years ago, Dr. James Ballenger, Chair, Department of Psychiatry, University of South Carolina Health Sciences, proposed a randomized trial of valproate, carbamazepine, or lithium in acute mania with continuation of long-term prophylaxis. It was rejected because of design issues. If the study had been funded, performed, and completed by this time, as it would have been if approved as submitted, the field would now be in possession of at least a modicum of new data on the comparative acute and long-term efficacy of these widely used agents. As it stands, there is virtually no information about their comparative efficacy or clinical or biological markers of response.

Dr. Joseph Calabrese at Case Western Reserve is conducting the only NIMH-funded prophylaxis drug trial of which we are aware; he is comparing lithium and valproate. This study also was rejected for NIMH funding for about four years despite Dr. Calabrese's consultation with most of the experts in clinical trials methodology in the field. Now, approximately the same study that was originally forwarded has been funded.

The extremely expensive long-term prophylactic study at multiple centers funded by Abbott Pharmaceuticals and presented by Dr. Charles Bowden at the American Psychiatric Association meetings in New York in May 1996, did not reveal a statistically significant antimanic effect of lithium or valproate compared with placebo. This outcome is difficult to fathom, but may be partially related to overly strict criteria for inclusion in the prophylactic phase after mood stabilization. Patients were required to remain stable for a considerable time prior to entry into a randomized comparison of lithium, divalproex-sodium, and placebo; thus, even the placebo-treated patient may not have been at very high risk at this phase of their illness. However, in comparison with depressive recurrences observed on placebo, these were significantly diminished on valproate but increased in those on lithium. Since a multitude of other studies with other designs have demonstrated the prophylactic efficacy of lithium against manic and depressive episodes, and many open studies with mirror-imaged designs in otherwise refractory bipolar patients have revealed a good prophylactic efficacy of valproate as well, it is likely that some methodological confounds continue to plague even this best attempt at a well-designed study when NIMH funding is not the issue.

It is likely that if those with the most severe illness were excluded from the study because of the requirement for stabilization, the very patients who would have the best chance of demonstrating efficacy compared to placebo (i.e., those having a difficult time getting stabilized) would not be included in the study. While there may be a variety of other reasons for the failure to demonstrate prophylaxis against manic episodes by the two drugs widely known and used for this purpose, our editorial emphasis here is that additional designs other than those utiliz-

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ing only parallel groups should be considered in patients with bipolar illness because of inherent variability in its presentation and the need to have cross-over data to help guide the clinician on what to do next in the face of non-response.

Therefore, instead of considering and funding only traditionally designed parallel group studies that may be particularly ill-suited to the variable presentation of bipolar illness, many study groups and review committees should: a) become more aware of the unique design problems in studies of bipolar illness; b) be amenable to other designs; c) acknowledge that a single study, no matter how well designed, is not going to be able to fill in answers to all of the needed gaps; d) acknowledge that almost any study funded is better than none-at-all in terms of the ability to advance knowledge in the field and help direct therapeutics (and the field has too long accepted the "none-at-all" option); e) consider that studies aimed at bipolar illness are at a special disadvantage because of the extreme variability of presentation of the illness, so that extra priority points are awarded for these types of studies; and f) make some amount of NIMH funds available specifically for the study of bipolar illness, rather than continuing the relative neglect of this devastating illness as it has been in the past ten years in NIMH-funded studies.

In 1984, Lewis and colleagues stated: "In a choice between a parallel and a crossover design, we think the burden of proof should be placed on those favoring the crossover design to show that it can succeed in improving on the parallel design, but we think that such proof will often be forthcoming". Given the inherently poor match of bipolar illness and bipolar patients to many parallel group designs, as discussed elsewhere (Post et al, 1995, *Psychiatry Research Society* and BNN Vol. 2, Issue 2, 1996), and considering the choice of design for bipolar patients, we believe the burden of proof should be on those suggesting that the parallel group design should be utilized to the exclusion of other possibilities. In this regard, we highlight "the clear value of self-controlled studies in the *initial investigation of new treatments*..." (Thomas Lewis et al, pg. 31, 1984) even while acknowledging that other randomized controlled trials (RCTs) are often needed before a new treatment is recommended for general use. ■

AROUND THE NETWORK

The Bethesda Site

(Gabriele S. Leverich, M.S.W., L.C.S.W., Director, Longitudinal Studies; Kirk Denicoff, M.D., Head of Outpatient Studies; Mark Frye, M.D., Chief, Unit on Inpatient Studies)

Gabriele S. Leverich, L.C.S.W., heads up the longitudinal assessment of all Section on Psychobiology patients hospitalized on the 3-West Clinical Research Unit of the Biological Psychiatry Branch, NIMH. In this capacity, for example, she has discovered that 43% of the patients maintained on a regimen of carbamazepine develop loss of efficacy via apparent tolerance mechanisms after an average of 3.6 years of treatment. Similarly, 27% of patients maintained on a long-term treatment regimen involving valproate develop loss of efficacy. However, these rates of loss of responsiveness may be higher than that in the general population. The NIMH inpatients were highly treatment-resistant and refractory to begin with, and, even then, the majority showed good long-term responsiveness. Given the possible hazards of experiencing breakthrough episodes on lithium, carbamazepine, and valproate that Ms. Leverich has documented, one should pursue treatments aggressively and with better compliance in order to minimize these occurrences.

In this regard, Ms. Leverich has made major contributions to the field codifying the NIMH Life-Chart Methodology (LCM) with manuals for its retrospective assessment on a monthly basis and for a prospective assessment on a daily basis (see monthly case presentation of LCM in each issue). This allows some of the most detailed descriptions of the course of illness in response to

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treatment available in the literature today. This LCM method is now not only being used throughout the Stanley Network and its affiliated sites, but it has also recently been adopted by a number of NIMH-funded sites and studies by the pharmaceutical industry. Furthermore, Abbott will be assisting in making a miniaturized, pocket-sized prospective LCM available, so that all patients with bipolar illness in whatever treatment setting or research study, will be better able to assess the efficacy of their treatment regimens. Additionally, Ms. Leverich has taken the lead in developing other outcome measures and questionnaires for the clinician and patient which have been implemented in the Network. This includes the Bipolar Illness Questionnaire which is being used in a study headed up by Ms. Leverich to discover variables that are predictive of a good response in patients to lithium in comparison with those patients who have not experienced a good sustained response to lithium. (Please see the recruitment ad for participation on the last page of this issue.)

Ms. Leverich has also directed the establishment of computer programs for the automation and integration of LCM-derived data into a research database so that a wealth of detail on patients collected longitudinally can be systematically analyzed in the Network. In her role as Director of Longitudinal Studies for the NIMH 3-West Inpatient Unit of the Biological Psychiatry Branch, she has also contributed in numerous ways to the evolution of our program including screening of patients for admission, and seeing inpatients in a twice-weekly group therapy session. Ms. Leverich is also studying the effects of psychosocial stress on the course of the illness and factors that are associated with suicidal ideation in the illness and the prevention of suicide. Thus, we are indeed fortunate to have Ms. Leverich's clinical and research skills applied to the Bipolar Network, to the research studies and administration of the 3-West inpatient unit, and the Stanley Network office on Grosvenor Lane. Her extraordinary and indefatigable efforts will surely make an important impact on developing the research base for better treatment of this potentially devastating illness. ■

Dr. Kirk Denicoff brings keen clinical skills and a wealth of medical knowledge to the outpatient studies at the NIMH which have recently been integrated as one of the sites in the Stanley Foundation Bipolar Treatment Outcome Network. Dr. Denicoff received his M.D. from Brown University and trained in psychiatry at Mt. Sinai Hospital in New York. He initially worked under the tutelage of David Rubinow, M.D., in his clinical research efforts in the Consultation-Liaison Service at the NIH. There, he studied the somatic and psychiatric side effects of interleukin-2 (IL-2) therapy for patients with advanced stages of cancer, finding that many of the endocrine effects of IL-2 increased in magnitude with repeated treatments and to a profile of side effects including disorientation, cognitive deterioration, behavioral changes, and psychosis, which then led to further revisions of this IL-2 protocol to allow it to have a better therapeutic index.

Dr. Denicoff was then recruited to: 1) develop and head the outpatient research program of the Biological Psychiatry Branch targeted to better understanding the course of illness; 2) assessing the efficacy of existing treatments, and 3) developing new treatment modalities. The first major study that he, virtually single-handedly, conducted compared one year of prophylaxis with lithium or carbamazepine on a randomized basis, a blind crossover to the other drug in the second year of treatment, and then a third year of treatment on the combination. During this study, he helped implement many of the methodologies that are now being widely used in the Stanley Network including daily prospective assessment of each patient with the LCM, the use of a new Clinical Global Impression scale specifically revised for bipolar illness (the CGI-BP), as well as the routine assessment with the Hamilton depression rating scale or the IDS depression rating scale (Inventory of Depressive Symptomatology) developed by Dr. John Rush.

Dr. Denicoff recruited and maintained a population of some 50 bipolar patients into this three-year randomized design. Patients then went

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to a fourth year with valproate plus lithium and a fifth year, if necessary, on triple mood stabilizer therapy. Treatment of breakthrough manic and depressive symptoms was allowed adjunctively with unimodal antidepressants or antimanic agents, either high potency benzodiazepines or neuroleptics, in order to maintain patients in the long-term study. Considerable disability was evident in patients on either monotherapy, even with adjunctive treatment in up to 74% of subjects. Substantially less than half the patients showed a good response as defined by marked or moderate on the CGI to either monotherapy, while approximately 50% of patients responded to the combination. Another four patients responded to the valproate phase and an additional one to the triple mood stabilizer combination phase involving lithium, carbamazepine, and valproate. Thus, up to 40% of the outpatients were inadequately responsive, even after sequential attempts at optimizing mood stabilizer treatment in combination after the initial randomized monotherapy phases.

While different patients appeared to respond differentially to different mood stabilizer regimens, clinical and biological markers of this putative differential responsivity were not always evident. However, patients who were treated for their first episode earlier in their course of illness did eventually respond better to lithium monotherapy. These observations are in concert with a variety of other data indicating that patients with fewer numbers of episodes prior to lithium do better than those in whom treatment is initiated after many episodes. Rapid cyclers did poorly on both monotherapies while over 50% responded to the combination of carbamazepine and lithium. Tricyclic antidepressants appeared to be incriminated in switching patients into mania in approximately 1/3 of patients as assessed by a complex algorithm for rating the relative likelihood of this event (the switch occurred at a time that was unexpected, earlier in the course of the episode, and with greater severity than previously predicted or unlikely related to the drug and more likely related to the natural course of illness). These more detailed prospective data mirror the retrospective data of Altshuler et al (1995) based on the retrospective LCM. In the current prospective data, we were able to utilize daily ratings of mood and behavior in attempting to reach these preliminary conclusions. These two studies, and the general uncertainty about which antidepressant is best for bipolar patients in terms of acute efficacy and continued long-term prevention without inducing manic episodes, led to our first randomized Network study of three of the newer antidepressants with different mechanisms of action—bupropion (dopaminergic), sertraline (serotonergic), and venlafaxine (noradrenergic and serotonergic); i.e., the current AD-1 protocol.

With Dr. Denicoff's skilled clinical and research judgments, almost all of the bipolar patients enrolled in his study could be evaluated and treated on a long-term systematic basis. The Network is indeed fortunate to have such an accomplished clinical investigator among its ranks. ■

Dr. Mark Frye is the head of our inpatient unit as well as recently moving to the outpatient clinic where he plays an important role in integrating these two clinical research domains. Dr. Frye received his M.D. degree from the University of Minnesota. He completed his psychiatry residency at UCLA. He was highly recruited from his training grounds with Dr. Lori Altshuler at UCLA.

Dr. Frye is taking the lead in a comparative study of two new anticonvulsants—lamotrigine (Lamictal®) and gabapentin (Neurontin®) compared with placebo in treatment-refractory unipolar and bipolar affectively ill patients. Fifteen patients have been evaluated and 20 randomized in this protocol with preliminary data suggesting an overall response rate of 64% for lamotrigine, and 67% for gabapentin. In these highly preliminary data, lamotrigine appeared to have useful antidepressant and mood-stabilizing properties while gabapentin appeared to have particularly good antimanic properties. These initial blind randomized data with lamotrigine in monotherapy complement the previous reports of Calabrese

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and associates of an excellent antidepressant and mood-stabilizing effect in a series of refractory patients studied in an open fashion, largely as an add-on therapy to previously ineffective regimens (see details in BNN Vol. 2, Issue 1, 1996). Dr. Frye has organized the inpatient study to assess possible biological markers of clinical response as well as establish correlates of clinical response with the use of imaging techniques and CSF and plasma studies before and during drug administration.

Dr. Frye, in collaboration with Dr. Denicoff, is now moving to establish a parallel long-term prophylaxis protocol in outpatient treatment with a randomized augmentation with gabapentin versus lamotrigine versus placebo as add-on to other mood-stabilizer pharmacotherapies. Ultimately, these prophylactic studies will be able to be viewed in concert with the continuation prophylactic phases of pharmaceutical-sponsored protocols involving the evaluation of acute treatment with lamotrigine and gabapentin with their provision of a continuation phase. These studies are being performed at some Stanley Network sites and some affiliated sites using some elements of the Network standardized methodology. In this way the field should rapidly be able to develop a detailed picture of the relative efficacy of these two drugs in different phases and subtypes of manic-depressive illness as well as to begin to evaluate possible ways to match patients to optimum therapeutic regimens based on any evolving definitions of clinical and biological correlative response.

Dr. Frye has also taken the lead in the clinical application of neuropeptide alterations in the affective illnesses based on his intensive study of CSF and neurotransmitters and peptides. Not only are some neuropeptide systems dysregulated in affective illness with absolute increases in some substances such as corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), or decreases in somatostatin (SRIF), but Dr. Frye has found evidence of their abnormal regulation even when the absolute levels are not different from controls. For example, he finds that some neuropeptide systems that are tightly correlated in normal volunteers such as somatostatin and TRH, are not correlated in patients with affective illness, while a variety of other neuropeptide systems that are not correlated in normal volunteers are highly correlated in the affectively ill patients. This provides further evidence that neurotransmitter and neuropeptide systems are becoming dysregulated, compared with their normal set points, in the course of affective illness.

Dr. Frye has begun to attempt to utilize this information for therapeutic purposes. Previous work in our Branch by Drs. Lauren Marangell and Ann Callahan found that TRH might be a potential compensatory adaptive mechanism in the illness, since it tends to be over-secreted and yet, when patients are given TRH into their spinal fluid in order to avoid the blood-brain-barrier, they feel better and not worse. This suggests that TRH may be an endogenous adaptation and possible antidepressant substance. Dr. Frye is now spearheading a protocol to assess the relative efficacy of TRH and T_3 in speeding the onset of antidepressant response. Should these prove positive, it would illustrate how using one's own neurotransmitter and peptide systems to advantage could assist in therapeutics. A variety of drug companies are attempting to run clinical trials of CRH antagonists which should decrease the effects of hypersecretion of CRH and its downstream consequence of hypercortisolemia, but in a parallel but opposing fashion, it may be beneficial to ultimately augment rather than suppress the TRH and thyroid systems.

Thus, our Branch and the Network are fortunate indeed to have Dr. Frye's clinical expertise and research skills directed toward innovative approaches for the treatment of this devastating illness. ■

CONSUMER CORNER

Bipolar Questionnaire for Clear Responders and *Non*-Responders to Lithium

The Stanley Foundation Bipolar Network is conducting a questionnaire study to identify the characteristics of bipolar illness that are associated with either an excellent response to lithium (well for five or more years) or a poor response to lithium. Appropriate participants for the poor response group are those who have not had a good long-term response to an adequate trial of lithium (at least six months, with good medication compliance, at therapeutic blood levels) for preventing manic and depressive recurrences. If you have had such an unsuccessful experience in the past and would be willing to complete a questionnaire about your bipolar illness, please call 1-800-518-SFBN or Nancy Palmer at (301) 496-6827, E-mail: stanley@sparky.nimh.nih.gov, or write to: NIMH/BPB; Bldg. 10 - Rm. 3N212; 10 Center Drive, MSC 1271; Bethesda, MD 20892.

Many thanks to all who have responded to the recruitment for the "lithium-well" study (i.e., an excellent, sustained response to lithium for five or more years) and have filled out the Bipolar Illness Questionnaire. We continue to recruit for this study as well. Please use the above address and/or phone number to contact us so that the questionnaire can be mailed to you. The response up to this point has been wonderful and we truly enjoy collaborating with all of you in this important project. ■

RECRUITMENT FOR NIMH STUDIES

We are seeking unipolar and bipolar depressed patients who need inpatient hospitalization and would like to participate in a study comparing the efficacy of gabapentin (Neurontin) vs. lamotrigine (Lamictal) vs. placebo. We are also recruiting depressed patients for an inpatient or outpatient study comparing the efficacy of different frequencies of repeated transcranial magnetic stimulation (rTMS). Please call (301) 496-6827 for further information. ■

Bipolar Network News

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